Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Clinical Packet
May 11, 2016

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Pharmacy and Therapeutics (P&T) Committee
Helpful Hints/Reference Document

P&T Charge

As defined by §22-6-122

The Medicaid Pharmacy and Therapeutics (P&T) Committee shall review and recommend classes of drugs to the Medicaid Commissioner for inclusion in the Medicaid Preferred Drug Plan. Class means a therapeutic group of pharmaceutical agents approved by the FDA as defined by the American Hospital Formulary Service.

The P&T Committee shall develop its preferred drug list recommendations by considering the clinical efficacy, safety and cost effectiveness of a product. Within each covered class, the Committee shall review and recommend drugs to the Medicaid Commissioner for inclusion on a preferred drug list. Medicaid should strive to insure any restriction on pharmaceutical use does not increase overall health care costs to Medicaid.

The recommendations of the P&T Committee regarding any limitations to be imposed on any drug or its use for a specific indication shall be based on sound clinical evidence found in labeling, drug compendia and peer reviewed clinical literature pertaining to use of the drug. Recommendations shall be based upon use in the general population. Medicaid shall make provisions in the prior approval criteria for approval of non-preferred drugs that address needs of sub-populations among Medicaid beneficiaries. The clinical basis for recommendations regarding the PDL shall be made available through a written report that is publicly available. If the recommendation of the P&T Committee is contrary to prevailing clinical evidence found in labeling, drug compendia and/or peer-reviewed literature, such recommendation shall be justified in writing.

Preferred Drug List/Program Definitions

Preferred Drug: Listed on the Agency's Preferred Drug Lists and will not require a prior authorization (PA).

Non Preferred Drug: Covered by the Agency, if it is determined and supported by medical records to be medically necessary, but will require a PA.

Non Covered Drug: In accordance with Medicaid Drug Amendments contained in the Omnibus Budget Reconciliation Act of 1990 (OBRA 90 federal legislation), the Agency has the option to not cover (or pay for) some drugs. Alabama Medicaid does not cover/pay for the following:

- Drugs used for anorexia, weight loss or weight gain, with the exception of those specified by the Alabama Medicaid Agency
- Drugs used to promote fertility with the exception of those specified by the Alabama Medicaid Agency
- Drugs used for cosmetic purposes or hair growth
- Over-the-counter/non prescription drugs, with the exception of those specified by the Alabama Medicaid Agency
- Covered outpatient drugs when the manufacturer requires as a condition of sale that associated test and/or monitoring services be purchased exclusively from the manufacturer or designee
- DESI (Drug Efficacy Study Implementation [less than effective drugs identified by the FDA]) and IRS (Identical, Related and Similar [drugs removed from the market]) drugs which may be restricted in accordance with Section 1927(d) (2) of the Social Security Act
- Agents when used for the symptomatic relief of cough and colds except for those specified by the Alabama Medicaid Agency
- Prescription vitamin and mineral products, except prenatal vitamins and fluoride preparations and others as specified by the Alabama Medicaid Agency
- Benzodiazepines and barbiturates with the exception of those specified by the Alabama Medicaid Agency
- Agents used to promote smoking cessation, unless authorized for pregnant females or plan first recipients
- Agents when used for the treatment of sexual or erectile dysfunction, unless authorized for pulmonary hypertension.

(From Alabama Medicaid Agency Administrative Code, Chapter 16 and Alabama Medicaid Agency Provider Billing Manual, Chapter 27.)

Prior Authorization (PA): Process that allows drugs that require approval prior to payment to be reimbursed for an individual patient. Drugs may require PA if they are in Non-preferred status or if they required PA prior to the PDL

Medicaid may require prior authorization for generic drugs only in instances when the cost of the generic product is significantly greater than the net cost of the brand product in the same AHFS therapeutic class or when there is a clinical concern regarding safety, overuse or abuse of the product.

Although a product may require PA, the product is considered a covered product and Medicaid will pay for the product only once the PA has been approved.

Override: Process where drugs require approval prior to payment to be reimbursed for an individual patient if the claim falls outside a predetermined limit or criteria. Overrides differ from PA in that drugs or drug classes that require an override will automatically allow payment of the drug unless something on the claim hits a predetermined limit or criteria. The different types of overrides include:

Maximum Unit Limitations
Early Refill
Brand Limit Switchover
Therapeutic Duplication

Electronic PA (EPA): The EPA system checks patient-specific claims history to determine if pharmacy and medical PA requirements are met at the Point-of-Sale claim submission for a non-preferred drug. If it is determined that all criteria are met and the request is approved, the claim will pay and no manual PA request will be required. Electronic PA results in a reduction in workload for providers because the claim is electronically approved within a matter of seconds with no manual PA required.

Prior Authorization Criteria Definitions

Appropriate Diagnosis: Diagnosis(es) that justifies the need for the drug requested. Diagnosis(es) **or** ICD-9 code(s) may be used. Use of ICD-9 codes provides specificity and legibility and will usually expedite review.

Prior Treatment Trials: Prior authorization requires that two (2) prescribed generic or brand name drugs have been utilized unsuccessfully relative to efficacy and/or safety within six (6) months prior to requesting the PA. The PA request must indicate that two (2) generic or other brand drugs have been utilized for a period of at least thirty (30) days each (14 days for Triptans, 3 days for EENT Vasoconstrictor Agents), **unless** there is an adverse/allergic response or contraindication. If the prescribing practitioner feels there is a medical reason for which the patient should not be on a generic or brand drug or drug trial, medical justification may be submitted in lieu of previous drug therapy. One prior therapy is acceptable in those instances when a class has only one preferred agent, either generic, or brand.

Stable Therapy: Allows for approval of a PA for patients who have been determined to be stable on a medication (same drug, same strength) for a specified timeframe and who continue to require therapy. Medications provided through a government or state sponsored drug assistance program for uninsured patients may be counted toward the stable therapy requirement. Medications paid for through insurance, private pay or Medicaid are also counted toward the requirement. Providers will be required to document this information on the PA request form and note the program or method through which the medication was dispensed.

Medical Justification: An explanation of the reason the drug is required and any additional information necessary. Medical justification is documentation to support the physician's choice of the requested course of treatment. Documentation from the patient record (history and physical, tests, past or current medication/treatments, patient's response to treatment, etc) illustrates and supports the physician's request for the drug specified. For example, if a recommended therapy trial is contraindicated by the patient's condition or a history of allergy to a first-line drug, and the physician wants to order a non-preferred drug, documentation from the patient record would support that decision. In addition, medical justification may include peer reviewed literature to support the use of a non-preferred medication.

External Criteria

Alzheimer's Agents

Appropriate Diagnosis

- The patient must have an appropriate diagnosis supported by documentation in the patient record.

Prior Treatment Trials

- The patient must also have failed 30-day treatment trials with at least one other prescribed and preferred Alzheimer's agent in this class, either generic, OTC or brand, within the past 6 months, or have a documented allergy or contraindication to all preferred agents in this class.

Stable Therapy

- Stable therapy for this class is defined as a 90-day or greater timeframe. Approval may be given for those who have documented stable therapy on the requested medication for 90 consecutive days or greater.

Medical Justification

- Medical justification may include peer-reviewed literature, medical record documentation, or other information specifically requested.

PA Approval Timeframes

- Approval may be given for up to 12 months.

Electronic Prior Authorization (PA)

- Alzheimer's agents are included in the electronic PA program.

Verbal PA Requests

- PA requests that meet prior usage requirement for approval may be accepted verbally.

Antidepressants

Appropriate Diagnosis

- The patient must have an appropriate diagnosis supported by documentation in the patient record.

Prior Treatment Trials

- The patient must also have failed 30-day treatment trials with at least two prescribed and preferred antidepressant agents in this class, either generic, OTC or brand within the past 6 months, or have a documented allergy or contraindication to all preferred agents in this class.

Stable Therapy

- Approval may be given to those who have documented stable therapy on the requested medication for 60 consecutive days or greater.

Medical Justification

- Medical justification may include peer reviewed literature, medical record documentation, or other information specifically requested.

PA Approval Timeframes

- Approval may be given for up to 12 months.

Electronic Prior Authorization (PA)

- Antidepressants are included in the electronic PA program.

Verbal PA Requests

- PA requests that meet prior usage requirement for approval may be accepted verbally.

Cerebral Stimulants/Agents Used for ADHD

Appropriate Diagnosis

- The patient must have an appropriate diagnosis supported by documentation in the patient record.

- For agents with an FDA-approved indication of Idiopathic hypersomnia in children 18 and under, narcolepsy, or obstructive sleep apnea, the patient must have an appropriate diagnosis supported by documentation in the patient record of appropriate diagnostic testing.

Prior Therapy

- If the request is for a *short- or intermediate-acting* cerebral stimulant/agent used to treat ADHD, the patient must also have failed 30-day treatment trials with at least two prescribed and preferred short- or intermediate-acting cerebral stimulants/agents used for ADHD, either generic, OTC or brand, within the past 6 months.

- If the request is for a *long-acting* cerebral stimulant/agent used for ADHD, the patient must also have failed 30-day treatment trials with at least two prescribed and preferred long-acting cerebral stimulants/agents used for ADHD, either generic, OTC or brand within the past 6 months.

- If the request is for Strattera®, the patient must also have failed 30-day treatment trials with at least two prescribed and preferred cerebral stimulants (short-, intermediate- or long-acting), either generic, OTC or brand within the past 6 months. If prior usage requirements have not been met, approval may be given if there is a history of substance abuse or concern regarding substance abuse in the patient's household.

- If the request is for Kapvay®, the patient must also have failed a 30-day treatment trial with immediate-release clonidine within the past 6 months. If prior usage requirements have not been met, approval may be given if there is a history of substance abuse or concern regarding substance abuse in the patient's household.

- In lieu of prior usage requirements, approval may be given if there is a documented allergy or contraindication to all preferred agents in this class.

Stable Therapy

- Approval may be given to those who have documented stable therapy on the requested medication for 60 consecutive days or greater.

Medical Justification

- Medical justification may include peer-reviewed literature, medical record documentation, or other information specifically requested.

PA Approval Timeframes

- Approval may be given for up to 12 months.

Electronic Prior Authorization (PA)

- Cerebral Stimulant/Agent Used for ADHD agents are included in the electronic PA program.

Verbal PA Requests

- PA requests that meet prior usage requirement for approval may be accepted verbally.

Anxiolytics/Sedatives/Hypnotics

Appropriate Diagnosis

- The patient must have an appropriate diagnosis supported by documentation in the patient record.

Prior Treatment Trials

- The patient must also have failed 30-day treatment trials with at least two prescribed and preferred agents in this class, either generic, OTC or brand within the past 6 months, or have a documented allergy or contraindication to all preferred agents in this class.

- If the request is for Onfi® for a diagnosis of Lennox-Gastaut syndrome, the patient must also be ≥2 years of age, have a diagnosis by a pediatric neurologist and have failed 30-day treatment trials of valproic acid, lamotrigine, and topiramate within the past 6 months, or have a documented allergy or contraindication to all of those agents.

- If the request is for Onfi® for a diagnosis of intractable seizures, the patients must also have a diagnosis by a neurologist (diagnosis by a pediatric neurologist is required for patients <18 years of age) and have failed 30-day treatment trials with a minimum of four anti-convulsant medications within the past 6 months, or have a documented allergy or contraindication to other anti-convulsant medications.

Stable Therapy

- Approval may be given for children age 18 years and under who have documented stable therapy on the requested medication for 60 consecutive days or greater.

Medical Justification

- Medical justification may include peer-reviewed literature, medical record documentation, or other information specifically requested.

PA Approval Timeframes

- Approval may be given for up to 3 months for initial request and up to 6 months for renewal requests.

Electronic Prior Authorization (PA)

- Anxiolytic, sedative and hypnotic agents are included in the electronic PA program.

Verbal PA Requests

- PA requests that meet prior usage requirement for approval may be accepted verbally.

Genitourinary Smooth Muscle Relaxants

Appropriate Diagnosis

- The patient must have an appropriate diagnosis supported by documentation in the patient record.

Prior Treatment Trials

- The patient must also have failed 30-day treatment trials with at least two prescribed and preferred agents in this class, either generic, OTC or brand, within the past 6 months or have a documented allergy or contraindication to all preferred agents in this class.

Stable Therapy

- Approval may be given for children age 18 years and under who have documented stable therapy on the requested medication for 60 consecutive days or greater.

Medical Justification

- Medical justification may include peer-reviewed literature, medical record documentation, or other information specifically requested.

PA Approval Timeframes

- Approval may be given for up to 12 months.

Electronic Prior Authorization (PA)

- Genitourinary smooth muscle relaxants are included in the electronic PA program.

Verbal PA Requests

- PA requests that meet prior usage requirement for approval may be accepted verbally.

AGENDA

ALABAMA MEDICAID AGENCY
PHARMACY AND THERAPEUTICS (P&T) COMMITTEE

May 11, 2016
9:00 a.m. – 12:00 noon

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1. Opening remarks…….....…..Chair
2. Approval of February 10, 2016 P&T Committee Meeting minutes…….....…..…Chair
3. Pharmacy program update…….…..…..…….....…...Alabama Medicaid
4. Oral presentations by manufacturers/manufacturers' representatives
   (prior to each respective class review)
5. Pharmacotherapy class re-reviews…University of Massachusetts Medical School Clinical Pharmacy Services
   - **Alzheimer's Agents**
     - Parasympathomimetic (Cholinergic) Agents – AHFS Class 120400 (to include Aricept®, Aricept ODT®, Exelon®, Razadyne®, and Razadyne ER® only)
     - Central Nervous System Agents, Miscellaneous – AHFS Class 289200 (to include Namenda®, Namenda XR®, and Namzaric® only)
   - **Antidepressants** – AHFS 281604
   - **Cerebral Stimulants/Agents Used for ADHD**
     - Central Alpha-Agonists – AHFS 240816 (to include Kapvay® only)
     - Amphetamine Derivatives – AHFS 282004 (to include Adderall®, Adderall XR®, Desoxyn®, Dexedrine®, Evekeo®, ProCentra®, Vyvanse® and Zenzedi® only)
     - Respiratory and CNS Stimulants – AHFS 282032 (to include Aptensio XR®, Concerta®, Daytrana®, Focalin®, Focalin XR®, Metadate CD®, Metadate ER®, Methylin®, Quillivant XR®, Ritalin®, and Ritalin LA® only)
     - Central Nervous System Agents, Miscellaneous – AHFS 289200 (to include Intuniv® and Strattera® only)
   - **Wakefulness Promoting Agents** – AHFS 282080 (to include Nuvigil®, Provigil®, and Xyrem® only)
   - **Anxiolytics, Sedatives, and Hypnotics – Barbiturates** – AHFS 282404
   - **Anxiolytics, Sedatives, and Hypnotics – Benzodiazepines** – AHFS 282408
   - **Anxiolytics, Sedatives, and Hypnotics – Miscellaneous** – AHFS 282492
   - **Genitourinary Smooth Muscle Relaxants** – AHFS 861200 (including 861204 – Antimuscarinics and 861208 – Selective Beta-3-Adrenergic Agonists)
6. Pharmacotherapy class review…University of Massachusetts Medical School Clinical Pharmacy Services
   - **Disease-Modifying Antirheumatic Agents** – AHFS 923600
7. New drug review
   - **Kitabis®** (Aminoglycosides) – AHFS 081202
8. Pharmacotherapy Update
   - **Opiate Agonists** – AHFS 280808
9. Results of voting announced……...…….....…….Chair
10. Next meeting date
    - August 10, 2016
11. Adjourn

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Alzheimer's Agents
Parasympathomimetic (Cholinergic) Agents, AHFS Class 120400
Central Nervous System Agents, Miscellaneous, AHFS Class 289200
May 11, 2016

I. Overview

Alzheimer's disease is a progressive neurodegenerative disorder in older adults that affects cognition, behavior, and activities of daily living.[1,2] It is the most common form of dementia and the average life expectancy from the onset of symptoms to death is approximately eight to 10 years.[1-3] Diagnostic features include memory impairment and one or more of the following: aphasia, apraxia, agnosia, and/or disturbance in executive functioning.[1]

The pathophysiologic mechanisms are not entirely understood; however, the disease is characterized by the accumulation of intracellular neurofibrillary tangles and extracellular amyloid plaques in various regions of the brain. Inflammation and free radical processes lead to neuron dysfunction and death. It is thought that memory loss is partially the result of a deficiency of cholinergic neurotransmission.[2-3] Glutamate, an excitatory neurotransmitter, may also play a role in the pathophysiology of Alzheimer's disease. Glutamate activates N-methyl-D-aspartate (NMDA) receptors and is involved in learning and memory. However, excessive amounts of glutamate in the brain may lead to excitotoxicity and cell death.[3]

There are five agents approved for the treatment of Alzheimer's disease, including cholinesterase inhibitors (donepezil, galantamine, and rivastigmine), an NMDA receptor antagonist (memantine), and a combination product (memantine-donepezil).[4-12] Although none of the agents delay the progression of neurodegeneration, they do delay the progression of symptoms. The cholinesterase inhibitors enhance cholinergic function by increasing the concentration of acetylcholine through reversible inhibition of its hydrolysis by acetylcholinesterase. Memantine blocks NMDA receptors and inhibits their overstimulation by glutamate. The combination product containing memantine and donepezil (Namzaric®) was launched in May 2015 with the indication for the treatment of moderate to severe dementia of the Alzheimer's type in patients stabilized on memantine and donepezil.[12]

In February of 2014, Forest Laboratories notified the prescriber community that they plan to discontinue the sale of Namenda® tablets on August 15, 2014. They also noted that they will continue to sell the Namenda® oral solution and Namenda XR® extended release capsules.[13] In May 2015 the U.S. Court of Appeals upheld a ruling requiring the continued manufacturing of Namenda® tablets.[14]

The Alzheimer's agents that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. All products with the exception of memantine-donepezil are available in a generic formulation. This class was last reviewed in May 2014.

Table 1. Alzheimer's Agents Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Parasympathomimetic (Cholinergic Agents)			
Donepezil	orally disintegrating tablet, tablet	Aricept®*, Aricept ODT®*	donepezil, Aricept®*
Galantamine	extended-release capsule, solution, tablet	Razadyne®*, Razadyne ER®*	galantamine
Rivastigmine	capsule, transdermal patch	Exelon®*	rivastigmine
Central Nervous System Agents, Miscellaneous			
Memantine	extended-release capsule, solution, tablet	Namenda®*, Namenda XR®	memantine
Combination Products			
Memantine and donepezil	extended-release capsule	Namzaric®	none

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the Alzheimer's agents are summarized in Table 2.

Table 2. Treatment Guidelines Using the Alzheimer's Agents

Clinical Guideline	Recommendation(s)
European Federation of Neurological Societies: **Guidelines for the Diagnosis and Management of Alzheimer's Disease (2010)**[15]	• Patients and caregivers should be provided with education and support. • There is insufficient evidence to support the use of any drugs purely for the primary prevention of dementia. Cholinesterase inhibitors, vitamin E, gingko and estrogens should not be used as treatments for those with mild cognitive impairment. • In patients with Alzheimer's disease, treatment with cholinesterase inhibitors (donepezil, galantamine, or rivastigmine) should be considered at the time of diagnosis, taking into account expected therapeutic benefits and potential safety issues. Benefits on cognitive and non-cognitive symptoms have been demonstrated in those with mild, moderate and severe disease. Realistic expectations for treatment effects and potential side effects should be discussed with the patient and caregivers. • In patients with moderate to severe Alzheimer's disease, treatment with memantine should be considered taking into account expected therapeutic benefits and potential safety issues. Benefits on cognitive and noncognitive symptoms are apparent, some non-cognitive symptoms (agitation, delusions) may respond better than others. Realistic expectations for treatment effects and potential side effects should be discussed with the patient and caregivers. • Regular patient follow-up should be an integral part of management. • Aspirin should not be used as a treatment for Alzheimer's disease, though it can be used in those with Alzheimer's disease who also have other indications for its use (e.g. to prevent cardiovascular events). • Vitamin E should not be used as a treatment for Alzheimer's disease. • Currently, there is insufficient evidence to support the use of other agents including, anti-inflammatory drugs, nootropics (including piracetam, nicergoline), selegiline, oestrogens, pentoxyphylin, or statins in the treatment or prevention of Alzheimer's disease. • Cognitive stimulation or rehabilitation may be considered in patients with mild to moderate Alzheimer's disease. • Management of behavioral and psychological symptoms of dementia should begin with a careful search for triggers and causative factors (i.e. physical illness). Where possible, initial treatment should be non-pharmacological. • Antipsychotics should only be used for moderate or severe behavioral and psychological symptoms of dementia causing significant distress which have either not responded to other treatments (like non-pharmacological measures or cholinesterase inhibitors) or when other treatments are not appropriate. Low dose of atypical agents should be used only after assessment of risk benefit and full discussion with patient (when capacity allows) and caregiver. • Atypical agents have fewer side effects and do not confer a greater risk of stroke or mortality than conventional drugs. • Selective serotonin reuptake inhibitors rather than tricyclic antidepressants should be used to treat depression in Alzheimer's disease.
American College of Physicians/American Academy of Family Physicians: **Current Pharmacologic**	• The decision to initiate therapy should be based on evaluation of benefits and risks associated with an individual patient. All of the drugs have known adverse events, and the decision to manage patients with dementia should balance harms against modest or even no benefit. • Although the evidence shows statistically significant benefits of treatment with some cholinesterase inhibitors and memantine for all kinds of dementia, these

Clinical Guideline	Recommendation(s)
Treatment of Dementia: A Clinical Practice Guideline (2008)[16] **Reaffirmed April 2013 by American Academy of Family Physicians**	benefits, on average, are not clinically significant for cognition and are modest for global assessments. Currently, there is no way to predict which patients might have a clinically important response. The evidence does not support prescribing these medications for every patient with dementia. • Evidence is insufficient to determine the optimal duration of therapy. No evidence demonstrates when it is appropriate to stop the treatment if the patient becomes unresponsive or shows decline in various domains of dementia. If slowing decline is no longer a goal, treatment with memantine or a cholinesterase inhibitor is no longer appropriate. • The evidence is insufficient to compare the effectiveness of different pharmacologic agents for the treatment of dementia. Because few trials compare one drug with another, evidence about effectiveness is insufficient to support the choice of specific drugs for the treatment of dementia. Assessment of the effectiveness of combination therapy is lacking. • Clinicians should base the choice of pharmacologic agents on tolerability, adverse effect profile and ease of use.
American Psychiatric Association: **Practice Guideline for the Treatment of Patients with Alzheimer's Disease and other Dementias (2007)**[17]	• The primary goal of medication treatment for cognitive symptoms in dementia is to delay the progression of symptoms, with the hope that this delay will translate into a preservation of functional ability, maintaining the patient for as long as possible at a particular level of symptom severity. However, no medication treatment has been shown to delay the progression of neurodegeneration. • Given the evidence from randomized controlled trials for modest improvement in some patients treated with cholinesterase inhibitors and the lack of established alternatives, it is appropriate to offer a trial of one of these agents for patients with mild or moderate Alzheimer's disease for whom the medication is not contraindicated. • Results of the numerous large placebo-controlled trials of individual cholinesterase inhibitors have suggested similar degrees of efficacy, although tolerability may differ among the medications. Currently available data do not allow a fair, unbiased direct comparison among the cholinesterase inhibitors. There is also no data on whether or how to switch from one cholinesterase inhibitor to another. • Reversible, direct medication-induced hepatotoxicity with hepatocellular injury is a unique property of tacrine. Because of this hepatotoxicity, tacrine is very uncommonly used. Hepatotoxicity has not been associated with donepezil, rivastigmine, or galantamine. • Donepezil, rivastigmine and galantamine are preferred over tacrine because of reversible hepatic toxicity and the requirement that it be given four times per day. • It is uncertain how long patients should be treated with cholinesterase inhibitors. The decision whether to continue treatment with cholinesterase inhibitors is highly individualized. Reasons that patients choose to stop taking these medications include side effects, adverse events, lack of motivation and lack of perceived efficacy. • Memantine should be considered for the treatment of patients with moderate to severe Alzheimer's disease. Memantine can be prescribed for people either currently taking or not taking a cholinesterase inhibitor. There is modest evidence that the combination of memantine and donepezil is better than donepezil alone, but there is no evidence that this combination is better than memantine alone. • Vitamin E (α-tocopherol) is no longer recommended for the treatment of cognitive symptoms of dementia because of limited evidence for its efficacy as well as safety concerns. • Nonsteroidal anti-inflammatory agents, statin medications, and estrogen supplementation (with conjugated equine estrogens) have shown a lack of efficacy and safety in placebo-controlled trials in patients with Alzheimer's

Clinical Guideline	Recommendation(s)
	disease and therefore are not recommended. • Cholinesterase inhibitors should be considered for patients with mild to moderate dementia associated with Parkinson's disease. Only rivastigmine has been approved by the Food and Drug Administration for this indication, but there is no reason to believe the benefit is specific to this cholinesterase inhibitor. Dosing and titration are similar to those for patients with Alzheimer's disease.
American Academy of Neurology: **Practice Parameter: Management of Dementia (An Evidence-Based Review) (2001; reaffirmed 2003)**[18]	<u>Pharmacologic treatment of Alzheimer's disease</u> • Cholinesterase inhibitors should be considered in patients with mild-to-moderate Alzheimer's disease, although studies suggest a small average degree of benefit. • Vitamin E (1,000 IU by mouth twice a day) should be considered in an attempt to slow progression of Alzheimer's disease. • There is insufficient evidence to support the use of other antioxidants, anti-inflammatory or other putative disease-modifying agents specifically to treat Alzheimer's disease because of the risk of significant side effects in the absence of demonstrated benefits. • Estrogen should not be prescribed to treat Alzheimer's disease. • Some patients with unspecified dementias may benefit from ginkgo biloba, but evidence-based efficacy data are lacking. <u>Pharmacologic treatment for noncognitive symptoms of dementia</u> • Antipsychotics should be used to treat agitation or psychosis in patients with dementia where environmental manipulation fails. Atypical agents may be better tolerated compared to traditional antipsychotics. • Selected antidepressants (e.g., selective serotonin-reuptake inhibitors and tricyclics) should be considered in the treatment of depression in individuals with dementia with side effect profiles guiding the choice of agent. <u>Educational Interventions for patients with dementia and/or caregivers</u> • Short-term programs directed toward educating family caregivers about Alzheimer's disease should be offered to improve caregiver satisfaction. • Intensive long-term education and support services should be offered to caregivers of patients with Alzheimer's disease to delay time to nursing home placement. • Staff of long-term care facilities should receive education about Alzheimer's disease to reduce the use of unnecessary antipsychotics. • As part of this practice guideline, additional interventions other than education for patients and caregivers are available for functional behaviors, problem behaviors, and care environment alterations.
American Academy of Neurology: **Practice Parameter: Evaluation and Treatment of Depression, Psychosis, and Dementia in Parkinson Disease (2006)**[19]	• For patients with Parkinson's disease dementia or dementia with Lewy bodies, rivastigmine is probably effective in improving cognitive function. However, the magnitude of the benefit is modest and tremor may be exacerbated. • For patients with Parkinson's disease dementia, donepezil is probably effective in improving cognitive function. However, the magnitude of the benefits is modest. Donepezil should be considered for the treatment of dementia in Parkinson's disease.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the Alzheimer's agents are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo

clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Single Entity Alzheimer's Agents[6-11]

Indication	Parasympathomimetic (Cholinergic Agents)			Central Nervous System Agents, Miscellaneous
	Donepezil	Galantamine	Rivastigmine	Memantine
Dementia of the Alzheimer's type*	✔			
Mild-to-moderate dementia of the Alzheimer's type		✔	✔ †	
Mild, moderate, and severe dementia of the Alzheimer's type			✔ ‡	
Moderate-to-severe dementia of the Alzheimer's type				✔
Mild-to-moderate dementia associated with Parkinson's disease			✔	

*Efficacy has been demonstrated in patients with mild, moderate, and severe Alzheimer's disease.
†Capsule and solution.
‡Transdermal patch.

Table 4. FDA-Approved Indications for the Combination Product Alzheimer's Agents[12]

Indication	Memantine and Donepezil
Moderate-to-severe dementia of the Alzheimer's type	✔ *

*In patients stabilized on memantine hydrochloride (10 mg twice daily or 28 mg extended-release once daily) and donepezil hydrochloride 10 mg; or memantine hydrochloride (5 mg twice daily or 14 mg extended-release once daily) and donepezil hydrochloride 10 mg (in patients with severe renal impairment).

IV. Pharmacokinetics

The pharmacokinetic parameters of the Alzheimer's agents are listed in Table 5. Pharmacokinetic properties of the combination products are in line with the properties of their individuals components listed below.

Table 5. Pharmacokinetic Parameters of the Alzheimer's Agents[5]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Parasympathomimetic (Cholinergic Agents)					
Donepezil	100	96	Liver (% not reported)	Renal (57) Feces (9 to 15)	70
Galantamine	Tablet: 90 to 100 Solution: 83 to 90	18	Liver (75)	Renal (95) Feces (5)	7
Rivastigmine	Oral: 36 to 72	40	Liver, extensive Brain, extensive	Renal (>90)	Oral: 1.4 to 1.7 Transdermal: 3.0
Central Nervous System Agents, Miscellaneous					
Memantine	Well absorbed	45	Liver, partial	Renal (48)	60 to 80

V. Drug Interactions

Major drug interactions with the Alzheimer's agents are listed in Table 6.

Table 6. Major Drug Interactions with the Alzheimer's Agents[5]

Generic Name(s)	Interaction	Mechanism

Generic Name(s)	Interaction	Mechanism
Parasympathomimetic (Cholinergic Agents)		
Donepezil	Azole antifungals	Concomitant use of donepezil, a CYP3A4 substrate that is associated with prolongation of the QT interval, is contraindicated with certain drugs that prolong QT interval and strongly inhibit CYP3A4.
Donepezil	Anticholinergic agents	Concomitant use of a cholinesterase inhibitor, such as donepezil, and an anticholinergic agent may result in interference with the efficacy of both agents
Donepezil	QT interval prolonging agents	Concurrent use of donepezil and QT interval prolonging agents may result in increased risk of QT-interval prolongation and torsade de pointes.
Donepezil	CYP3A4 inhibitors and inducers	Concurrent use of donepezil and CYP3A4 inhibitors/inducers may results in increased/decreased donepezil exposure.
Donepezil	Select CYP2D6 inhibitors (clobazam, terbinafine, cinacalcet, peginterferon alfa-2b)	Concurrent use of donepezil and selected CYP2D6 inhibitors may result in increased donepezil exposure.
Donepezil	Seizure threshold lowering agents	Concurrent use of donepezil and seizure threshold lowering agents may result in reduced seizure threshold.
Galantamine	QT interval prolonging agents	Concurrent use of galantamine and QT interval prolonging agents may result in increased risk of QT-interval prolongation and torsade de pointes.
Rivastigmine	Metoclopramide	The concomitant use of metoclopramide and rivastigmine is contraindicated due to potential additive effects of extrapyramidal reactions.
Rivastigmine	Beta blockers	Concomitant use of rivastigmine and beta-blockers, especially cardioselective agents, is not recommended due to additive bradycardic effects resulting in syncope.
Central Nervous System Agents, Miscellaneous		
Memantine	Dextromethorphan, Amantadine, Ketamine	Concurrent use of memantine and selected N-methyl-D-aspartate antagonists may result in increased adverse events of N-methyl-D-aspartate antagonists.
Memantine	Carbonic anhydrase inhibitors	Concurrent use of memantine and carbonic anhydrase inhibitors may result in reduced clearance of memantine due to urinary alkalinization.

VI. Adverse Drug Events

The most common adverse drug events reported with the Alzheimer's agents are listed in Table 7. Adverse drug reactions associated with the combination products are in line with the individuals components listed below.[4]

Table 7. Adverse Drug Events (%) Reported with the Single Entity Alzheimer's Agents[4,6-12]

Adverse Events	Parasympathomimetic (Cholinergic Agents)			Central Nervous System Agents, Miscellaneous
	Donepezil	Galantamine	Rivastigmine	Memantine
Cardiovascular				
Angina pectoris	-	-	≥1	-

Adverse Events	Parasympathomimetic (Cholinergic Agents)			Central Nervous System Agents, Miscellaneous
	Donepezil	**Galantamine**	**Rivastigmine**	**Memantine**
Atrial fibrillation	≥1	-	≥1	-
Bradycardia	≥1	2	≥1	-
Chest pain	1 to 2	≥1	-	-
Heart failure	-	-	≥1	≥1
Hemorrhage	2	-	-	-
Hypertension	1 to 3	-	3	4
Hypotension	≥1	-	≥1	-
Myocardial infarction	-	-	≥1	-
Palpitation	-	-	≥1	-
Peripheral edema	≥1	-	-	≥2
Postural hypotension	-	-	≥1	-
Syncope	2	2	3	≥1
Vasodilation	≥1	-	-	-
Central Nervous System				
Abnormal crying	≥1	-	-	-
Abnormal dreams	3	-	-	-
Aggression	≥1	-	3	≥1
Agitation	-	-	≥1	≥2
Anxiety	-	-	4 to 5; 3*	≥2
Aphasia	≥1	-	-	-
Bradykinesia	-	-	≥1	-
Cerebrovascular accident	-	-	-	≥1
Confusion	2	-	1 to 8	6
Convulsion	≥1	-	≥1	-
Delusions	≥1	-	-	-
Depression	2 to 3	7	1 to 6; 4*	≥2
Dizziness	2 to 8	9	6 to 21; 2 to 7*	7
Dyskinesia	-	-	≥1	-
Emotional lability	2	-	-	-
Fatigue	5	5	4 to 9; 2*	2
Gait abnormality	-	-	≥1	≥2
Hallucination	3	-	4	3
Headache	4 to 10	8	4 to 17; 3 to 4*	6
Hostility	3	-	-	-
Hypokinesia	-	-	-	≥1
Insomnia	5 to 9	5	3 to 9; 1 to 4*	≥2
Irritability	≥1	-	-	-
Malaise	-	≥1	5	-
Nervousness	1 to 3	-	-	-
Paranoid reaction	-	-	≥1	-
Paresthesia	≥1	-	≥1	-
Parkinson's disease worsening	-	-	3	-
Parkinsonism	-	-	2	-
Personality disorder	2	-	-	-
Restlessness	≥1	-	≥1	-
Somnolence	2	4	4 to 5	3
Transient ischemic attack	-	-	≥1	≥1
Tremor	≥1	3	4 to 10; ≥1*	-
Vertigo	≥1	-	≥1; 0 to 2*	≥1
Wandering	≥1	-	-	-

Adverse Events	Parasympathomimetic (Cholinergic Agents)			Central Nervous System Agents, Miscellaneous
	Donepezil	Galantamine	Rivastigmine	Memantine
Dermatological				
Diaphoresis	≥1	-	4	-
Eczema	3	-	-	-
Pruritus	≥1	-	≥1*	-
Rash	≥1	-	≥1	≥1
Skin ulcer	≥1	-	-	-
Urticaria	≥1	-	-	-
Gastrointestinal				
Abdominal pain	≥1	5	4 to 13; 2 to 4*	-
Anorexia	4 to 8	7 to 9	6 to 17; 3 to 9*	≥2
Bloating	≥1	-	-	-
Constipation	≥1	-	5; ≥1*	5
Diarrhea	10	6 to 12	7 to 19; 6 to 10*	≥2
Dyspepsia	≥1	5	1 to 9	-
Epigastric pain	≥1	-	-	-
Eructation	-	-	2	-
Fecal incontinence	≥1	-	≥1	-
Flatulence	-	≥1	4	-
Gastritis	-	-	≥1; ≥1*	-
Gastrointestinal bleeding	≥1	-	-	-
Nausea	6 to 11	13 to 24	29 to 47; 7 to 21*	≥2
Toothache	≥1	-	-	-
Vomiting	5 to 8	6 to 13	17 to 31; 6 to 19*	3
Weight decrease	1 to 3	5 to 7	3; 3 to 8*	≥1
Genitourinary				
Cystitis	≥1	-	-	-
Frequent urination	2	-	-	≥1
Glycosuria	≥1	-	-	-
Hematuria	≥1	3	≥1	-
Libido increased	≥1	-	-	-
Urinary incontinence	2	≥1	≥1*	≥2
Urinary tract infection	≥1	8	7; 2*	≥2
Laboratory Test Abnormalities				
Alkaline phosphatase increased	≥1	-	-	≥1
Creatinine increased	3	-	-	-
Hyperlipemia	2	-	-	-
Hypokalemia	-	-	≥1	-
Lactate dehydrogenase increased	≥1	-	-	-
Musculoskeletal				
Arthralgia	-	-	-	≥2
Arthritis	1 to 2	-	≥1	-
Asthenia	≥1	≥1	2 to 6; 2 to 3*	-
Ataxia	≥1	-	≥1	≥1
Back pain	3	-	≥1	3
Bone fracture	≥1	-	-	-
Leg cramps	-	-	≥1	-
Muscle cramps	6	-	-	-

Adverse Events	Parasympathomimetic (Cholinergic Agents)			Central Nervous System Agents, Miscellaneous
	Donepezil	Galantamine	Rivastigmine	Memantine
Myalgia	-	-	≥1	-
Rigors	-	-	≥1	-
Respiratory				
Bronchitis	≥1	-	-	≥2
Cough increased	≥1	-	-	4
Dyspnea	≥1	-	≥1	2
Pharyngitis	≥1	-	-	-
Pneumonia	≥1	-	≥1*	≥1
Respiratory tract infection	-	-	-	≥2
Rhinitis	-	4	4	-
Sore Throat	≥1	-	-	-
Special Senses				
Blurred vision	≥1	-	-	-
Cataract	≥1	-	≥1	≥1
Conjunctivitis	-	-	-	≥1
Eye irritation	≥1	-	-	-
Tinnitus	-	-	≥1	-
Other				
Accident	7 to 13	-	-	-
Accidental trauma	-	-	1 to 10	-
Allergy	-	-	≥1	-
Anemia	-	3	≥1; ≥1*	≥1
Dehydration	1 to 2	-	1 to 2; ≥1*	-
Ecchymosis	4 to 5	-	-	-
Edema	≥1	-	≥1	-
Epistaxis	-	-	≥1	-
Fall	-	-	≥1*	≥2
Fever	2	≥1	≥1	-
Flu syndrome	≥1	-	3	≥2
Hot flashes	≥1	-	≥1	-
Infection	1 to 11	-	-	-
Inflicted injury	-	-	-	≥2
Influenza	≥1	-	-	-
Pain	3 to 9	-	-	3

✔ Percent not specified.
- Event not reported or incidence <1%.
*Transdermal patch.

VII. Dosing and Administration

The usual dosing regimens for the Alzheimer's agents are listed in Table 8.

Table 8. Usual Dosing Regimens for the Alzheimer's Agents[6-12]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Parasympathomimetic (Cholinergic Agents)			
Donepezil	Dementia of the Alzheimer's type (mild to moderate): Tablet and orally disintegrating tablet: initial, 5 mg daily; may increase to 10 mg daily after four to six weeks; maintenance, 5 to 10 mg daily	Safety and efficacy not established in the pediatric population.	Orally disintegrating tablet: 5 mg 10 mg Tablet: 5 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Dementia of the Alzheimer's type (moderate to severe): Tablet: initial, 5 mg daily; may increase to 10 mg daily after four to six weeks; may increase to 23 mg daily after three months on 10 mg daily dose Orally disintegrating tablet: initial, 5 mg daily; may increase to 10 mg daily after four to six weeks		10 mg 23 mg
Galantamine	Mild-to-moderate dementia of the Alzheimer's type: Extended-release capsule: initial, 8 mg daily; maintenance, 16 to 24 mg daily Tablet and oral solution: initial, 4 mg twice a day with the morning and evening meals; maintenance: 8 to 12 mg twice a daily	Safety and efficacy not established in the pediatric population.	Extended release capsule: 8 mg 16 mg 24 mg Solution: 4 mg/mL Tablet: 4 mg 8 mg 12 mg
Rivastigmine	Mild-to-moderate dementia of the Alzheimer's type: Capsule: initial, 1.5 mg twice daily with the morning and evening meals; maintenance, 3 to 6 mg twice daily Transdermal patch: initial, 4.6 mg/24 hours; maintenance, 9.5 or 13.36 mg/24 hours Severe dementia of the Alzheimer's type: Transdermal patch: initial, 4.6 mg/24 hours; maintenance, 13.36 mg/24 hours Mild-to-moderate dementia associated with Parkinson's disease: Capsule: initial, 1.5 mg twice daily with the morning and evening meals; maintenance, 3 to 6 mg twice daily Transdermal patch: initial, 4.6 mg/24 hours; maintenance, 9.5 or 13.36 mg/24 hours	Safety and efficacy not established in the pediatric population.	Capsule: 1.5 mg 3 mg 4.5 mg 6 mg Transdermal patch: 4.6 mg/24 hours 9.5 mg/24 hours 13.3 mg/24 hours
Central Nervous System Agents, Miscellaneous			
Memantine	Moderate-to-severe dementia of the Alzheimer's type:	Safety and efficacy not established in the pediatric	Extended release capsule:

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Solution and tablet: initial, 5 mg once daily, increase dose by 5 mg at weekly intervals (twice daily dosing); maintenance, 10 mg twice daily Extended release capsule: initial, 7 mg once daily; maintenance, 28 mg once daily	population.	7 mg 14 mg 21 mg 28 mg Extended release capsule dose pack: 7 mg (7 count)-14 mg (7 count)-21 mg (7 count)-28 mg (7 count) Solution: 10 mg/5 mL Tablet: 5 mg 10 mg Tablet dose pack: 5 mg (28 count)-10 mg (21 count)
Combination products			
Memantine and donepezil	Moderate-to-severe dementia of the Alzheimer's type: Extended release capsule: patients stabilized on memantine hydrochloride (10 mg twice daily or 28 mg extended-release once daily) and donepezil hydrochloride 10 mg can be switched to 28 mg-10 mg combination capsule, taken once a day in the evening	Safety and efficacy not established in the pediatric population.	Extended release capsule: 14-10 mg 28-10 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the Alzheimer's agents are summarized in Table 9.

Table 9. Comparative Clinical Trials with the Alzheimer's Agents

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Alzheimer's Disease				
Geldmacher et al.[20] (2003) Donepezil 5 mg/day	OS Patients with Alzheimer's disease	N=1,115 Variable duration	Primary: Time to nursing home placement Secondary: Not reported	Primary: Use of donepezil of 5 mg/day or more was associated with significant delays in nursing home placement. A cumulative dose-response relationship was observed between longer-term sustained donepezil use and delay of nursing home placement. When donepezil was taken at effective doses for at least nine to 12 months, conservative estimates of the time gained before nursing home placement were 21.4 months for first-dementia-related nursing home placement and 17.5 months for permanent nursing home placement. Secondary: Not reported
Burns et al.[21] (2007) Donepezil 5 to 10 mg/day	MC, OL Patients ≥50 years of age with mild-to-moderate Alzheimer's disease	N=579 132 weeks	Primary: ADAS-cog, CDR-SB, IDDD, QoLS, and adverse events Secondary: Not reported	Primary: Mean changes in ADAS-cog scores of all patients were improved by approximately two points after six weeks (cumulative week 36) and one point after 12 weeks (cumulative week 42), with improvement compared to the start of OL treatment. At week 24 (cumulative week 54), mean ADAS-cog scores still showed improvement (approximately 0.5 points) compared to those scores reported at the start of OL treatment. From 24 weeks, ADAS-cog scores declined over the remainder of the study. At the end of 132 weeks of OL treatment (162 weeks total follow-up), the change from DB baseline was 15.6 points for all patients. No difference was seen between patients who had previously received placebo in the DB phase vs those receiving donepezil for the entire treatment period. CDR-SB scores improved slightly over the first 12 weeks (up to cumulative week 42) of OL treatment and then slowly declined for the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				remainder of the study period (up to cumulative week 162). Mean IDDD total scores were maintained over the first 24 weeks of OL treatment to within approximately 1 point relative to those at the beginning of this study period. Mean IDDD scores were 138.1 at week 0, 136.9 at week 12, 138.9 at week 24 and 170.8 at week 132 (162 weeks of total follow-up). At the start of the OL extension, QoLS scores were improved compared to baseline, with a mean change of 3.03. The scores remained above the baseline level at weeks six and 12 of OL treatment. At the end of 132 weeks of OL treatment, the decline from the baseline for the DB study was -46.2. Overall, 85% of patients experienced at least one treatment-emergent adverse event. The most common adverse events included diarrhea (12%), nausea (11%), infection (11%) and accidental injury (10%). Nonfatal all-causality and treatment-related serious adverse events were reported for 25 and 7% of patients, respectively. Seventeen patients died during the study or within four weeks after discontinuation of donepezil. The most common causes of death were pneumonia (seven patients) and cerebrovascular accident (two patients). Fifteen deaths were considered unrelated to donepezil. Two deaths, one due to a cerebral hemorrhage diagnosed on day five of treatment and another due to a suspected myocardial infarction on day 55, were considered by the investigators to be possibly related to donepezil. Secondary: Not reported
Hashimoto et al.[22] (2009) Donepezil 5 mg/day	OS, PRO Patients with Alzheimer's disease	N=416 12 weeks	Primary: MMSE Secondary: Not reported	Primary: There were significant changes in mean scores on the MMSE (0.9; P<0.01) from baseline to week 12. There was a significant decrease in the personal strain score at week 12 (P=0.002). There was no significant improvement was in role strain.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There was no significant decrease in the time spent supervising Alzheimer's disease patients. Secondary: Not reported
Homma et al.[23] (2009) Donepezil 10 mg/day	OL Japanese patients ≥50 years of age with severe Alzheimer's disease (modified Hachinski Ischemic Score ≤6, FAST ≥6, MMSE score of 1 to 12	N=189 52 weeks	Primary: SIB, and BEHAVE-AD Secondary: Not reported	Primary: The mean change in SIB scores during the OL study showed improvement until week 24, followed by a decline by week 36. For those patients receiving 52 weeks of treatment, the mean change in SIB from baseline (enrollment in OL study) was –6.1. The mean change in SIB declined more rapidly after 24 weeks. For the BEHAVE-AD, little change was observed during the OL study. The change from baseline to week 24 and week 52 was 0.7 and 0.5, respectively. The level of behavioral symptoms in the study population was low. Overall, 177 patients (93.7%) experienced at least one adverse event. Severe adverse events were reported by 15 patients (7.9%) and serious adverse events were reported by 33 patients (17.5%). The most common adverse events were nasopharyngitis, diarrhea, nausea and vomiting. Secondary: Not reported
Courtney et al.[24] (2004) Donepezil 5 to 10 mg/day vs placebo	DB, RCT Patients with Alzheimer's disease	N=565 156 weeks	Primary: MMSE, BADLS, time to entering institution Secondary: Not reported	Primary: Cognition averaged 0.8 MMSE points better (95% CI, 0.5 to 1.2; P<0.0001) and functionality 1.0 BADLS points better (95% CI, 0.5 to 1.6; P<0.0001) with donepezil over the first two years. No significant benefits were seen with donepezil compared to placebo in institutionalization (42 vs 44% at three years; P=0.4) or progression of disability (58 vs 59% at three years; P=0.4). The RR of entering institutional care in the donepezil group compared to placebo was 0.97 (95% CI, 0.72 to 1.30; P=0.8); the RR of progression of disability or entering institutional care was 0.96 (95% CI, 0.74 to 1.24; P=0.7).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Similarly, no significant differences were seen between donepezil and placebo in behavioral and psychological symptoms, caregiver psychopathology, adverse events or deaths, or between 5 and 10 mg donepezil. Secondary: Not reported
Sabbagh et al.[25] (2013) Donepezil 23 or 10 mg/day	Post hoc of a 24-week, DB, RCT Patients with moderate to severe Alzheimer's disease (baseline MMSE 0 to 20)	N= Duration not specified	Primary: Cognitive changes in subgroups of patients based on selected baseline and demographic characteristics Secondary: Not reported	Primary: Donepezil 23 mg/day provided statistically significant incremental cognitive benefits over donepezil 10 mg/day irrespective of baseline functional severity, measured by scores on the ADCS-ADL -severe version (P<0.05). When patients were categorized by baseline cognitive severity (MMSE score), significant benefits of donepezil 23 mg/day over 10 mg/day were seen in both subgroups when based on MMSE scores of 0 to 9 vs 10 to 20 (P<0.02 and P<0.01, respectively), and in the more severe subgroup when based on MMSE scores of 0 to 16 vs 17 to 20 (P<0.0001 and P>0.05). Statistically significant incremental cognitive benefits of donepezil 23 mg/day over 10 mg/day were also observed regardless of age, gender, weight, or pre-study donepezil 10mg/day treatment duration (P<0.05). In the multivariate analysis, the only significant interaction was between treatment and baseline MMSE score. Secondary: Not reported
Tariot et al.[26] (2012) Donepezil 23 mg/day	OL Patients with Alzheimer's disease	N=915 12 months	Primary: Safety analyses comprised examination of the incidence, severity, and timing of treatment-emergent adverse events;	Primary: In total, 674 patients (74.7%) reported at least one adverse event; in 320 of these patients (47.5%) at least one adverse event was considered to be possibly or probably study drug related. The majority of patients reporting adverse events (81.9%) had adverse events of mild or moderate severity. There were 268 patients (29.7%) who discontinued early, of which 123 (13.6%) were due to adverse events.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			changes in weight, electrocardiogram, vital signs, and laboratory parameters; and discontinuation due to adverse events all at months three, six, nine, and 12 Secondary: Not reported	Patients who had increased donepezil dose from 10 mg/day to 23 mg/day had slightly higher rates of adverse events than patients who were already receiving 23 mg (78.0 and 16.9 vs 72.8 and 14.0%, respectively). The incidence of new adverse events declined rapidly after the first two weeks and remained low throughout the duration of the study. Secondary: Not reported
Winblad et al.[27] (2006) <u>RCT</u> Donepezil 10 mg/day vs placebo <u>OL</u> Donepezil 5 mg daily for 28 days, then 10 mg/day per clinician's judgment	DB, OL, PC Patients 40 to 90 years of age with a probable or possible diagnosis of Alzheimer's disease	N=286 52-week RCT with a 2-year OL extension phase	Primary: GBS Secondary: MMSE, GDS, PDS, NPI	Primary: The GBS total scores indicate that both the continuous-treatment group and delayed-start groups had declined, with the difference between the two groups favoring the continuous-donepezil group, over the three-year period (P=0.056). Secondary: The MMSE declined significantly less in the continuous-treatment group than in the delayed-start group over the course of the study (P=0.004, P=0.057, respectively). GDS declined significantly less over the three-year study period in patients in the continuous-treatment group than in those in the delayed-start group (P=0.0231). There was a trend favoring continuous-donepezil treatment over delayed-start treatment on the PDS, although it was not statistically significant (P=0.091). NPI results showed no significant treatment differences between the groups.
Rogers et al.[28] (1998)	DB, MC, PC, RCT Patients with mild-	N=473 24 weeks	Primary: ADAS-Cog, CIBIC	Primary: Out of 473 patients, 80% of placebo patients, 85% of 5 mg patients and 68% of 10 mg patients completed the study. Those that discontinued due

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Donepezil 5 mg/day vs donepezil 10 mg/day vs placebo	to-moderate Alzheimer's disease		Secondary: Not reported	to adverse effects were 7, 6, and 16% in the placebo, 5 and 10 mg groups, respectively. Primary outcome measure was mean change in scores from baseline to endpoint in the ADAS-Cog. Both donepezil doses were statistically better than placebo (P<0.0001). Global functioning as measured by the CIBIC plus were statistically better for both donepezil groups compared to placebo at endpoint (P<0.005). Donepezil 5 and 10 mg treatment showed no statistical difference in improvements. Secondary: Not reported
Winblad et al.[29] (2006) Donepezil 10 mg/day vs placebo	DB, PC, PG Patients ≥50 years of age with severe Alzheimer's disease (MMSE score of 1 to 10 and a FAST rating of stage 5 to 7c)	N=248 6 months	Primary: SIB Secondary: MMSE, NPI, and CGI-I	Primary: At six months, patients assigned donepezil had significantly better mean change from baseline scores than those taking placebo for SIB (P<0.05). Secondary: CGI-I scores and the mean change from screening scores on the MMSE at six- month follow-up favored donepezil treatment over placebo (all P<0.05). There was no significant difference between treatment groups on the NPI for the modified intention-to-treat population (P=0.43).
Black et al.[30] (2007) Donepezil 10 mg/day vs placebo	DB, MC, PC, RCT Patients ≥50 years of age with severe Alzheimer's disease (MMSE score of 1 to 12, modified Hachinski Ischemic score ≤6, and FAST score ≥6)	N=343 24 weeks	Primary: SIB and CIBIC-Plus Secondary: ADCS-ADL-sev, NPI, MMSE, CBQ, RUSP	Primary: Donepezil was more efficacious when compared to placebo on SIB score change from baseline to endpoint, as well as on CIBIC-Plus score (P<0.05 for all results). Secondary: On the ADCS-ADL-sev, both the donepezil group and the placebo group declined from baseline, and the treatment difference was NS (P=0.3574). On the NPI, donepezil was not significantly different from placebo (P=0.4612).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The donepezil group showed significant improvement from screening to endpoint on the MMSE compared to placebo (P=0.0267). The CBQ stress measure showed no significant change from baseline for either group. The RUSP scores also had low average responses with little movement from baseline and no significant differences.
Homma et al.[31] (2008) Donepezil 5 to 10 mg/day vs placebo	DB, MC, PC, RCT Japanese patients ≥50 years of age with severe Alzheimer's disease (modified Hachinski Ischemic Score ≤6, FAST ≥6, MMSE score of 1 to 12 and diagnosis confirmed by neuroimaging)	N=302 24 weeks	Primary: SIB and CIBIC-Plus Secondary: ADCS-ADL-sev and BEHAVE-AD	Primary: Donepezil 5 and 10 mg/day were more effective than placebo on the SIB. At week 24, patients in the donepezil 5 mg/day group had a significant change from baseline of 2.5 points and those in the donepezil 10 mg/day group had a significant change from baseline of 4.7 points. Patients in the placebo group showed significant worsening (–4.2 points) during the course of the study (P<0.001 vs placebo). For the CIBIC-Plus, the analysis was performed on the seven categories of change as well as the three collapsed categories of improved, no change and worsened. In the seven-category analysis, the distribution of CIBIC-Plus scores in the donepezil 10 mg/day group was better than placebo (P=0.003); however, there was no difference with 5 mg/day (P=0.151). In the collapsed-category analysis, the distribution of CIBIC-Plus scores in the donepezil 10 mg/day group was better than placebo (P=0.001); however, there was no difference with 5 mg/day (P=0.129). Secondary: For the ADCS-ADL-sev, there was no significant differences between donepezil and placebo (placebo group, –1.1 points; donepezil 5 mg/day group, –0.1 points; donepezil 10 mg/day group, –0.3 points). For the BEHAVE-AD, there was no significant differences between donepezil and placebo (placebo group, –0.5; donepezil 5 mg/day group, –0.5; donepezil 10 mg/ day group, –0.1). Treatment-emergent adverse events were reported by 73.3% of placebo patients, 78.2% of donepezil 5 mg/day patients and 83.3% of donepezil 10

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				mg/day patients. There was no significant difference in adverse events between the donepezil groups and the placebo group. The most common adverse events reported are consistent with the known cholinergic side effects of donepezil. Serious adverse events were reported by 15 placebo patients (14.3%), 12 donepezil 5 mg/day patients (11.9%) and 10 donepezil 10 mg/day patients (10.4%). Five patients died during the treatment period. The causes of death were acute pneumonia (placebo group), acute myocardial infarction (donepezil 5 mg/day group), suspected stomach cancer (donepezil 5 mg/day group; the patient died 80 days after discontinuation), vomit-induced tracheal occlusion (donepezil 10 mg/day group; the patient died seven days after completion) and arrhythmia (donepezil 10 mg/day group).
Birks et al.[32] (2006) Donepezil 5 to 10 mg/day vs placebo	MA Patients with Alzheimer's disease	N=5,796 (24 trials) 12 to 60 weeks	Primary: ADAS-Cog, MMSE, CIBIC-Plus, ADL, withdrawals and adverse events Secondary: Not reported	Primary: A significant difference was seen on the ADAS-Cog scale for patients treated with donepezil 5 mg at 24 weeks (WMD, -2.02 points; 95% CI, -2.77 to -1.26; P<0.00001) and 10 mg at 24 weeks (WMD,–2.81 points; 95% CI, –3.55 to –2.06; P<0.00001). A significant difference was seen on the MMSE for patients treated with donepezil 10 mg/day as compared to placebo at 52 weeks (WMD, 1.84 points; 95% CI, 0.53 to 3.15; P=0.006). Global Clinical State, CIBIC-Plus scores showed significant benefit in patients treated with donepezil 5 and 10 mg/day (OR, 2.38; 95% CI, 1.78 to 3.19; P<0.00001 and OR, 1.82; 95% CI, 1.42 to 2.35; P<0.00001). Improvements were seen in ADL scores for patients in the donepezil group over those in the placebo group (P<0.01 for all scales used). Significantly more patients treated with donepezil 10 mg/day withdrew from treatment (24 vs 20%; P=0.003); however, there was no difference in withdrawal rates between the 5 mg/day and placebo group (P=0.56). Adverse events that occurred significantly more frequently in both the 5 and 10 mg/day treatment groups as compared to placebo are: anorexia, diarrhea, and muscle cramps.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Wallin et al.[33] (2007) Donepezil 5 to 10 mg/day vs historical data	MC, PRO Patients ≥40 years of age with probable Alzheimer's disease	N=435 3 years	Primary: MMSE, ADAS-Cog, CIBIC, IADL Secondary: Not reported	Primary: For the MMSE, patients had a mean score of 22.0 at baseline and 19.1 at 36 months. After 36 months of donepezil treatment, the mean decline was 3.8 points (95% CI, 3.0 to 4.7). For ADAS-Cog, patients had a mean score of 20.7 at baseline and 26.1 at 36 months. After 36 months, the mean increase was 8.2 points (95% CI, 6.4 to 10.0). A modeling equation predicts an increase in ADAS-Cog to be 4 to 9 points in 12 months without treatment. Scores for the treatment group were significantly better than predicted scores for non-treatment (95% CI, 14.5 to 16.6). For CIBIC, at two months, 34% of patients were considered improved, 59% unchanged and 7% were worse. At six months, 28% of patients were considered improved, 46% unchanged and 26% were worse. At 12 months, 20% of patients were considered improved, 29% unchanged and 51% were worse. At 36 months, 30% of patients were considered improved or unchanged. The IADL change from baseline at six months was 1.01, at 12 months 2.19, and at 36 months 6.18. Secondary: Not reported
Farlow et al.[34] (2010) Donepezil 10 mg/day vs donepezil 23 mg/day	DB, MC, RCT Patients 45 to 90 years of age with moderate-to-severe Alzheimer's disease who took donepezil 10 mg/day ≥12 weeks	N=1,467 24 weeks	Primary: Efficacy as measured by SIB-cognition and CIBIC-global function rating; tolerability Secondary: Not reported	Primary: After 24 weeks, the change in SIB-cognition score was significantly greater with donepezil 23 mg/day compared to donepezil 10 mg/day (2.6 vs 0.4, respectively; P<0.001). There was no significant different in CIBIC score with donepezil 23 mg/day compared to donepezil 10 mg/day (4.23 vs 4.29, respectively). In a post-hoc analysis, the least square mean changes in SIB score and CIBIC treatment effect at end point were greater with donepezil 23 mg/day compared to donepezil 10 mg/day in patients with more advanced

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Alzheimer's disease compared to less impaired patients (SIB, 1.6 vs -1.5, respectively; P<0.001; CIBIC, 4.31 vs 4.42; P=0.028). Treatment emergent adverse events were reported in 73.7% of patients who received donepezil 23 mg/day and in 63.7% of patients who received donepezil 10 mg/day. Adverse events were reported as follows with donepezil 23 mg/day: mild (30.8%), moderate (34.5%), and severe (8.4%). The most common treatment emergent adverse events were nausea (6.1%), vomiting (5%) and diarrhea (3.2%). Severe treatment emergent adverse events that were reported included nausea (0.9%), dizziness (0.7%) and vomiting (0.6%). Adverse events were reported as follows with donepezil 10 mg/day: mild (31.2%), moderate (25.3%), and severe (7.2%). The most common treatment emergent adverse events were nausea (1.9%), vomiting (0.8%) and diarrhea (1.5%). Severe treatment emergent adverse events that were reported included nausea (0.2%) and dizziness (0.2%). Secondary: Not reported
Ferris et al.[35] (2011) Donepezil 10 mg/day vs donepezil 23 mg/day	DB, MC, RCT (post-hoc analysis) Patients 45 to 90 years of age with moderate-to-severe Alzheimer's disease who took donepezil 10 mg/day ≥12 weeks	N=1,467 24 weeks	Primary: SIB-Language scale and 21-item SIB-derived language scale Secondary: Correlation of SIB-Language scale and SIB-derived language scale with ADCS-ADL-sev, CIBIC-plus/CIBIC-plus, and MMSE	Primary: At week 24, there was an improvement in language noted with donepezil 23 mg/day compared to a decline in language function with donepezil 10 mg/day (SIB-Language scale treatment difference, 0.8; P=0.0013, SIB-derived language scale treatment difference, 0.8; P=0.0009). Secondary: At week 24, SIB-Language scale and SIB-derived language scale scores were moderately correlated with scores on the ADCS-ADL-sev and CIBIC-plus. Results were similar in both moderate (MMSE, 17 to 20) and severe (MMSE, 0 to 16) Alzheimer's disease patients.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Farlow et al.[36] (2011) Donepezil 10 mg/day vs donepezil 23 mg/day	DB, MC, RCT (post-hoc analysis) Patients 45 to 90 years of age with moderate-to-severe Alzheimer's disease who took donepezil 10 mg/day ≥12 weeks	N=1,434 24 weeks	Primary: Safety and tolerability Secondary: Not reported	Primary: Of the 963 patients receiving donepezil 23 mg/day and 471 patients receiving donepezil 10 mg/day, a total of 71.1 and 84.7% completed the study, respectively. The most common adverse events causing early discontinuation were higher in the donepezil 23 mg/day group compared to the donepezil 10 mg/day group (18.6 vs 7.9%, respectively). Adverse events that contributed the most to the discontinuations were vomiting (2.9 vs 0.4%, respectively), nausea (1.9 vs 0.4%, respectively), diarrhea (1.7 vs 0.4%, respectively), and dizziness (1.1 and 0%, respectively). The most common adverse events with donepezil 23 mg/day compared to donepezil 10 mg/day were nausea (11.8 vs 3.4%, respectively), vomiting (9.2 vs 2.5%, respectively) and diarrhea (8.3 vs 5.3%, respectively). Serious adverse events occurred in 8.3% of patients receiving donepezil 23 mg/day and in 9.6% of patients receiving donepezil 10 mg/day. These included urinary tract infection (0.6 vs 0.4%, respectively), fall (0.6 vs 0.4%, respectively), pneumonia (0.3 vs 0.6%, respectively), syncope (0.2 vs 1.1%, respectively), aggression (0.2 vs 0.8%, respectively), and confusional state (0.1 vs 0.6%, respectively). Secondary: Not reported
Doody et al.[37] (2012) Donepezil 23 mg/day vs donepezil 10 mg/day Patients were	DB, MC Patients with moderate-to-severe Alzheimer's disease	N=not specified 24 weeks	Primary: Efficacy and safety Secondary: Not reported	Primary: At week 24, donepezil 23 mg/day provided significant cognitive benefits over 10 mg/day (P<0.01) on the SIB, with or without concomitant memantine. The higher dose showed no benefit on the global function, MMSE or ADL measures in either memantine subgroup. Rates of treatment-emergent adverse events were higher for donepezil 23 mg/day with memantine (80.7%) than 23 mg/day without memantine (69.7%) or 10 mg/day with/without memantine (66.7/62.0%); across all treatment groups, most events were mild/moderate in severity. Individual

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
allowed to also take memantine.				rates of serious adverse events were low (<1.0%), regardless of concomitant memantine use. Secondary: Not reported
Raskind et al.[38] (2004) Galantamine 24 mg/day	OL Patients with mild-to-moderate Alzheimer's disease	N=194 36 months	Primary: ADAS-Cog, adverse events Secondary: Not reported	Primary: Patients treated continuously with galantamine for 36 months increased a mean of 10.2±0.9 points on the ADAS-Cog. This was a substantially smaller cognitive decline (approximately 50%) than that predicted for the placebo group. Patients discontinuing galantamine therapy before 36 months had declined at a similar rate before discontinuation as those completing 36 months of treatment. Almost 80% of patients who received galantamine for 36 months seemed to demonstrate cognitive benefits compared to those predicted for untreated patients. Secondary: Not reported
Rockwood et al.[39] (2008) Galantamine 24 mg/day	MC, OL Patients with Alzheimer's disease who had received galantamine treatment for up to 36 months	N=240 Up to 48 months	Primary: ADAS-Cog, DAD, adverse events Secondary: Not reported	Primary: Mean ADAS-Cog worsened from 22.6±8.6 at baseline to 31.3±13.1 at 48 months. DAD worsened from 73.4±18.1 at baseline to 36.1±29.0 at 48 months. Fifty one patients withdrew from the study. Secondary: Not reported
Wallin et al.[40] (2011) Galantamine 24 mg/day	MC, OL, PRO Patients with Alzheimer's disease and no previous cholinesterase	N=280 36 months	Primary: MMSE, ADAS-cog, IADL, CIBIC Secondary: Subgroup analysis	Primary: From baseline to 36 months, MMSE decreased from 23.3 to 21.74. The MMSE score was significantly better at two months (P<0.001) and at six months (P=0.006) compared to baseline, and was stable at 12 months (P=0.616) compared to baseline. The total mean decline in MMSE score from baseline after three years of treatment was 2.6

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	inhibitor therapy		by K-means cluster analysis	From baseline to 36 months, ADAS-cog increased from 16.85 to 19.39. The total change in ADAS-cog score after three years of treatment was 5.6 points above baseline values. The ADAS-cog scores at six months were not different from baseline (P=0.248), but deteriorated after that. Mean IADL scores demonstrated deteriorated at all time points compared to baseline (12.76 to 17.13). According to CIBIC scores at two months, 93% of patients remaining in the study were "improved or unchanged", at months six, 12, 24, and 36; 81, 69, 50, and 41% of the patients were "improved or unchanged", respectively. Secondary: Cluster analysis identified two response clusters. Cluster 1 included patients with low ability in ADAS-cog and IADL scores at baseline. These patients were older and less educated, but responded better at six months compared to cluster two patients. Cluster 2 patients included better ADAS-cog and IADL scores at baseline. Cluster 2 patients had a higher frequency of the APOE ε4 allele.
Brodaty et al.[41] (2006) Galantamine 2 to 50 mg/day	OL, OS, PRO Patients diagnosed with mild-to-moderately severe dementia	N=345 ITT N= 229 PP 6 month follow-up	Primary: MMSE, ADAS-Cog, CIBIC-Plus, IADL Secondary: Not reported	Primary: For the MMSE 65% of PP patients had an increased score at the three-month assessment as compared to baseline with an overall 92% response rate. 70% of PP patients had an increased score at the six-month assessment as compared to baseline with an overall 91% response rate. 44% of ITT patients had an increased score at the six-month assessment as compared to baseline (P values were not reported). For ADAS-Cog at 6 months, 86% of the PP patients and 33% of the ITT patients had a decrease in ADAS-Cog score. P value was not reported. For CIBIC-Plus at three months, 91% of PP patients were considered responders by their physicians; 28% were unchanged, 38% were minimally improved, 22% were much improved, 4% were very much

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				improved (P values not reported). For CIBIC-Plus at six months, 86% of PP patients were considered responders by their physicians; 20% were unchanged, 26% were minimally improved, 32% were much improved, 7% were very much improved. In the ITT patients, 54 % were classified as responders at six months (P values not reported). Most PP patients had no change in IADL scores at three and six months (P value not reported). Most PP patients had no change in behavior scores at three and six months (P value not reported). Secondary: Not reported
Richarz et al.[42] (2014) Galantamine 8 to 24 mg/day	OL, PRO Patients ≥45 years of age with mild to moderate Alzheimer's disease	N=75 (36 months) N=159 (24 months) N=269 (6 months) Up to 36 months	Primary: ADAS-cog/11 Secondary: Bayer-ADL, NPI, CGI-C, adverse events	Primary: Mean ADAS-cog score improved significantly during the first six months, with improvement maintained until month 12. During follow-up, mean ADAS-cog score returned to baseline levels between months 18 and 24; after 36 months, it had deteriorated (increased) by 2.87 ± 11.07 points. Secondary: Mean NPI score improved significantly in the first 12 months and worsened thereafter. In the 36-month sample, patient self-rated Bayer ADL scores remained stable until 24 months of treatment; then, a significant deterioration had occurred; a significant deterioration from baseline in caregivers' Bayer ADL scores occurred after month 12. After six months of treatment, 84% of the patients who completed the six-month observation period were considered to be improved or unchanged compared with baseline on the CGI-C. In the 36-month sample, the corresponding value was 54%. In the 36-month sample, 54 patients (72%) reported at least one treatment-emergent adverse event throughout the treatment period, with most events occurring during the first two years of treatment.
Cummings et al.[43] (2004)	DB, PC, RCT Patients with mild-	N=978 21 weeks	Primary: NPI, caregiver distress related to	Primary: NPI scores worsened with placebo, whereas patients treated with 16 or 24 mg/day of galantamine had no change in NPI scores.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Galantamine 8 to 24 mg/day vs placebo	moderate Alzheimer's disease		patients' behavior Secondary: Not reported	Behavioral improvement in patients symptomatic at baseline ranged from 29 to 48%. Changes were evident in patients receiving 16 and 24 mg/day of galantamine. High-dose galantamine was associated with a significant reduction in caregiver distress. Secondary: Not reported
Scarpini et al.[44] (2011) <u>Phase 1</u> Galantamine 8 to 16 mg/day <u>Phase 2</u> Galantamine 16 mg/day vs placebo	<u>Phase 1</u> MC, OL <u>Phase 2</u> DB, MC, RCT Mild to moderate Alzheimer's disease in patients ≥50 years of age (MMSE, 11 to 24)	N=393 36 months	Primary: ADAS-cog/11 deterioration ≥4 points Secondary: CIBIC-plus, adverse events	<u>Phase1</u> Primary: Cognitive functions improved significantly on the ADAS-cog/11 scale with galantamine treatment at month seven relative to baseline (from 24.1 to 22.9, difference, -1.2; 95% CI, -2.3 to -0.1; P<0.01). Scores were similar to baseline values at the end of the OL phase at month 12 (mean score at baseline, 24.1; mean score at month 12, 24.7; 95% CI, -0.5 to 1.7, P=0.16). Secondary: CIBIC-plus score improved in 34.3%, was unchanged in 30.9%, and worsened in 34.9% of patients when compared to baseline. A total of 50.4% of patients reported adverse events, of which the most common was gastrointestinal disorders (21.3%), nervous system disorders (9.8%), and psychiatric disorders (19.7%). Serious adverse events were reported in 12.2%. <u>Phase 2</u> Primary: Patients receiving placebo were more likely to discontinue therapy prematurely compared to galantamine for any reason (HR, 1.76; 95% CI, 1.10 to 2.81; P=0.02) or lack of efficacy (HR, 1.80; 95% CI, 1.02 to 3.18; P=0.04). No significant difference was observed by ADAS-cog >4 between the groups (HR, 1.66; 95% CI, 0.78 to 3.54; P=0.19). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There were no significant differences between the treatment groups concerning mean values of the CIBIC-plus scale. A total of 34.1% of patients receiving galantamine and 27% of patients receiving placebo experienced adverse events. The most common adverse events were nervous system disorders (6.6%) and psychiatric disorders (5.3%). Serious adverse events were reported in 14.5% of galantamine-treated patients compared to 6.3% of patients in the placebo group.
Kavanagh et al.[45] (2011) Galantamine 16 to 24 mg/day vs placebo	OL, RCT Patients with mild-to-moderate Alzheimer's disease	N=3,523 (5 trials) 5 to 6 months	Primary: Changes from baseline in ADAS-Cog 11 at trial endpoint (two to five months after reaching maintenance doses) Secondary: Not reported	Primary: The proportion of patients who met criteria for "improved", "stable", or "non-rapid decline" at trial endpoint were 45.8, 59.5, and 87.6%, respectively with galantamine compared to 27.2, 37.1, and 67.7%, respectively with placebo. Changes in ADAS-Cog 11 scores with galantamine were -4.9, -4.7, and -2.9 points, respectively, for "improved", "stable" and "non-rapid decline" compared to -3.6, -3.4, and -1.2, respectively with placebo. Patients receiving galantamine who were reported to be "improved" or "stable" experienced improvement in ADAS-Cog 11 scores until 18 months after starting treatment, and attenuated deterioration thereafter. For galantamine-treated patients exhibiting "non-rapid decline", mean ADAS-Cog 11 score returned to baseline after approximately 12 months. Secondary: Not reported
Burns et al.[46] (2009) Galantamine 24 mg/day vs placebo	DB, MC, PC, RCT Patients 40 to 95 years of age with severe dementia of the Alzheimer type or probable Alzheimer's disease (MMSE, 5 to 12 points)	N=407 6 months	Primary: SIB, MDS-ADL, and adverse events Secondary: Not reported	Primary: In the completer analysis, the mean total SIB score of the galantamine group increased to 69.1 points at week 26. The mean SIB score in the placebo group decreased to 66.9. The between group least squares mean difference was 4.36 (95% CI, 1.3 to 7.5; P=0.006). In the completer analysis, the mean total MDS-ADL self-performance score worsened in both groups: scores at week 26 were 13.0 points in the galantamine group and 13.6 points in the placebo group. The between-group least squares mean difference was –0.41 points (95% CI, –1.3 to 0.5; P=0.383).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				In the LOCF analysis, the mean SIB score in the galantamine group increased to 69.3 points. In the placebo group, the mean SIB score decreased by 3.2 points. The between-group least squares mean difference was 5.02 points (95% CI, 2.17 to 7.86; P=0.0006). In the LOCF analysis, the mean total seven-item MDS-ADL self-performance score in the galantamine group worsened at endpoint to 13.1 points and to 14.0 points in the placebo group. Changes from baseline in the seven-item MDS-ADL self-performance score were 1.3 points and 1.7 points, respectively. The between-group least squares mean difference was –0.50 (95% CI, –1.39 to 0.39; P=0.394). Significant between-group differences were seen in the galantamine group for memory (P=0.006), praxis (P=0.010), and visuospatial ability (P=0.002). There were no significant differences in language (P=0.064) or attention (P=0.075). Scores for all eleven-item MDS-ADL self-performance subscales worsened in both treatment arms. The deterioration in the subscale score for locomotion on unit was significantly less in the galantamine group (P=0.021). During the study, 88% of patients who received galantamine and 89% who received placebo had at least one adverse event. The most common adverse events in both treatment groups were urinary tract infections, vomiting, diarrhea, nausea, and falls. Secondary: Not reported
Raskind et al.[47] (2004) Galantamine 24 mg/day vs	DB, PC, RCT Patients with mild-moderate Alzheimer's disease	N=194 36 months	Primary: ADAS-Cog, adverse events Secondary: Not reported	Primary: Patients treated continuously with galantamine for 36 months increased a mean of 10.2±0.9 points on the ADAS-Cog. This was a substantially smaller cognitive decline (approximately 50%) than that predicted for the placebo group. Patients discontinuing galantamine therapy before 36 months had declined

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				at a similar rate before discontinuation as those completing 36 months of treatment. Almost 80% of patients who received galantamine for 36 months seemed to demonstrate cognitive benefits compared to those predicted for untreated patients. Secondary: Not reported
Wilcock et al.[48] (2000) Galantamine 24 mg/day vs galantamine 32 mg/day vs placebo	DB Patients with mild-moderate Alzheimer's disease	N=653 6 months	Primary: ADAS-Cog, adverse events Secondary: Not reported	Primary: Both doses of galantamine were statistically better than placebo in the mean change in ADAS-Cog from baseline to endpoint (P<0.0001). Patients taking galantamine 24 mg had a -0.5 point mean change on the ADAS-Cog scale, while the 32 mg group had a -0.8 change. This compares to a +2.4 change for the placebo group. Statistical comparisons between the 24 mg group and the 32 mg group were not conducted. Discontinuations due to adverse events were 9, 14 and 22% in the placebo, 24 and 32 mg dose groups, respectively. Secondary: Not reported
Dunbar et al.[49] (2006) Galantamine IR 8 to 16 or 24 mg/day vs galantamine ER 8 to 16 or 24 mg/day vs	Post hoc analysis, DB, MC, PC, RCT Patients with mild-to-moderate probable Alzheimer's disease	N=965 7 months	Primary: Nausea and vomiting Secondary: Not reported	Primary: Nausea reports were as follows: 16.9% of the galantamine ER group, 13.8% of galantamine IR group and 5.0% of placebo group. Vomiting reports were as follows: 6.6% of the galantamine ER groups, 8.6% of the galantamine IR group and 2.2% of the placebo group. During dose titration, the area under the curve of daily percentage of patients reporting nausea or vomiting was significantly higher in the galantamine IR group compared to placebo (320.9 vs 102.9; P=0.01) but for galantamine ER vs placebo and galantamine ER vs galantamine IR no significant differences were seen ([173.5 vs 102.9; P=NS], [320.9 vs 173.5; P=NS]).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				The mean daily nausea rate and the mean daily vomiting rate for galantamine ER and galantamine IR were not significantly different but when both were compared to placebo, significance was seen (P<0.05). The galantamine IR had a greater mean percentage of days with nausea compared to galantamine ER (38 vs 18.4%; P=0.014) while there was no significance for both galantamine groups compared to placebo. Secondary: Not reported
Brodaty et al.[50] (2005) Galantamine IR 8 to 16 or 24 mg/day vs galantamine ER 8 to 16 or 24 mg/day vs placebo	AC, DB, MC, PC, PG, RCT Patients with mild-to-moderate probable Alzheimer's disease	N=971 6 months	Primary: ADAS-cog/11, CIBIC-Plus Secondary: ADCS-ADL, NPI, ADAS-cog/13, nonmemory ADAS-cog/ memory, ADAS-Cog	Primary: Compared to placebo, galantamine was significantly more effective with improvement from baseline in ADAS-cog/11 scores (mean change, 1.3 and -1.4, respectively; P<0.001; 95% CI, –3.74 to –1.68; LOCF mean change, 1.2 and -1.3, respectively; P<0.001; 95% CI, –3.34 to –1.49). Galantamine also showed similar results when compared to placebo (OC mean change, –1.8 and 1.3, respectively; P<0.001; 95% CI, –4.17 to –2.08; LOCF mean change, –1.6 and 1.2, respectively; P<0.01; 95% CI, –3.70 to –1.86). Secondary: ADCS-ADL scores were significantly improved in the galantamine group vs placebo (P=0.003; 95% CI, 0.85 to 4.03; LOCF; P<0.001; 95% CI, 1.09 to 3.91). In galantamine groups vs placebo, NPI scores were not statistically significant but instead numerically significant (P=0.451; 95% CI, –2.77 to 1.23; LOCF; P=0.941; 95% CI, –1.85 to 1.82), (OC; P<0.205; 95% CI, –3.31 to 0.71; LOCF; P<0.102; 95% CI, –3.42 to 0.23). Statistical significance was found in cognition improvement from baseline for both galantamine groups compared to placebo based on ADAS-cog/13, non-memory ADAS-Cog, and memory ADAS-Cog scores.
Loy et al.[51] (2006)	MA (10 trials) Patients diagnosed	N=6,805 12 weeks-2	Primary: CIBIC-plus, ADAS-Cog,	Primary: Statistically significant difference was seen on the global rating scales for patients treated with galantamine, at all durations and all doses but 8

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Galantamine 8 to 36 mg/day vs placebo	with mild cognitive impairment or Alzheimer's disease	years	ADCS-ADL, DAD, NPI Secondary: Not reported	mg/day (P values varied). Statistically significant difference was seen on the ADAS-Cog scale for patients treated with galantamine at all doses, with greater effect at six months than three months (P values varied). When reported, ADCS-ADL, DAD, and NPI scores for patients treated with galantamine were significantly improved over those in the placebo group (P values not reported). Secondary: Not reported
Herrmann et al.[52] (2011) Memantine 20 mg/day	OL Patients with moderate-to-severe Alzheimer's disease	N=31 3 months	Primary NPI-NH change in agitation and aggression subscale, CGI-C scale, caregiver impact, and effect on nursing burden measured by M-NCAS Secondary: Caregiver distress subscale of the NPI-NH, changes in psychotropic medications	Primary: There was a significant decrease in the NPI-NH agitation/aggression subscale score with memantine (P=0.014). According to the CGI-C scores, 48% of patients were improved (much improved or minimally improved). A total of 52% of patients did not benefit from treatment (no change, minimally worse or much worse). There was a significant decrease in the M-NCAS total score (P=0.005), as well as decreases on the attitude (P=0.009) and strain (P=0.013) subscales with memantine therapy. Secondary: The NPI-NH subscale score decreased significantly with memantine therapy (P=0.009). Psychotropic medications were available in 28 patients, with 64.3% receiving at least one dose during the study. Lorazepam was the most commonly used psychotropic (P=0.046). Overall, seven patients decreased psychotropic medication use during the study, while three increased usage; Most remained the same for psychotropic usage.
Bakchine et al.[53] (2007) Memantine 20	DB, PC Patients with mild-to-moderate	N=470 24 weeks	Primary: ADAS-COG and CIBIC-plus	Primary: Patients in the memantine group showed a statistically significant improvement relative to placebo in ADAS-COG and CIBIC-plus at weeks 12 and 18. There was no significant difference between the groups at week

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/day vs placebo	Alzheimer's disease		Secondary: Not reported	24. Secondary: Not reported
Reisberg et al.[54] (2003) Memantine 20 mg/day vs placebo	DB, PG Patients with moderate-to-severe Alzheimer's disease	N=252 28 weeks	Primary: CIBIC-Plus and ADCS-ADL Secondary: SIB	Primary: A significantly greater effect was observed in the memantine group compared to the placebo group on the ADCS-ADL (P=0.03). There was a significant difference in favor of memantine at week 28 on the CIBIC-Plus using the observed-cases analysis (mean score, 4.7 placebo vs 4.4, memantine; P=0.03), and a numerical difference at study endpoint in favor of memantine using the last-observed-carried-forward analysis (mean score, 4.8 placebo vs 4.5 memantine; P=0.06). Secondary: Memantine patients showed significantly less cognitive decline on the SIB total score compared to placebo-treated patients over the 28-week study period (P=0.002).
Winblad et al.[55] (1999) Memantine 10 mg/day vs placebo	DB, PC Patients in Latvia with severe dementia, either Alzheimer's disease or vascular dementia	N=166 12 weeks	Primary: CGI-C and BGP Secondary: Safety	Primary: Significantly greater improvement was observed in the memantine group compared to the placebo group on the BGP and the CGI-C (P<0.016 and P<0.001, respectively). Separate analyses of the Alzheimer's disease population alone also yielded statistically significant results in favor of patients receiving memantine, by either the last-observed-carried-forward analysis or the observed-cases analysis on both outcome measures. At study endpoint, memantine patients showed significantly greater functional improvement compared to patients who received placebo, at study endpoint (P=0.012). Secondary: No significant differences in safety were found between the groups.
Winblad et al.[56] (2007)	MA	N=1,826 in subgroup with	Primary: CIBIC-Plus, SIB,	Primary: There was a statistically significant advantage for the memantine group

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Memantine 20 mg/day vs placebo	Four studies: memantine as monotherapy, 2 studies of memantine vs placebo in patients already taking an acetylcholinesterase inhibitor; patients diagnosed with moderate-to-severe Alzheimer's disease	moderate-to-severe Alzheimer's disease 24 to 28 weeks	ADAS-Cog, ADCS-ADL, NPI Secondary: Not reported	over the placebo group in all 4 efficacy domains: CIBIC-Plus or global status (P<0.001), SIB or ADAS-Cog status (P<0.001), ADCS-ADL (P<0.001) and NPI (P=0.03). Secondary: Not reported
Wilkinson et al.[57] (2007) Memantine 20 mg/day vs placebo	MA Patients diagnosed with moderate-to-severe Alzheimer's disease	N=1,826 24 to 28 weeks	Primary: ADAS-Cog, SIB, CIBIC-Pus, ADCS-ADL Secondary: Not reported	Primary: Significantly more patients in the placebo group (21%) had marked clinical worsening, as demonstrated by deteriorating scores, than in the memantine group (11%; P<0.001). Significantly more patients in the placebo group (28%) compared to the memantine group (18%) had documentation of worsening in any outcome measure (P<0.001). Secondary: Not reported
McShane et al.[58] (2006) Memantine 10 to 30 mg/day vs placebo	MA (12 trials) Patients diagnosed with mild-to-moderate, moderate-to-severe and mild-to-moderate vascular dementia	N=3,731 (15 trials) Variable duration	Primary: CIBIC-Plus, SIB, ADAS-Cog, ADCS-ADL, NPI Secondary: Not reported	Primary: Significant improvement at six months was seen for patients with mild-to-moderate dementia treated with memantine on the ADAS-Cog scale (P=0.03); however, there was no significant difference seen for behavior and ADL scales. Significant improvement at six months was seen for patients with moderate-to-severe dementia treated with memantine for the following scales: CIBIC-Plus (P<0.00001), SIB (P<0.00001), ADCS-ADL (P=0.003) and NPI (P=0.004). Patients with vascular dementia treated with memantine had significant improvement in cognition scores and behavior scores but no significant change in global rating scales (ADAS-Cog; P=0.0002, NPI; P=0.03).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Grossber et al.[59] (2013) Memantine extended-release 28 mg once daily vs placebo	DB, MC Outpatients with Alzheimer's disease (MMSE scores of 3 to 14)	N=677 24 week	Primary: Baseline-to-endpoint score change on the SIB and the endpoint score on the CIBIC-Plus. Secondary: Baseline-to-endpoint score change on the ADCS-ADL19; additional parameters included the baseline-to-endpoint score changes on the NPI and verbal fluency test	Primary: At 24 weeks memantine-treated patients significantly outperformed placebo-treated patients on the SIB (2.6; 95% CI, 1.0 to 4.2; P=0.001) and CIBIC-Plus (P=0.008). Secondary: At 24 weeks memantine-treated patients significantly outperformed placebo-treated patients on the NPI (P=0.005), and verbal fluency test (P=0.004); the effect did not achieve significance on ADCS-ADL19 (P=0.177). Adverse events with a frequency of >5.0 % that were more prevalent in the memantine group were headache (5.6 vs 5.1 %) and diarrhea (5.0 vs 3.9 %).
Burns et al.[60] (2004) Rivastigmine	RETRO Patients with moderately severe Alzheimer's disease/dementia	N=2,126 3 trials, each 6 months	Primary: Effectiveness Secondary: Not reported	Primary: Mean ADAS-Cog score declined by 6.3 points in the placebo group and increased by 0.2 points in the rivastigmine group (P<0.001). Clinical benefits were also observed with the MMSE, the six-item PDS, and items of the BEHAV-AD assessed efficacy. Rivastigmine showed the same pattern of adverse events as in other studies, but the RR of dropping out due to adverse events was lower than in subjects with milder Alzheimer's disease. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Dantoine et al.[61] (2006) Rivastigmine 3 to 12 mg/day Addition of memantine 5 to 20 mg/day was allowed for non-responders of rivastigmine at the end of week 16.	MC, OL Patients at least 50 years of age with probable Alzheimer's disease according to criteria of DSM-IV, baseline scores of <18 for MMSE or scores of >4 on GDS, previously treated for at least 6 months prior with donepezil 5 to 10 mg/day or galantamine 16 to 24 mg/day and considered not stabilized, current stabilized medications allowed	N=202 16 weeks of rivastigmine monotherapy (Phase 1) Additional 12 weeks of rivastigmine and memantine combination therapy for non-responders of rivastigmine monotherapy (Phase 2) Total 28 weeks	Primary: MMSE Secondary: MMSE, Mini-Zarit inventory, NPI, Ten-point Clock-drawing Test, D-KEFS verbal fluency test, CGI-C	Primary: Based on MMSE scores, 46.3% of patients improved or stabilized on rivastigmine monotherapy at the end of Phase 1. For those patients previously on donepezil or galantamine, responder rates were also similar (46.6 and 46.4%). At the end of Phase 2 with combination therapy of rivastigmine and memantine, according to MMSE scores, 77.9% of patients improved or stabilized. Patients switching to combination therapy from galantamine responded more significantly than those who switched from donepezil (84.2 vs 72.3%; P=0.047). Secondary: According to CGI-C data, no change or improvement was seen in 76.5% of patients who completed the study at the end of Phase 1. For the 82.6% who worsened from baseline at the end of Phase 1, 81.4% improved or had no change at the end of Phase 2 with the addition of memantine on the CGI-C. At the end of Phase 1, MMSE and NPI showed significant improvements (P<0.001 and P<0.05, respectively) while there was no change from baseline for Ten-point Clock-drawing Test and D-KEFS verbal fluency test scores and the Mini-Zarit interview. At the end of Phase 2, D-KEFS verbal fluency test, Mini-Zarit, and especially MMSE scores showed significant improvement (P<0.05, P<0.001 and P<0.001, respectively).
Olin et al.[62] (2010) Rivastigmine 6 to 12 mg/day and memantine 20	MC, OL, PRO Patients ≥50 years of age with moderate-to-severe Alzheimer's disease	N=116 26 weeks	Primary: Safety and tolerability Secondary: ADCS-CGIC,	Primary: Nausea and vomiting occurred in 26.7 and 10.3% of patients, respectively. Most cases were mild with few severe cases reported (2.6 and 2.6%, respectively). At least one treatment-emergent adverse event was experienced by 81.9%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/day	(MMSE ≥10 to ≤20)		ADCS-ADL measured	of patients. The most common adverse events were nausea (26.7%), dizziness (11.2%), vomiting (10.3%), and diarrhea (10.3%). No patients exhibited clinically significant ECG abnormalities. Secondary: At week 26, 59% of patients experienced no decline in MMSE total score from baseline. The mean change from baseline in MMSE total score was 0.7. At week 26, there was no change in global ADCS-CGIC scores. Patient and caregiver assessed mental/cognitive state, behavior and functioning severity scores were maintained to a similar extent throughout the study. The mean overall rating on the ADCS-CGIC was 4.0. At week 26, 64.5% of patients were considered unchanged or improved. The mean ADAS-ADL scores significantly declined by -2.9. At week 26, cognition, behavior and global functioning were unchanged or improved in 63.2, 71.1 and 77.6% of patients respectively.
Gauthier et al.[63] (2010) Rivastigmine 3 to 12 mg/day	MC, OL, OS, PRO Patients with mild-moderate Alzheimer's disease	N=3,800 12 months	Primary: Physician-assessed abbreviated CGI-C, MMSE, psychotropic medication use Secondary: Not reported	Primary: At six months, the proportion of patients who were reported as being improved vs no change vs deteriorating were 46.4 vs 44.9 vs 8.8% for attention; 42.8 vs 50.0 vs 7.2% for apathy; 41.1 vs 49.5 vs 9.4% for anxiety; 33.8 vs 68.4 vs 7.7% for agitation; 35.1 vs 54.8 vs 10.1% for irritability; and 30.8 vs 63.8 vs 5.4% for sleep disturbance. At 12 months, the proportion of patients who were reported as being improved vs no change vs deteriorating were 47.9 vs 41.0 vs 11.1 for attention; 44.1 vs 46.7 vs 9.2% for apathy; 41.8 vs 47.3 vs 10.9% for anxiety; 33.5 vs 57.6 vs 8.9% for agitation; 33.8 vs 56.4 vs 9.8% for irritability; and 29.7 vs 64.7 vs 5.6% for sleep disturbance. Overall, CGI-C at six and 12 months demonstrated a larger percentage of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				patients with improvement vs deterioration. At six months, 54% of patients overall demonstrated no change. At 12 months, 52% of patients overall demonstrated no change. MMSE scores were 20.8 at baseline, 21.5 after three months, 21.3 after six months, and 21.3 after 12 months. At baseline, 61.3% of patients were not taking a psychotropic medication. At six months, the proportion of patients not taking any psychotropic medications increased to 70.8%; at 12 months, it was 84.7%.
Birks et al.[64] (2000) Rivastigmine 6 to 12 mg/day vs placebo	MA (8 trials) Patients diagnosed with Alzheimer's disease	N=3,660 12 to 52 weeks	Primary: ADAS-Cog, ADL, adverse events Secondary: Not reported	Primary: Statistically significant differences were seen in patients treated with rivastigmine at doses of 6 to 12 mg/day as compared to placebo for the following outcomes: ADAS-Cog (WMD, -2.09; 95% CI, –2.65 to –1.54) and ADL (WMD, -2.15; 95% CI, –3.16 to –1.13). At 26 weeks, 55% of patient had severe dementia in the rivastigmine group as compared to 59% in the placebo group (OR, 0.78; 95% CI, 0.64 to 0.94). Adverse events (nausea, vomiting, diarrhea, anorexia, headache, syncope, abdominal pain and dizziness) were reported significantly more frequently in the rivastigmine group than with placebo. Secondary: Not reported
Birks et al.[65] (2009) Rivastigmine vs placebo	MA Patients diagnosed with probable Alzheimer's disease	N=4,775 (9 trials) Variable duration	Primary: Cognitive function, global impression, activities of daily living, behavioral disturbance, withdrawal rates, and incidence of adverse effects Secondary:	Primary: <u>Cognitive function</u> The meta-analysis, using WMD, demonstrated benefit on cognitive function as measured by ADAS-Cog test scores for rivastigmine compared to placebo as follows: rivastigmine 1 to 4 mg/day at 18 weeks (WMD, -1.07; 95% CI, -1.66 to -0.48; P=0.0004) and 26 weeks (WMD, -0.84; 95% CI, -1.48 to -0.19; P=0.01); rivastigmine 6 to 12 mg/day at 12 weeks (WMD, -1.49; 95% CI, -1.96 to -1.01; P<0.00001), 18 weeks (WMD, -1.79; 95% CI, -2.30 to -1.29; P<0.00001) and 26 weeks (WMD, -1.99; 95% CI, -2.49 to -1.50; P<0.00001).

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			Not reported	An additional analysis of ADAS-Cog dichotomized into those showing less than four points improvement and those showing four or more points improvement at 26 weeks shows benefit for cognitive function for the 6 to 12 mg daily of rivastigmine compared to placebo (83% did not show four points improvement compared to 89%; OR, 0.6; 95% CI, 0.4 to 0.8). There was no difference for the 1 to 4 mg/day dose compared to placebo (88% did not show four points improvement compared to 90%; OR, 0.84; 95% CI, 0.60 to 1.19). MMSE shows similar results in favor of rivastigmine at 26 weeks compared to placebo as follows: rivastigmine 1 to 4 mg/day at 26 weeks (WMD, 0.43; 95% CI, 0.08 to 0.78; P=0.02) and rivastigmine 6 to 12 mg/day at 26 weeks (WMD, 0.82; 95% CI, 0.56 to 1.08; P<0.00001). One study used the SIB, which shows benefit associated with higher dose rivastigmine compared to placebo at 26 weeks (WMD, 4.53; 95% CI, 0.47 to 8.59; P=0.03). <u>Global assessment</u> Using the CIBIC-Plus scale or the ADCS-CGIC scale, there were benefits associated with rivastigmine compared to placebo as follows: rivastigmine 6 to 12 mg/day at 12 weeks (OR, 0.74; 95% CI, 0.60 to 0.92; P=0.008), 18 weeks (OR, 0.79; 95% CI, 0.64 to 0.98; P=0.03) and at 26 weeks (OR, 0.66; 95% CI, 0.55 to 0.79; P<0.00001); rivastigmine 1 to 4 mg/day at 26 weeks (OR, 0.71; 95% CI, 0.55 to 0.93; P=0.01). Using GDS, there were benefits associated with rivastigmine 6 to 12 mg/day compared to placebo (55% showed the worse condition compared to 59%; OR, 0.78; 95% CI, 0.64 to 0.94; P=0.01) but not with 1 to 4 mg daily rivastigmine compared to placebo. <u>ADL</u> The PDS showed an improvement associated with rivastigmine compared to placebo as follows: rivastigmine 6 to 12 mg/day at 12 weeks (WMD, 1.08; 95% CI, 0.19 to 1.98; P=0.02), 18 weeks (WMD, 1.90; 95% CI, 0.93 to 2.88; P=0.0001), and 26 weeks (WMD, 2.15; 95% CI, 1.13 to 3.16; P<0.0001). One study assessing ADL using the ADCS-ADL scale and

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				showed benefit for rivastigmine 6 to 12 mg/day at 24 weeks (WMD, 1.80; 95% CI, 0.20 to 3.40; P=0.03). <u>Behavioral disturbance</u> There was no difference between rivastigmine and placebo in behavioral disturbance found in two studies using the neuropsychiatric instrument (NPI-10, and NPI-12). <u>Withdrawals before the end of treatment</u> There were no significant differences in withdrawal rates with rivastigmine 1 to 4 mg/day and placebo at 12, 18 and 26 weeks. There were significant differences in withdrawal rates for the higher dose group in favor of placebo as follows: rivastigmine 6 to 12 mg/day at 12 weeks (OR, 2.60; 95% CI, 1.19 to 5.68; P=0.02), 18 weeks (OR, 4.02; 95% CI, 1.31 to 12.32; P=0.01), and 26 weeks (OR, 2.19; 95% CI, 1.83 to 2.63; P<0.00001). <u>Adverse events</u> There were no significant differences in the numbers of patients with at least one adverse event between the lower dose rivastigmine (1 to 4 mg/day) and placebo groups. There were significant differences between the higher dose rivastigmine (6 to 12 mg/day) and placebo groups in favor of placebo by the end of the titration period (OR, 2.96; 95% CI, 2.39 to 3.68; P<0.00001) and by 26 weeks (OR, 2.49; 95% CI, 2.05 to 3.02; P<0.00001). There were no significant differences in the numbers of patients with at least one severe adverse event between the lower dose rivastigmine (1 to 4 mg/day) and placebo groups. There were significant differences between the higher dose rivastigmine (6 to 12 mg daily) and placebo groups in favor of the placebo group for the titration period (OR, 1.88; 95% CI, 1.39 to 2.55; P<0.0001). There were significant differences, in favor of placebo, for the rivastigmine 6 to 12 mg/day group by the end of the titration period, and by 26 weeks for the number of patients suffering nausea, vomiting,

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				diarrhea, anorexia, headache, syncope, abdominal pain and dizziness. There were significant differences in favor of placebo, for the rivastigmine 1 to 4 mg/day group by the end of the titration period and by 26 weeks for the number of patients suffering nausea, vomiting, diarrhea, and anorexia. Secondary: Not reported
Rosler et al.[66] (1999) Rivastigmine 1 to 4 mg/day vs rivastigmine 6 to 12 mg/day vs placebo	DB, MC, PC, RCT Patients 50 to 85 years of age and not able to bear children, all patients met criteria for Alzheimer's type dementia as described in the DSM-IV and criteria for probable Alzheimer's disease	N=725 Dose titration over the first 12 weeks with a subsequent assessment period of 14 weeks, total of 26 weeks	Primary: Improvements in cognitive function and overall clinical status measured by the ADAS-Cog, CIBIC, PDS, MMSE and GDS Secondary: Safety and tolerability	Primary: Significant improvement in cognitive function assessed by the ADAS-Cog was observed with the higher dose group by ≥4 points compared to placebo (P<0.05). At week 26, significantly more patients in both rivastigmine groups had improved in global function as assessed by the CIBIC compared to those in the placebo group (P<0.05). Mean scores on the PDS improved from baseline in the higher dose group but fell in the placebo group (P<0.05). At week 26, mean scores in the MMSE and the GDS significantly improved in patients receiving rivastigmine 6 to 12 mg/day (P<0.05). Secondary: Discontinuation rates for any reason were significantly higher in the higher dose group than in the lower dose or placebo group (33% vs 14%). Adverse events related to treatment including nausea, vomiting, diarrhea, abdominal pain and anorexia, were generally mild and occurred most frequently during the dose escalation phase (23% in higher dose group, 7% in lower dose group and 7% in placebo group).
Articus et al.[67] (2011) Rivastigmine patch 9.5 mg/24 hours	MC, OL Patients with Alzheimer's disease	N=208 24 weeks	Primary: Proportion of patients treated with rivastigmine for ≥8 weeks at week 24	Primary: In the ITT population, 80.8% of patients (95% CI, 75.0 to 86.5) were treated for at least eight weeks with rivastigmine. A total of 74.2% of patients (95% CI, 67.8 to 80.5) were treated for at least eight weeks and completed the study. A total of 74.2% of patients treated rivastigmine patch were able to reach

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			Secondary: Tolerability, week 24 MMSE, ADCS-CGIC, ADCS-ADL, ADCPQ, Zarit Burden Interview Score	and maintain the maximum dose for at least eight weeks. The most common adverse events being nausea (10.1%), erythema (8.7%), pruritus (8.2%), and vomiting (7.2%). Secondary: The most common adverse events were nausea (10.1%), erythema (8.7%), pruritus (8.2%), vomiting (7.2%), diarrhea (4.3%) and agitation (4.3%). At week 24, improvements were seen on: MMSE (1.3), and ADCS-ADL (1.3). At week 24, improvements in ADCS-CGIC were demonstrated in 34.6% of patients as assessed by patients, and in 29.7% of patients as assessed by the caregiver. ADCPQ scores improved 18.5 points, and Zarit Burden Interview Score improved slightly at each visit until week 24 (-0.4).
Grossberg et al.[68] (2009) Rivastigmine patch 9.5 mg/24 hours to 17.4 mg/24 hours	OL Patients 50 to 85 years of age with Alzheimer's disease (MMSE scores 10 to 20)	N=870 28 weeks (weeks 25 to 52 of open-label extension)	Primary: Safety and tolerability Secondary: ADAS-cog	Primary: During the first four weeks of the open-label extension, patients formerly randomized to rivastigmine treatment (capsule or patch) reported fewer adverse events than those formerly randomized to placebo (≤15.2 vs 28.2%). This prior exposure effect was noted for nausea (≤2.5 vs 8.5%) and vomiting (≤1.9 vs 6.0%). A total of 57.6% of patients reported adverse events during the OL extension (weeks 25 to 52), with nausea and vomiting being reported most frequently (15.7 and 14.3%, respectively). During the OL extension, over 90% of all patients experienced ''no, slight, or mild'' skin irritation as their most severe application-site reaction. The symptoms that were most commonly reported as moderate or severe were erythema and pruritus (7.7 and 5.6%, respectively). Serious adverse events occurred in 1.0% of patients during the first four weeks of the OL extension phase (weeks 25 to 28) and 9.4% of patients during the full open-label extension phase (weeks 25 to 52). The most common serious adverse events were gastrointestinal disorders (2.0%),

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				infections and infestations (2.0%), cardiac disorders (1.7%), and nervous system disorders (1.5%). Eight deaths occurred during the OL extension phase and a further two occurred during the 30-day follow-up period. The causes of death were most commonly cardiac disorders (n=5) and nervous system disorders (n=3). None were considered treatment related. Secondary: Patients previously randomized to placebo who were switched to the 9.5 mg/24 hour rivastigmine patch during the OL extension experienced a 1.3-point increase in their ADAS-cog scores during weeks 24 to 40. There was no overall change in ADAS-cog score at week 40 compared to baseline (95% CI, -1.4 to 0.6). The increase in ADAS-cog score was not sustained beyond week 40. Patients receiving rivastigmine treatment for the entire study (weeks 0 to 52) showed a deterioration of 0.3 points (95% CI, -0.4 to 0.9) on the ADAS-cog at week 52. Those receiving placebo for weeks 0 to 24, followed by the patch, showed a deterioration of 0.9 points [95% CI, -0.4 to 2.1).
Gauthier et al.[69] (2013) Rivastigmine transdermal patch 4.6 mg/24 hours or 9.5 mg/24 hours, once daily	OS Patients with Alzheimer's disease with MMSE score of 10 to 26 and GDS score of 4 to 6	N=1,204 18 months	Primary: Change in MMSE from baseline to 18 months Secondary: Change in MMSE at six and 12 months and change in GDS, assessment of patient ability, overall patient assessment rating, caregiver-reported compliance and	Primary: Over 18 months of treatment there were no clinically significant changes in MMSE. Secondary: Over 18 months of treatment there were no clinically significant changes in GDS. The majority of patients showed improvement or no change in GDS, assessment of patient ability and overall patient assessment rating over 18 months. The proportion with reported improvement in GDS, assessment of patient ability and overall patient assessment rating was higher than the proportion that deteriorated. Compliance improved from baseline to 18 months and for 88.2% of patients caregivers preferred the transdermal

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			treatment satisfaction at six, 12, and 18 months	patch to oral medications.
Sadowsky et al.[70] (2010) US13 and US18 Rivastigmine capsules 3 to 12 mg/day US38 Rivastigmine patch 4.6 mg/24 hours for 5 weeks, then rivastigmine patch 9.5 mg/24 hours for 20 weeks	US13 and US18 PRO, MC, OL US38 RCT, MC, OL Patients ≥49 years of age with a diagnosis of dementia of the Alzheimer type (MMSE ≥8 to ≤26 or MMSE ≥10 to ≤24) who showed a poor response to donepezil	N=592 25 to 26 weeks	Primary: Safety and tolerability	Primary: In US13 and US18, 67.7% of patients completed the studies and 32.3% of patients withdrew due to adverse events (59.8%), unsatisfactory treatment effect (15.9%), withdrawal of consent (15%), and loss to follow-up (6.5%). The remaining 2.7% of patients discontinued due to protocol deviation, administrative problem, or death. In US13 and US18, the most frequently reported adverse events (AEs) were nausea (32.9%), vomiting (24.1%), dizziness (11.8%), weight loss (9.1%) agitation (7.9%), fall (7.9%) and confused state (7.9%). Serious AE's were reported in 6% of patients and included pneumonia (1.8%), syncope (1.2%), dehydration (1.2%) and vomiting (1.2%). In US38, 67.4% of patients completed the study. The primary reasons for not completing the study were adverse events (44.7%), withdrawal of consent (29.4%), unsatisfactory treatment effect (10.6%), protocol deviation (7.1%), and loss to follow-up (3.5%). The remaining 4.7% of patients discontinued due to administrative problems, abnormal test procedure, or death. In US38, 70.5% of patients reported at least 1 AE. More patients in the immediate-switch group (73.3%) experienced at least one AE during the study than in the delayed-switch group (67.7%). The most common adverse events were application site reaction (15.3%), and agitation (6.9%). The most common serious AEs reported were syncope (1.1%), dehydration (0.8%) and pneumonia (0.4%). Discontinuation due to AE (14.6%) was the most common reason for patients not completing the extension phase in both immediate- and delayed-switch groups; the differences between the groups were NS. Discontinuations occurred for the following reasons: application site reaction (4.2%), disease progression (2.3%), and agitation (1.5%). Discontinuation due to gastrointestinal AEs was lower for the rivastigmine patch compared to the capsules.

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Cummings et al.[71] (2012) 10 cm^2 rivastigmine patch (9.5 mg/24 hours) vs 15 cm^2 rivastigmine patch (13.3 mg/24 hours)	DB, PG. RCT Patients 50 to 85 years of age with MMSE scores of 10 to 24 diagnosed with Alzheimer's disease, all patients were required to be living with someone or to be in daily contact with a caregiver	N=567 48 weeks	Primary: ADCS-IADL scale and ADAS-cog Secondary: Time to functional decline on the ADCS-IADL, change in the Trail Making Test parts A and B, and change in the NPI-10, and the NPI-caregiver distress scale.	Primary: The 13.3 mg/24 hours patch was statistically superior to the 9.5 mg/24 hours patch on the ADCS-IADL scale from week 16 (P=0.025) onwards including week 48 (P = 0.002), and ADAS-cog at week 24 (P= 0.027), but not at week 48 (P = 0.227). Secondary: Functional decline on the ADCS-IADL tended to occur later in the 13.3 mg/24 h patch group than in the 9.5 mg/24 hours patch group, but the observed difference did not reach significance. Proportion of patients with functional decline was 77.0% in the 13.3 mg/24 hours patch group compared to 81.2% with the 9.5 mg/24 hours patch Group. The difference was not statistically significant. Patients in the 13.3 mg/24 hours patch group had smaller increases in time to complete the Trail Making Test parts A at weeks 24 and 48 compared to those in the 9.5 mg/24 hours patch group, but the observed difference did not reach significance. Differences were not significantly different in changes in the change in the 10-item (NPI-10), and the NPI-caregiver distress scale. The most frequently reported adverse events by primary system organ class were gastrointestinal disorders (29.3 vs. 19.1%, 13.3 and 9.5 mg/24 hours patch, respectively), psychiatric disorders (25.4 vs. 21.6%, respectively) and nervous system disorders (21.4 vs. 18.4%, respectively). Skin and subcutaneous tissue disorders were less frequently observed with the 13.3 mg/24 hours than the 9.5 mg/24 hours patch (2.1 vs 6%).
Cummings et al.[72] (2010) Rivastigmine patch 9.5 mg/24 hours vs	DB, PC, PRO, RCT Patients 50 to 85 years of age with mild-to-moderate Alzheimer's disease	N=1,195 24 to 52 weeks	Primary: Tolerability at 24 weeks Secondary: Patients skin condition at the application site at	Primary: No serious skin reactions were reported in either the 24 or 28 week phases of the study. During the 24 week period, 574 patients wearing an active patch and 579 patients wearing a placebo patch underwent at least one assessment of application-site skin condition. Of patients on the 9.5 mg/24 hour patch, erythema and pruritus were the most commonly reported reactions

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
rivastigmine patch 17.4 mg/24 hours vs placebo			28 weeks	(moderate in 7.6% of patients and severe in 6.7% of patients). A total of 89.6% of patients in the patch group had "no, slight, or mild" signs and symptoms for their most severe application site reaction. Secondary: A total of 870 patients entered the 28 week phase of the study and received rivastigmine 9.5 mg/24 hours patch. Overall, the skin tolerability profile was similar to the DB phase. A total of 91.5% of patients experienced "no, slight, or mild" symptoms as their most severe application site reaction, with erythema and pruritus being the most common finding. A total of 3.7% of patients discontinued treatment due to skin reactions during the open-label extension, and there was no increase in the severity of skin reaction noted.
Molinuevo et al.[73] (2012) Rivastigmine patch 9.5 mg/24 hours vs rivastigmine 3 to 12 mg/day	MC, OS, PRO Patients with mild-to-moderate Alzheimer's disease	N=649 6 months	Primary: Adherence rates Secondary: Strategies followed by a physician to improve adherence and reasons for nonadherence reported by patients	Primary: At baseline, 0.6% of patients were taking ≥80% of their medication as prescribed. At three and six months, 77 and 88.1%, respectively, were noted to be taking more than 80% of their medication as prescribed (P<0.0001 vs baseline). The proportion of adherent patients at three months was 73.6% and at six months was 85.9% (P<0.0001). Secondary: Modification of Alzheimer's disease treatment was the only intervention that substantially improved adherence at three months (P<0.0001). At the six month visit, psychoeducation was the only effective strategy that reached statistical significance (P<0.0001). The most common reasons for nonadherence include forgetfulness (56.4%), avoidance of adverse events (30.7%), and refusal of treatment (25.3%).
Boada et al.[74] (2013) Rivastigmine transdermal patch vs	OL Patients treated with rivastigmine	N=1,078 Duration not specified	Primary: Patient satisfaction (Treatment Satisfaction with Medicines and the Morisky-Green questionnaires)	Primary: Satisfaction reported was greater with transdermal than oral rivastigmine: mean+standard deviation of the total Treatment Satisfaction with Medicines score, 72.5+14.1 vs 65.2+12.5; P<0.001. The proportion of adherent patients was greater with transdermal than with oral rivastigmine (65.0 vs 41.4%; P<0.001).

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rivastigmine capsules			Secondary: Not reported	Satisfaction, in turn, was significantly greater in adherent cases than in nonadherent cases. Secondary: Not reported
Blesa González et al.[75] (2011) Rivastigmine 6 to 12 mg/day (RO) vs rivastigmine patch titrated to 9.5 mg/24 hours (RPT) vs rivastigmine patch 9.5 mg/24 hours (RP)	MC, OL, RCT Patients ≥60 years of age with mild-to-moderate Alzheimer's disease who were previously treated with oral rivastigmine	N=142 3 months	Primary: Gastrointestinal adverse events Secondary: Overall tolerance, local tolerance for those patients on patches, satisfaction level, and cognitive state by MMSE	Primary: Gastrointestinal adverse events were reported in <5% of patients receiving patches (4.7% in RPT and 4.3% in RP) vs 6.1% in RO patients. No statistical significance was reached (P=0.8667). Gastrointestinal adverse events were noted in 11 cases, two in RPT patients, six in RP patients, and three in the RO patients (P=0.3067). Secondary: Overall tolerability did not reveal any significant differences among the groups (P=0.8239). Local tolerability revealed skin or subcutaneous tissue adverse events reported in 11.6% of patients in the RPT group vs 17% of patients in the RP group (P=0.4055). All skin adverse events were reported as slight or moderate intensity. RP was defined by 72% of patients as very easy to use, while RO was considered very easy to use by 30% of patients (P=0.0005). In RP patients, 67% considered it very easy to follow compared to 19% of RO patients (<0.0001). A total of 72% of RP patients confirmed the treatment never interfered with their daily lives vs 40% of the RO group (P=0.0085). Overall satisfaction comparisons revealed that in RP patients, 60% were very satisfied vs 14% in RO patients (P<0.0001). MMSE did not demonstrate significant differences among treatment groups when compared at one and three month visits.
Winblad et al.[76] (2007) Rivastigmine patch 9.5 mg/24 hours	DD, PC, RCT Patients 50 to 85 years of age with MMSE scores of 10	N=1,195 Dose titration in 4-week intervals over	Primary: ADAS-Cog subscale (assess orientation, memory, language,	Primary: Patients in all rivastigmine groups (patch and capsule) showed significant improvements compared to placebo at week 24 with respect to ADAS-Cog and the ADCS-CGIC (all P<0.05 vs placebo).

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vs rivastigmine patch 17.4 mg/24 hours vs rivastigmine 12 mg/day vs placebo	to 20 diagnosed with Alzheimer's disease, all patients were required to be living with someone or to be in daily contact with a caregiver	16 weeks and maintained at their highest well-tolerated dose for a further 8 weeks, total of 24 weeks	visuospatial and praxis function), ADCS-CGIC (assess single global rating) Secondary: ADCS-ADL, MMSE, NPI, Ten Point Clock-drawing Test, and Trail-making Test part A	Secondary: All rivastigmine groups (patch and capsule) showed statistically significant benefits over placebo on the ADCS-ADL, MMSE and Trail-making Test part A (all P<0.05 vs placebo). Statistically significant treatment effects were not attained on the NPI or Ten Point Clock-drawing Test (P value not reported).
Winblad, Kawata et al.[77] (2007) 10 cm^2 rivastigmine patch (9.5 mg/24 hours) vs 20 cm^2 rivastigmine patch (17.4 mg/24 hours) vs rivastigmine 6 mg capsules twice daily vs placebo	DB, DD, PC ACs included different size rivastigmine patches and rivastigmine capsules	N=1,059 24 week	Primary: ADCPQ Secondary: Not reported	Primary: At 8 weeks, general preference was seen for the patch: 68% of caregivers preferred the patch over capsule form (P<0.0001). 70% of caregivers preferred the patch due to ease of schedule (P<0.0001). 55% of caregivers preferred the patch due to ease of use (P=0.0008). At 24 weeks, general preference was seen for the patch: 72% of caregivers preferred the patch over capsule form (P<0.0001). 74% of caregivers preferred the patch due to ease of schedule (P<0.0001). 64% of caregivers preferred the patch due to ease of use (P<0.0001). Caregivers preferred the patch over capsule dosage form, regardless of size of patch (P<0.0001). At 8 weeks, caregivers indicated greater satisfaction overall (P<0.0001), greater satisfaction with administration (P<0.0001), less interference with daily life with the patch than the capsule (P<0.01). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Winblad et al.[78] (2007) Rivastigmine patch 9.5 mg/24 hours vs rivastigmine patch 17.4 mg/24 hours vs rivastigmine 12 mg/day vs placebo	DB, DD, MC, PG Women or men 50 to 85 years of age with a diagnosis of dementia of the Alzheimer's type according to the DSM-IV, and probable Alzheimer's disease	N=1,195 24 weeks	Primary: ADAS-Cog, ADCS-CGIC Secondary: ADCS-ADL scale; NPI for behavior and psychiatric symptoms; MMSE for cognition; Ten Point Clock-drawing Test for assessment of visuospatial and executive functions; Trail Making Test Part A for assessment of attention, visual tracking and motor processing speed	Primary: Patients receiving rivastigmine patches or capsules showed significant benefits compared to placebo at week 24 on the ADAS-Cog subscale (P<0.05 vs placebo for all rivastigmine groups). Treatment differences on the ADCS-CGIC were statistically significant for the 10 cm² patch and capsule group (all P<0.05 vs placebo). The 20 cm² patch did not achieve statistical significance compared to placebo in the analysis (P=0.054). Secondary: Rivastigmine patches and capsule provided statistically significant benefits over placebo on the ADCS-ADL, MMSE and Trail-making Test A (all P<0.05 vs placebo). Changes from baseline on the NPI, NPI-distress subscale, and Ten-point Clock-drawing Test in the rivastigmine groups were not significantly different from those in the placebo groups (all P>0.05).
Blesa et al.[79] (2007) Rivastigmine patch 9.5 mg/24 hours vs rivastigmine patch 17.4 mg/24 hours vs rivastigmine 12 mg/day	DB, DD, PC ACs included different size rivastigmine patches and rivastigmine capsules, caregiver preference based on data generated during the IDEAL trial (Winblad et al)	N=1,059 24 week	Primary: ADCPQ Secondary: Not reported	Primary: At 8 weeks, general preference was seen for the patch: 68% of caregivers preferred the patch over capsule form (P<0.0001). 70% of caregivers preferred the patch due to ease of schedule (P<0.0001). 55% of caregivers preferred the patch due to ease of use (P=0.0008). At 24 weeks, general preference was seen for the patch: 72% of caregivers preferred the patch over capsule form (P<0.0001). 74% of caregivers preferred the patch due to ease of schedule (P<0.0001). 64% of caregivers preferred the patch due to ease of use (P<0.0001). Caregivers preferred the patch over capsule dosage form, regardless of size of patch (P<0.0001). At eight weeks, caregivers indicated greater satisfaction overall (P<0.0001), greater satisfaction with administration (P<0.0001), less interference with daily life with the patch than the capsule (P<0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				Secondary: Not reported
Farlow et al.[80] (2011) Rivastigmine patch 9.5 mg/24 hours vs rivastigmine patch 17.4 mg/24 hours vs rivastigmine 12 mg/day vs placebo	RETRO Patients with mild-to-severe Alzheimer's disease	N=1,050 24 weeks	Primary: ADAS-cog, ADCS-CGIC, and ADCS-ADL Secondary: Not reported	Primary: In patients with moderate disease, there was a significant improvement on ADAS-cog scores with the rivastigmine 17.4 mg/24 hour patch (P=0.0009) and rivastigmine capsule (P=0.0128). For patients with moderately severe disease, there was a significant improvement in ADAS-cog scores with the rivastigmine 17.4 mg/24 hour patch (P=0.006), rivastigmine 9.5 mg/24 hour patch (P=0.0163), and rivastigmine capsule (P=0.0071) compared to placebo. For patients with severe disease, there was a significant improvement on ADCS-CGIC scores with the rivastigmine 9.5 mg/24 hour patch (P=0.037) and rivastigmine capsule (P=0.0073) compared to placebo. For patients with moderately severe disease, there was a significant improvement on ADCS-CGIC scores with the rivastigmine 17.4 mg/24 hour patch (P=0.043) and rivastigmine 9.5 mg/24 hour patch (P=0.0116) compared to placebo. Significant improvement on ADCS-CGIC scores were seen with the rivastigmine 17.4 mg/24 hour patch in patients with moderate disease (P=0.03) and mild to moderate disease (P=0.0455) compared to placebo. For patients with moderately severe disease, there was a significant improvement on ADCS-ADL scores with the rivastigmine 17.4 mg/24 hour patch (P=0.0211) compared to placebo. For patients with moderate disease, there was a significant improvement on ADCS-ADL scores with the rivastigmine 17.4 mg/24 hour patch (P=0.0194) and rivastigmine capsule (P=0.0077) compared to placebo. There was no significant difference in ADCS-ADL scores among the treatment groups in patients with severe AD.
Choi et al.[81]	MC, OL, RCT	N=172	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2011) Rivastigmine patch 4.6 mg/24 hours for 4 weeks, then rivastigmine patch 9.5 mg/24 hours for 4 weeks, then rivastigmine patch 9.5 mg/24 hours and memantine 5 mg/day titrated to 20 mg/day vs rivastigmine patch 9.5 mg/24 hours	Patients with mild-to-moderate Alzheimer's disease	24 weeks	Tolerability Secondary: Efficacy as measured by CMAI-K, ADAS-cog, K-MMSE, FAB, CGA-NPI, ADCS-ADL and CDR-SB scores	The incidence of adverse events (53.4 vs 50.6%) and discontinuation due to adverse events (6.8 vs 4.8%) was not different between patients with and without memantine, respectively. The most common adverse events were skin irritation in both treatment groups (42 vs 34.9%; P=0.71), but discontinuation was rare (4.5 vs 2.4%; P=0.74). Secondary: CMAI-K scores favored rivastigmine monotherapy vs combination therapy at the end of treatment (P=0.01). Changes in other efficacy measures (ADAS-cog, K-MMSE, FAB, CGA-NPI, ADCS-ADL and CDR-SB) were not significantly different.
Farlow et al.[82] (2010) Rivastigmine patch 9.5 mg/24 hours and memantine vs rivastigmine patch 9.5 mg/24 hours	OL, RCT Patients ≥50 years of age with mild-to-moderate Alzheimer's disease who had been receiving donepezil for at least 6 months and at a stable dose of 5-10 mg/day for a minimum of 3 months	N=261 25 weeks	Primary: Safety and tolerability of rivastigmine transdermal patch, with or without concomitant memantine Secondary: Changes in cognition, global functioning and activities of daily living measured by MMSE and ADCS-ADL using the CGIC	Primary: The incidences of adverse events (73.3 vs 67.5%) and serious adverse events (10.4 vs 7.1%) were both slightly higher in patients receiving concomitant memantine, but the differences were NS (95% CIs, -5.2 to 16.9 and -3.6 to 10.1 for adverse events and serious adverse events, respectively). The most frequent adverse events in the combination therapy group and the rivastigmine monotherapy group were application site reactions (17.5 vs 13.5%, respectively) and agitation (5.9 vs 7.9%, respectively). Secondary: Concomitant memantine was associated with no significant changes in efficacy, as assessed by CGIC and MMSE scores. Global functioning remained unchanged or improved (CGIC rating ≤4) in 57.7 and 67.2% of patients with memantine and patients without memantine, respectively (P=0.604). ADCS-ADL scores deteriorated from baseline in both groups, with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				significant worsening in patients receiving memantine compared to those not receiving memantine (mean change from baseline rivastigmine and memantine vs rivastigmine monotherapy: -5.3 vs -2.0; P=0.043).
Harry et al.[83] (2005) Donepezil with doses ranging from 5 to 10 mg/day or galantamine with doses ranging from 8 to 36 mg/day vs placebo	MA Patients with mild-to-moderate Alzheimer's disease, and without diagnosis of any other psychiatric or neurological disorder	N=3,353 3 donepezil studies 5 galantamine studies Duration varied	Primary: ADAS-Cog or MMSE Secondary: Not reported	Primary: The majority of patients showed no difference compared to placebo. There was no significant difference in efficacy between the groups. Secondary: Not reported
Wilcock et al.[84] (2003) Donepezil 10 mg/day vs galantamine 24 mg/day	MC, PG, RCT Patients with Alzheimer's disease	N=182 52 weeks	Primary: BrADL Secondary: MMSE, ADAS-Cog, NPI	Primary: BrADL total score showed no significant difference between treatment groups in mean change from baseline to week 52. Secondary: Galantamine patients' scores on the MMSE at week 52 did not differ significantly from baseline, whereas donepezil patients' scores deteriorated significantly from baseline (P<0.0005).The between group difference in MMSE change did not reach statistical significance. In the ADAS-Cog analysis, between group differences for the total population were NS, whereas galantamine treated patients with MMSE scores of 12 to 18 demonstrated an increase (worsening) in the ADAS-Cog score of 1.61+/-0.80 vs baseline, compared to an increase of 4.08+/-0.84 for patients treated with donepezil. More caregivers of patients receiving galantamine reported reductions in burden compared to donepezil.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Changes from baseline in NPI were similar for both treatments.
Jones et al.[85] (2004) Donepezil 10 mg/day vs galantamine 12 mg twice daily	OL, RCT Patients with Alzheimer's disease	N=120 12 weeks	Primary: Ease of use and tolerability, ADAS-Cog, effects on cognition and activities of daily living Secondary: Not reported	Primary: Physicians and caregivers reported statistically significant greater satisfaction/ ease of use with donepezil compared to galantamine at weeks four and 12. Significantly greater improvements in cognition were observed for donepezil vs galantamine on the ADAS-Cog at week 12 and at endpoint. Activities of daily living improved significantly in the donepezil group compared to the galantamine group at weeks four and 12 (P<0.05). Forty-six percent of galantamine patients reported gastrointestinal adverse events vs 25% of donepezil patients. Secondary: Not reported
Modrego et al.[86] (2010) Donepezil 10 mg/day vs memantine 20 mg/day	PG, RCT, SB Patients with mild-to-moderate Alzheimer's disease	N=63 6 months	Primary: ADAS-cog, NPI, DAD, changes in N-acetylaspartate metabolite levels Secondary: Not reported	Primary: There were no significant differences in the clinical scales with donepezil and memantine (donepezil: ADAS-cog, -0.12; P=NS, NPI, -0.04; P=NS, DAD, 6.67; P=0.014) (memantine: ADAS-cog, -1.37; P=NS, NPI, 1.25; P=NS, DAD, 4.46; P=NS). More patients worsened than improved on either drug. Daily living activities decreased by 4.4% in the memantine group and 6.6% in the donepezil group (P=0.6). At baseline, N-acetylaspartate/Cr ratio in the PCG correlated significantly with the ADAS-cog (P=0.02) and MEC (P=0.02). The N-acetylaspartate/Cr ratio correlated with the baseline ADAS-cog (P=0.02) in the left temporal lobe. At week 24, the PCG was the only area where the correlation was significant. The patients who improved in the ADAS-cog showed increases in the N-acetylaspartate/Cr ratios (P=0.004). None of the baseline metabolite levels predicted response to treatment in any of the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				examined areas. Secondary: Not reported
Wilkinson et al.[87] (2002) Donepezil 10 mg/day vs rivastigmine 6 mg twice daily	OL, RCT Patients with mild-to-moderate Alzheimer's disease	N=111 12 weeks	Primary: ADAS-Cog, tolerability Secondary: Not reported	Primary: More patients taking donepezil completed the study (89.3%) compared to the rivastigmine group (69.1%; P=0.009). 10.7% of the donepezil group and 21.8% of the rivastigmine group discontinued treatment due to adverse events. 87.5% of the donepezil patients and 47.3% of the rivastigmine patients remained on the maximum approved dose of each drug at the last study visit. Both groups showed comparable improvements in ADAS-Cog administered at weeks four and 12. Secondary: Not reported
Van Puyvelde et al.[88] (2011) Galantamine vs donepezil or rivastigmine (safety control group)	MC, OS, PRO Patients with mild-to-moderate Alzheimer's disease	N=128 6 months	Primary: Safety, patients and caregiver satisfaction, global impression as reported by the physician Secondary; Not reported	Primary: Adverse events were similar among both treatment groups (galantamine, 34%; SCG, 34.4%). The incidence of serious (12 events) and severe (15 events) adverse events with galantamine was similar to the SCG group (serious: galantamine 9.3% vs safety control group 9.7%); severe: galantamine 11.3% vs safety control group 12.9%. A total of 84.5% of patients treated with galantamine continued their treatment after six months. Patients receiving galantamine reported their condition as improved (49%), unchanged (47%) and worsened (4%). Caregivers rated global evaluation as better (37%), unchanged (41%) and worse (22%) with galantamine. Physicians rated global clinical impression of change as better (46%),

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				unchanged (34%) and worse (20%) with galantamine. Measurements of cognition and behavior remained stable. The appreciation of physicians and caregivers corresponded well (P<0.001). Secondary: Not reported
Tariot et al.[89] (2004) Memantine 20 mg/day vs donepezil	DB, MC, PC, RCT Patients with moderate-to-severe Alzheimer's disease who received stable doses of donepezil	N=404 24 weeks	Primary: SIB, ADCS-ADL, CIBIC-Plus, BGP Secondary: Not reported	Primary: A significantly greater therapeutic effect was observed in the memantine group than in the placebo group on the ADCS-ADL, SIB and CIBIC-Plus. Patients receiving memantine in combination with donepezil demonstrated significantly less decline in ADCS-ADL scores compared to patients receiving donepezil-placebo over the 24-week study period (P=0.02). Patients receiving memantine showed significantly less cognitive decline in SIB scores compared to patients receiving placebo. Therapy with memantine-donepezil resulted in sustained cognitive performance above baseline compared to the progressive decline seen with the donepezil-placebo treatment. The change in total mean scores favored memantine vs placebo for the CIBIC-Plus (possible score range was 1-7), 4.41 vs 4.66, respectively (P=0.03). Treatment discontinuations due to adverse events for memantine vs placebo were 7.4% of the patients compared to 12.4%. Secondary: Not reported
Bullock et al.[90] (2005) Rivastigmine 3 to 12 mg/day vs	DB, MC, RCT Patients 50 to 85 years of age with moderate to moderately-severe Alzheimer's disease	N=994 24 months	Primary: SIB Secondary: GDS, ADCS-ADL, MMSE, NPI	Primary: Donepezil-treated patients declined 9.91 points from baseline on the SIB as compared to rivastigmine-treated patients, who declined by 9.30 points (P=NS). Secondary: Rivastigmine was more effective than donepezil on the ADCS–ADL, on

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donepezil 5 to 10 mg/day	(MMSE score 10-20)			which there was a between-treatment difference of 2.1 points after two years (P=0.007), and greater efficacy on the GDS (P=0.049). There were no significant differences in MMSE and NPI between the treatment groups. More patients receiving rivastigmine reported 'any adverse event' compared to those receiving donepezil during the titration phase (82.0 and 64.7%, respectively). Adverse events were higher with rivastigmine during the titration phase and included nausea (32.9 vs 15.2%) and vomiting (27.9 vs 5.8%). In the maintenance phase, adverse event rates in the two groups were similar (78.7% for the rivastigmine group and 76.9% for the donepezil group). Premature discontinuations due to adverse events were higher in the rivastigmine group during the titration phase (14.1 vs 7.0% for donepezil) but similar in the maintenance phase (17.9 vs 14.1% for donepezil).
Mossello et al.[91] (2004) Donepezil 5 to 10 mg/day vs galantamine 16 to 24 mg/day vs rivastigmine 6 to 12 mg/day	OL, OS Patients with mild-to-moderate Alzheimer's disease	N=407 9 months	Primary: MMSE, ADL and IADL Secondary: Not reported	Primary: There were no differences amongst the three groups in regards to any of the outcome measures (galantamine was not included in the MMSE comparison due to the small number of treated patients). Discontinuation due to adverse effects was lower in those patients on donepezil (3%) vs rivastigmine (17%; P=0.01) and vs galantamine (21%; P=0.01). Secondary: Not reported
Aguglia et al.[92] (2004) Donepezil vs	OL Patients with Alzheimer's disease	N=242 6 months	Primary: MMSE, ADAS-Cog, ADL and IADL Secondary: Not reported	Primary: There were no statistical differences on changes in the MMSE, ADAS-Cog, ADL or IADL measures amongst the three groups. There were no differences on changes in the IADL measure among the three groups.

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galantamine vs rivastigmine				In the ADL measure, donepezil and galantamine patients showed a decrease while there was no change for rivastigmine patients. Rivastigmine showed a small numerical advantage (but not statistically) compared to donepezil and galantamine on the ADAS-Cog. Secondary: Not reported
Lopez-Pousa et al.[93] (2005) Donepezil vs galantamine vs rivastigmine vs historical controls	OL, PRO Patients with mild-to-moderate Alzheimer's disease	N=147 6 months	Primary: MMSE Secondary: Not reported	Primary: All three treatment groups had better MMSE scores compared to control (donepezil; P<0.001, galantamine; P<0.01, and rivastigmine; P<0.03). There were no statistical differences between the groups on measures of cognitive decline (via MMSE). Secondary: Not reported
Rodda et al.[94] (2009) Donepezil 5 to 10 mg/day vs galantamine 8 to 24 mg/day vs	RETRO Patients with Alzheimer's disease being treated with donepezil, rivastigmine or galantamine monotherapy	N=6,110 12 to 170 weeks	Primary: NPI Secondary: Not reported	Primary: Three of the 14 studies reviewed reported statistically significant improvement in overall NPI score or in the agitation/aggression item of the NPI only. One study demonstrated a significant difference in NPI score between groups randomized to either continuation or discontinuation of donepezil (placebo following an initial OL treatment phase. Of these four positive studies, two specified a minimum level of behavioral disturbance at baseline and used behavioral scores as a primary outcome. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
rivastigmine 9 to 17.4 mg/day				
Howard et al.[95] (2012) Donepezil 10 mg/day vs memantine 20 mg/day vs donepezil 10 mg/day and memantine 20 mg/day vs placebo	DB, MC, RCT Community-based patients with moderate-to-severe Alzheimer's disease who were taking donepezil 10 mg/day for ≥3 months	N=295 52 weeks	Primary: Standardized Mini-Mental State Examination and BADLS scores Secondary: NPI, caregiver health status assessed by General Health Questionnaire 12	Primary: Mean donepezil vs placebo Standardized Mini-Mental State Examination scores were higher with donepezil (better cognitive function) by an average of 1.9 points (95% CI, 1.3 to 2.5; P<0.001) and BADLS scores were lower (less functional impairment) by 3.0 points (95% CI, 1.3 to 2.5; P<0.001). Both outcomes demonstrated significant heterogeneity in treatment efficacy over tome (P=0.002 and P=0.004, respectively), with less benefit apparent at the six week assessment than at later time points. From six weeks onward, differences were roughly parallel. Mean donepezil+memantine vs placebo+memantine Standardized Mini-Mental State Examination scores were higher with donepezil by an average of 1.2 points (95% CI, 0.6 to 1.8; P<0.001) and BADLS scores were lower by 1.8 points (95% CI, 0.3 to 2.8; P<0.001). Both outcomes were smaller than the minimum clinically important difference. Interactions of memantine therapy with visit were NS. Both donepezil and memantine demonstrated benefits on both Standardized Mini-Mental State Examination and BADLS larger in the absence of other agents alone, though statistically insignificant (P=0.14 and P=0.09, respectively). No significant benefits were seen adding memantine to donepezil on Standardized Mini-Mental State Examination scores (0.8 points higher with memantine and placebo; 95% CI, -0.1 to 1.6; P=0.07) or BADLS scores (0.5 points lower with memantine than placebo; 95% CI, 2.2 to 1.2; P=0.57). Secondary: NPI scores were lower for patients on memantine compared to placebo, indicating fewer behavioral and psychological symptoms by 4.0 points (99% CI, 0.6 to 7.4; P=0.002). No observable NPI differences noted with continuation, as compared to discontinuation of donepezil therapy (2.3 points lower with continuation; 95% CI, -1.1 to 5.7; P=0.08). Donepezil+memantine vs donepezil

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				demonstrated a lower NPI score by 5.1 points (99% CI, 0.3 to 9.8; P=0.006). Continuation of donepezil and donepezil+memantine compared to the placebo and memantine + placebo demonstrated larger average decreases (indicating fewer psychological symptoms) across trial visits in General Health Questionnaire 12 scores for caregiver health status. There was a 0.5 point larger decrease with continuation vs discontinuation of donepezil (99% CI, -0.01 to 1.0; P=0.01) and 0.5 point larger decrease with memantine vs placebo (95% CI, -0.1 to 0.9; P=0.03), though significance was not reached to allow for multiple secondary outcomes.
Porsteinsson et al.[96] (2008) Memantine 20 mg/day plus cholinesterase inhibitor vs cholinesterase inhibitor plus placebo	PC, R Patients with probable Alzheimer's disease, MMSE scores between 10 to 22, concurrently taking a cholinesterase inhibitor	N=433 24 weeks	Primary: ADAS-cog, CIBIC-Plus Secondary: ADCS-ADL, NPI, MMSE	Primary: No significant difference in ADAS-cog and CIBIC-Plus was found between memantine and placebo. Secondary: No significant difference in ADCS-ADL, NPI or MMSE was found between memantine and placebo.
Cumming et al.[97] (2006) Memantine 20 mg/day plus donepezil vs donepezil	DB, PC, PG, PRO Patients with moderate-to-severe Alzheimer's disease who received stable doses of donepezil	N=404 24 weeks	Primary: NPI Secondary: Not reported	Primary: NPI scores significantly favored the memantine group at 12 weeks and at 24 weeks. At week 12, NPI scores increased (worsening behavior) 1.7 points in the placebo group and decreased 2.5 points in the memantine group (P<0.001). At week 24, NPI scores increased 3.7 points (worsening behavior) in the placebo groups and the memantine group returned to baseline (P=0.002). Fewer patients developed delusions in the memantine treatment group than the placebo group (P=0.011). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Maidment et al.[98] Memantine 20 mg daily vs placebo or memantine 20 mg daily in combination with a cholinesterase inhibitor (doses varied) vs placebo in combination with a cholinesterase inhibitor (doses varied)	MA Patients with probable Alzheimer's disease	N=1,750 Duration varied	Primary: NPI Secondary: Not reported	Primary: Compared to the placebo group patients receiving memantine improved by 1.99 on the NPI scale (95% CI, -0.08 to -3.91; P=0.041). Secondary: Not reported
Wilkinson et al.[99] (2009) Cholinesterase inhibitors (donepezil 5 or 10 mg/day) vs placebo	MA Patients with mild-to-moderate Alzheimer's disease	N=906 (3 trials) 24 weeks	Primary: MMSE Secondary: Not reported	Primary: A significantly greater percentage of placebo patients than donepezil-treated patients met the specified criteria for all three definitions of clinical worsening. The OR for clinical worsening were significantly reduced for donepezil-treated patients compared to placebo patients (P<0.0001 for all definitions). Among patients meeting criteria for clinical worsening, mean declines in MMSE scores were greater for placebo than donepezil-treated patients. This outcome was also apparent when milder (MMSE, 18 to 26) and more

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				moderate (MMSE, 10 to 17) subgroups were analyzed separately. Secondary: Not reported
Feldman et al.[100] (2009) Cholinesterase inhibitors	OS, PRO Alzheimer's disease patients with and without cerebrovascular disease	N=548 7 years	Primary: Time to nursing home placement Secondary: Identify factors noted to reduce risk of NHP, including measurement of DAD and MMSE	Primary: The overall median time to permanent institutional admission was 42.4 months (95% CI, 38.0 to 48.0 months). Secondary: Factors noted to reduce the risk of being admitted to a nursing home included higher baseline DAD and MMSE scores, Alzheimer's disease diagnosis, living with caregiver, country, and treatment duration (P<0.05). Each year of treatment demonstrated a reduced risk of nursing home admission (galantamine, -31%, other cholinesterase inhibitors, -29%).
Trinh et al.[101] (2003) Cholinesterase inhibitors vs placebo	MA Trials included outpatients with mild or moderate Alzheimer's disease who were treated for at least one month with a cholinesterase inhibitor	29 trials Duration varied	Primary: NPI, ADAS-noncog, ADL and IADL Secondary: Not reported	Primary: Cholinesterase inhibitors improved the NPI statistically better than placebo (95% CI, 0.87 to 2.57). Cholinesterase inhibitors improved the ADAS-noncog measure numerically but not statistically compared to placebo (95% CI, 0.0 to 0.05). Cholinesterase inhibitors improved ADL numerically but not significantly better than placebo (95% CI, 0.0 to 0.19). Cholinesterase inhibitors improved IADL statistically compared to placebo (95% CI, 0.01 to 0.17). Secondary: Not reported
Lanctot et al.[102] (2003) Cholinesterase inhibitors	MA Adult patients diagnosed with Alzheimer's disease	N=7,954 16 trials that varied in duration	Primary: Global responders, using CGI-C, CIBIC, adverse, events, dropouts	Primary: For cholinesterase inhibitors the pooled mean proportion of global responders was in excess by 9% when compared to the placebo treatment (9%; 95% CI, 6 to 12). In the cholinesterase inhibitor treatment groups the rates of adverse events,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo			Secondary: Not reported	dropout for any reason and dropout because of adverse events were higher compared to the placebo treatment groups (8%; 95% CI, 5 to 11; 8%; 95% CI, 5 to 11; and 7%; 95% CI, 3 to 10). The number needed to treat for one additional patient to benefit was 7 (95% CI, 6 to 9) for stabilization or better, 12 (95% CI, 9 to 16) for minimal improvement or better and 42 (95% CI, 26 to 114) for marked improvement. The number needed to treat for one additional patient to experience an adverse event was 12 (95% CI, 10 to 18). Secondary: Not reported
Birks et al.[103] (2006) Cholinesterase inhibitors vs placebo	MA Patients diagnosed with mild, moderate or severe dementia due to Alzheimer's disease	N=7,298 Minimum 6 months	Primary: CIBIC-Plus, GBS, GDS, ADAS-Cog, MMSE, SIB, NPI, ADL scored by PDS and DAD Secondary: Withdrawals prior to six months, adverse events	*Cholinesterase inhibitor vs placebo (12 trials)* Primary: Significant benefit was seen in CIBIC-Plus for patients treated with a cholinesterase inhibitor over placebo; more patients were scored as "showed improvement" than "showed decline/no change" (OR, 1.56; 95% CI, 1.32 to 1.85; P<0.00001): eight studies. No significant difference was seen in GBS between the cholinesterase inhibitor and placebo groups at one year (P value not reported): one trial. Significant improvement in ADAS-Cog was found for patients treated with donepezil, galantamine, or rivastigmine over placebo (WMD, –2.66; 95% CI, –3.02 to –2.31; P<0.00001): 10 studies. Significant benefit was seen in MMSE for patients treated with a cholinesterase inhibitor over placebo (WMD, 1.37; 95% CI, 1.13 to 1.61; P<0.00001): nine studies. Significant benefit was seen in ADL-PDS and DAD for patients treated with a cholinesterase inhibitor over placebo (WMD, 2.40; 95% CI, 1.55 to 3.37; P<0.00001 for PDS; and WMD, 4.39; 95% CI, 1.96 to 6.81; P=0.0004 for DAD).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Significant benefit was seen in NPI for patients treated with a cholinesterase inhibitor over placebo (WMD, –2.44; 95% CI, –4.12 to –0.76; P=0.004). Secondary: Significantly more patients treated with a cholinesterase inhibitor (29%) withdrew prior to six months than those in the placebo groups (18%; P<0.00001). Adverse events that occurred significantly more frequently in the cholinesterase inhibitor group than the placebo group, from pooled data from at least 6 trials included: abdominal pain, anorexia, dizziness, diarrhea, headache (P<0.0001), insomnia (P=0.007), nausea, vomiting (P<0.00001 unless noted). *Donepezil vs rivastigmine (one trial)* Primary: There was no statistically significant difference between the treatment groups for cognitive function, ADL scales, behavior disturbances and global assessment (P values not reported). Secondary: Significantly fewer patients in the donepezil group withdrew from treatment after 2 years than in the rivastigmine group (OR, 0.64; 95% CI, 0.50 to 0.83; P=0.0006). Adverse events that occurred significantly more frequently at 12-16 weeks of treatment in the rivastigmine group than in the donepezil group included: nausea (P<0.00001), vomiting (P<0.00001), falls (P=0.01), hypertension (P=0.01), anorexia (P=0.0005) and weight loss (P=0.001), and after 16 weeks to 2 years of treatment: nausea (P=0.0002), vomiting (P<0.00001) and anorexia (P=0.02). No significant difference between treatment groups for serious adverse events was noted (P value not reported).
Hansen et al.[104] (2008)	MA	26 trials	Primary: Cognition (ADAS-	Primary: <u>Cognition (14 studies)</u>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Cholinesterase inhibitors	Patients with Alzheimer's disease	Variable duration	cog), function, behavior (NPI), global assessment of change (CIBIC+ and CGI-C) Secondary: Not reported	The pooled WMD in change between active treatment and placebo was -2.67 (95% CI -3.28 to -2.06) for donepezil, -2.76 (95% CI -3.17 to -2.34) for galantamine, and -3.01 (95% CI -3.80 to -2.21) for rivastigmine. <u>Function (14 studies)</u> The pooled standardized mean difference between active treatment and placebo was 0.31 (95% CI, 0.21 to 0.40) for donepezil, 0.27 (95% CI, 0.18 to 0.36) for galantamine, and 0.26 (95% CI, 0.11 to 0.40) for rivastigmine. <u>Behavior (seven studies)</u> The pooled WMD in NPI score between active treatment and placebo was -4.3 (95% CI, -5.95 to -2.65) for donepezil and -1.44 (95% CI, -2.39 to -0.48) for galantamine. <u>Global assessment of change (nine studies)</u> The pooled RR of responding for active treatment compared to placebo was 1.88 (95% CI, 1.50 to 2.34) for donepezil, 1.15 (95% CI, 0.96 to 1.39) for galantamine, and 1.64 (95% CI, 1.29 to 2.09) for rivastigmine. Secondary: Not reported
Kim et al.[105] (2011) Cholinesterase inhibitors	MA Cognitively impaired older adults	54 trials Variable duration	Primary: Falls, syncope, fracture and accidental injury reported Secondary: Not reported	Primary: Cholinesterase inhibitors usage was associated with the greatest risk of syncope compared to placebo (OR, 1.53; 95% CI, 1.02 to 2.30), but not with any other events: falls (OR, 0.88; 95% CI, 0.74 to 1.04); fracture (OR, 1.39; 95% CI, 0.75 to 2.56); accidental injury (OR, 1.13; 95% CI, 0.87 to 1.45). Memantine was associated with fewer fractures (OR, 0.21; 95% CI, 0.05 to 0.85), but not with other events: falls (OR, 0.92; 95% CI, 0.72 to 1.18), syncope (OR, 1.04; 95% CI, 0.35 to 3.04); accidental injury (OR, 0.80; 95% CI, 0.56 to 1.12). There were no differential effects noted according to type and severity of cognitive impairment, residential status, or length of follow-up.
Parkinson's Disease				
Emre et al.[106]	DB, MC, PC, RCT	N=541	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2004) Rivastigmine 3 to 12 mg/day; average dose 8.6 mg/day vs placebo	Patients at least 50 years of age with mild-to-moderate dementia developed 2 years after the diagnosis of Parkinson's disease	Dose titration over the first 16 weeks with a subsequent assessment period of 8 weeks Total of 24 weeks	ADAS-Cog, ADCS-CGIC Secondary: ADCS-ADL, NPI-10, MMSE, CDR power of attention tests, D-KEFS verbal fluency test, Ten Point Clock-drawing Test	Patients who were receiving rivastigmine had significant improvement of 2.1 points in the 70-point ADAS-Cog scores vs worsening of 0.7 point in the placebo group from baseline (P<0.001). 19.8% of patients in the rivastigmine group and 14.5% in the placebo group clinically improved in the ADCS-CGIC scores. 13% of patients in the rivastigmine group and 23.1% in the placebo group clinically worsened in the ADCS-CGIC scores (P=0.007). Secondary: All secondary outcomes were significantly better in the rivastigmine group compared to placebo, as reflected by the changes in the ADCS-ADL score (P=0.02), NPI-10 (P=0.02), MMSE (P=0.03), CDR power of attention tests (P=0.009), D-KEFS verbal fluency test (P<0.001), and the Ten Point Clock-drawing Test (P=0.02).
Wesnes et al.[107] (2005) Rivastigmine 3 to 12 mg/day, average dose 8.6 mg/day vs placebo	DB, MC, PC, RCT Patients at least 50 years old with Parkinson's disease	N=487 24 weeks	Primary: Power of attention, continuity of attention, cognitive reaction time, reaction time variability Secondary: Not reported	Primary: At week 16, there was no statistical significance from baseline scores between rivastigmine and placebo for power of attention (P=0.11) but there was a significance at week 24 (P<0.01). By week 16, there was a significant improvement with continuity of attention (P=0.001) compared to placebo and this parameter continued to improve at week 24 (P=0.0001). Cognitive reaction time showed significant improvement by the end of week 24 (P<0.001) vs week 16 (P=0.064) but declined with placebo. Reaction time variability continued to show improvement over placebo from week 16 (P<0.05) to week 24 (P<0.001). Secondary: Not reported
Schmitt et al.[108] (2010) Rivastigmine 3 to 12 mg/day	DB, MC, PC, RCT Patients with Parkinson's disease dementia	N=541 24 weeks	Primary: Executive function as assessed by D-KEFS measures	Primary: Rivastigmine was associated with significantly more correct responses, fewer set loss errors, and more total responses made (within time available), compared to placebo (all P<0.05). There was no significant difference in total repetition errors (P=0.57).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo			Secondary: Not reported	Rivastigmine was associated with a significantly higher Card Sorting recognition description score than placebo (P=0.03). Word reading errors, word comprehension, and sort recognition errors were NS. There were significantly more correct substitutions on the Symbol Digit Modalities Test compared to placebo (P=0.02). Rivastigmine was associated with significantly fewer self-corrected errors on the Color-Word Interference inhibition/switching subtest compared to placebo (P=0.049). Treatment differences in numbers of correct responses were near statistical significance (P=0.050). Other treatment differences in this battery of executive function tests were not statistically significant. Secondary: Not reported
Olin et al.[109] (2010) Rivastigmine 3 to 12 mg/day vs placebo	DB, MC, PC, RCT Patients ≥50 years of age with Parkinson's disease dementia	N=541 24 weeks	Primary: Tolerability and efficacy as measured by ADCS-ADL Secondary: Not reported	Primary: A total of 75.8% of patients completed the study (rivastigmine, 72.7% vs placebo, 82.1%). The primary reasons for discontinuation were adverse events (17.1% for rivastigmine vs 7.8% for placebo) and withdrawal of consent (5.8% rivastigmine vs 1.1% placebo). At 24 weeks, rivastigmine was associated with significantly less deterioration compared to placebo based on ADCS-ADL total scores (-1.1 vs -3.6, respectively; P=0.023). Similar improvement were seen with rivastigmine compared to placebo on the basic ADCS-ADL subscale (-0.5 vs -1.7, respectively; P=0.025), and on high level function ADLs (0.1 vs -1.0; P=0.017). No other measures were significantly different among the treatment groups. Secondary: Not reported
Maidment et al.[110] (2006) Rivastigmine 3 to 12 mg/day	MA Patients diagnosed with mild-to-moderately severe dementia, which	N=541 (1 study) 24 weeks	Primary: ADAS-Cog, ADCS-CGIC Secondary: MMSE, ADCS-	Primary: Significant improvement in ADAS-Cog was found for patients treated with rivastigmine over placebo (WMD, –2.80; 95% CI, –4.26 to –1.34; P=0.0002). Results in ADCS-CGIC significantly favored patients treated with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	developed at least 2 years after Parkinson's disease was diagnosed		ADL, NPI, CDR, D-KEFS, Ten Point Clock-drawing Test, UPDRS, adverse events	rivastigmine over placebo (WMD, –0.50; 95% CI, –0.77 to –0.23; P=0.0004). 19.8% of rivastigmine patients experienced "clinically meaningful (moderate or marked) improvement" compared to 14.5% of the placebo group; 13.0% of rivastigmine patients experienced "clinically meaningful worsening" compared to 23.1% in the placebo group (P values not reported). Secondary: Results for MMSE significantly favored patients treated with rivastigmine over placebo (WMD, 1.00; 95% CI, 0.33 to 1.67; P=0.003). Results for ADCS-ADL significantly favored patients treated with rivastigmine over placebo (WMD, 2.50; 95% CI, 0.43 to 4.57; P=0.02). Results for NPI significantly favored patients treated with rivastigmine over placebo (WMD, –2.00; 95% CI, –3.91 to –0.09; P=0.04). For CDR no statistically significant difference was found (P=0.25). For D-KEFS, results significantly favored patients treated with rivastigmine over placebo (WMD, 2.80; 95% CI, 1.47 to 4.13; P<0.0001). Full UPDRS was not reported. No statistically significant difference was found for motor score, including tremor (P=0.83 and P=0.84). Significantly more patients in the rivastigmine group than the placebo group experienced one or more adverse events (P=0.0006). Adverse events included: nausea, vomiting, tremor, and dizziness. Significantly more patients treated with rivastigmine withdrew from treatment for any reason than those treated with placebo (P=0.02).
Emre et al.[111] (2014) Rivastigmine capsules 6 mg twice daily	OL, PRO, RCT Patients 50 to 85 years of age with mild-to-moderately severe Parkinson	N=583 76 weeks	Primary: Incidence of predefined adverse events due to worsening Parkinson's	Primary: The incidence of adverse effects due to worsening motor symptoms in the capsule groups was 36.1% (95% CI, 30.6 to 41.8), with tremor the most commonly reported (24.5%; 95% CI, 19.7 to 29.8). Overall, 4.4% (95% CI, 2.4 to 7.4) of capsule-treated patients discontinued due to worsening motor symptoms.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs rivastigmine patch 9.5 mg/24 hours	disease dementia, which developed at least one year after Parkinson's disease was diagnosed		disease motor symptoms (tremor, rigidity, bradykinesia, and falls) and discontinuation rate due to predefined potential adverse effects with capsules Secondary: Same as primary but with patch Efficacy: Mattis Dementia Rating Scale, ADCS-ADL, NPI-10	Secondary: The incidence of adverse effects due to worsening motor symptoms in the patch group (31.9%; 95% CI, 26.6 to 37.7) was similar to capsules. Fewer patients experienced tremor with patch (9.7%; 95% CI, 6.6 to 13.7) compared to capsules. The incidences of bradykinesia, rigidity, and fall were similar between groups. The incidence of discontinuation due to worsening of motor symptoms was 2.4% (95% CI, 1.0 to 4.9) with patch. Efficacy: Improvements on Mattis Dementia Rating Scale and NPI-10 from baseline were observed in both groups at weeks 24 and 52. Deterioration in ADCS-ADL score from baseline was observed in both groups at all time points. The size of initial improvement on the Mattis Dementia Rating Scale and NPI-10 gradually declined in both groups; decline was greater in the patch group. In the overall population, there was a statistically significant difference in favor of capsules compared with patch at weeks 24 to 76 for MDRS; weeks 52 and 76 for ADCS-ADL; and weeks 24 and 76 for NPI-10.

Study abbreviations: AC=active control, CI=confidence interval, DB=double blind, DD=double dummy, ER=extended release, HR=hazard ratio, IR=immediate release, ITT=intent to treat, LOCF=last observation carried forward, MA=meta-analysis, MC=multicenter, NS=not significant, OL=open label, OR=odds ratio, OS=observational study, PC=placebo controlled, PG=parallel group, PP=per protocol, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk, SB=Single-blind, WMD=weighted mean difference

Efficacy Measures Key: ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive subscale, ADAS-cog/10=10-item cognitive subscale of the Alzheimer's Disease Assessment Scale, ADAS-cog/11=11-item cognitive subscale of the Alzheimer's Disease Assessment Scale, ADAS-cog/13=13-item cognitive subscale of the Alzheimer's Disease Assessment Scale, ADAS-cog/memory=Alzheimer's Disease Assessment Scale-Cognitive/Memory, ADAS-noncog=Alzheimer Disease Assessment Scale-Noncognitive, ADCPQ=Alzheimer's Disease Caregiver Preference Questionnaire, ADCS-ADL=Alzheimer's Disease Cooperative Study-Activities of Daily Living scale, ADCS-ADL-sev=Alzheimer Disease Cooperative Study-Activities of Daily Living-severe version, ADCS-CGIC=Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change, ADL=Activity of Daily Living, BADLS=Bristol Activities of Daily Living Scale, BEHAV-AD=Behavioral Pathology in Alzheimer's Disease Rating Scale, BGP=Behavioral Rating Scale for Geriatric Patients, BrADL=Bristol Activities of Daily Living Scale, CBQ=Caregiver Burden Questionnaire, CDR=Cognitive Drug Research, CDR-SB=Clinical Dementia Rating Scale-Sum of Boxes, CGA-NPI=Caregiver-Administered Neuropsychiatric Inventory, CGI-C=Clinical Global Impression of Change, CGI-I=Clinical Global Impression of Improvement scale, CIBIC=Clinician Interview-Based Impression of Change Scale, CIBIC-Plus=Clinician's Interview-Based Impression of Change Plus Caregiver Input, CMAI-K=Cohen Mansfield Agitation Inventory-Korean type, DAD=Disability Assessment, D-KEFS=Delis-Kaplan Executive Function System, ECG=electrocardiogram, FAB=Frontal Assessment Battery, FAST=Functional Assessment Staging, GBS=Gottfried-Bråne-Steen scale, GDS=Global Deterioration Scale, IADL=Instrumental Activity of Daily Living, IDDD=Interview for Deterioration in Daily Functioning Activities in Dementia, K-MMSE=Korean Mini-Mental Status Exam, MDS-ADL=Minimum Data Set-Activities of Daily Living, MMSE=Mini-Mental Status Exam, M-NCAS=Modified Nursing Care Assessment Scale, NPI=Neuropsychiatric Inventory, NPI-10=10-item Neuropsychiatric Inventory, QOL=quality of life, QoLS=Quality of Life Scale, PDS=Progressive Deterioration Scale, RUSP=Resource Utilization for Severe Alzheimer Disease Patients, SIB=Severe Impairment Battery, UPDRS=Unified Parkinson's Disease Rating Scale

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
The cholinesterase inhibitors exhibit similar pharmacologic properties, and evidence from comparative studies support a switch strategy when patients are intolerant to one drug or when a therapeutic dose cannot be reached.[112] Gauthier et al. reported that when switched from donepezil to rivastigmine, approximately 50% of those who had adverse events or a lack of efficacy with donepezil tolerated or responded well to rivastigmine.[113] Wilkinson et al. found no difference in tolerability when patients were switched from donepezil to galantamine using either a four-day washout period or a seven-day washout period.[114] Sadowsky et al. evaluated immediate switch (no washout) or delayed switch (seven-day washout) from oral donepezil to transdermal rivastigmine following a four-week treatment period with donepezil.[115] The authors found that the rates of discontinuation due to any reason or adverse events were similar between the treatment groups. They concluded that both switch strategies were safe and well tolerated. Sakka et al. evaluated patients with moderate-to-severe Alzheimer's disease who were switched to donepezil after experiencing a treatment failure or intolerance with memantine.[116] The authors concluded that donepezil was effective and well tolerated in patients who discontinued memantine monotherapy, including those patients with previous exposure to cholinesterase inhibitors. A post-hoc analysis of five-month trial data with galantamine demonstrated that patients had similar efficacy outcomes, whether or not they had received prior anticholinesterase therapy, suggesting that a previous failure did not predict response to galantamine.[117]

Impact on Physician Visits
Fillenbaum et al. evaluated the frequency of outpatient visits for patients with Alzheimer's disease.[118] Outpatient visit ranged from 81 to 95% and was not related to the stage of dementia or institutional status. Leibson et al. demonstrated that the onset of Alzheimer's disease is not associated with greater use of acute care services, nor is the high use of nursing home care offset by fewer emergency room or hospital encounters.[119] Clark et al. evaluated a telephone intervention program where healthcare professionals work with patients and caregivers to determine resources within the family of an Alzheimer's patient.[120] Alzheimer's patients in the program felt less embarrassed and isolated because of their memory problems and reported less problems coping with their disease. Intervention patients with more severe impairment had fewer physician visits, were less likely to have an emergency room visit or hospital admission, and had decreased depression and strain. Wimo et al. demonstrated that the use of memantine in patients with moderate-to-severe Alzheimer's disease was associated with less total caregiver time compared to placebo.[121] There were also fewer patients institutionalized at week 28 in the memantine group compared to placebo.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx

Relative Cost Index Scale	
$$$$$	Over $200 per Rx

Rx=prescription

Table 10. Relative Cost of the Alzheimer's Agents

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Parasympathomimetic (Cholinergic Agents)				
Donepezil	orally disintegrating tablet, tablet	Aricept®*, Aricept ODT®*	$$$$-$$$$$	$
Galantamine	extended-release capsule, solution, tablet	Razadyne®*, Razadyne ER®*	$$$$-$$$$$	$$$
Rivastigmine	capsule, solution, transdermal patch	Exelon®*	$$$$$	$$$$$
Central Nervous System Agents, Miscellaneous				
Memantine	extended-release capsule, solution, tablet	Namenda®*, Namenda XR®	$$$$$	$
Combination Products				
Memantine and donepezil	extended-release capsule	Namzaric®	$$$$$	N/A

*Generic is available in at least one dosage form or strength.
N/A=Not available.

X. Conclusions

The cholinesterase inhibitors are approved for the treatment of mild-to-moderate Alzheimer's disease. Donepezil is also approved for the treatment of severe disease. The N-Methyl-D-aspartate (NMDA) receptor antagonist, memantine, has only been approved for the treatment of moderate-to-severe Alzheimer's disease. Although these agents provide symptomatic benefit, they have not been shown to delay the progression of neurodegeneration. All products with the exception of memantine-donepezil are available in a generic formulation.

There are several guidelines which discuss the role of these agents in the management of Alzheimer's disease.[15-19] The primary goal of treatment is to delay the progression of symptoms and preserve functional ability.[17] The use of a cholinesterase inhibitor may lead to modest improvements in some patients; therefore, it is appropriate to offer a trial of one of these agents for patients with mild-to-moderate disease.[16-17] Memantine can be considered for the treatment of patients with moderate-to-severe disease and it may be prescribed as monotherapy or in combination with a cholinesterase inhibitor.[17] Guidelines do not give preference to one agent over another. Clinicians should base the treatment decision on tolerability, adverse events, and ease of use.[16]

Numerous clinical trials have evaluated the efficacy and safety of the cholinesterase inhibitors and memantine. Several outcomes have been assessed (using more than 40 different instruments), including cognition, global function, behavior, and quality of life. There is consistent evidence from well-designed studies that donepezil, galantamine, rivastigmine, and memantine positively affect cognition and global function, although the improvements are modest. The findings are less consistent for other outcomes, including behavior and quality of life. In most cases, the duration of these clinical trials were less than one year. Thus, there is insufficient evidence to determine the optimal duration of therapy.[16-17] There are relatively few studies that directly compare the efficacy and safety of the Alzheimer's agents. Most of the trials have compared active treatment to placebo or no treatment. The studies also differ with regards to design, patient population, and treatment duration, which make it difficult to compare the results.[20-111]

There is insufficient evidence to support that one brand Alzheimer's agent is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand Alzheimer's agents within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand Alzheimer's agent is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
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I. Overview

The antidepressants are approved to treat a variety of mental disorders, including anxiety disorders, depressive disorders, eating disorders (bulimia nervosa), and premenstrual dysphoric disorder.[1-34] Anxiety disorders include agoraphobia, anxiety disorder due to another medical condition, generalized anxiety disorder, other specified anxiety disorder, panic disorder, selective mutism, separation anxiety disorder, social anxiety disorder or social phobia, specific phobia, substance/medication induced anxiety disorder, and unspecified anxiety disorder.[35] Some of the antidepressants are also approved to treat nonpsychiatric conditions, such as chronic musculoskeletal pain, diabetic peripheral neuropathy, fibromyalgia, insomnia, moderate to severe vasomotor symptoms associated with menopause, nocturnal enuresis, and tobacco abuse.[1-34]

The antidepressants are categorized into six different American Hospital Formulary Service (AHFS) subclasses, including monoamine oxidase inhibitors (MAOIs), selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs), selective serotonin-reuptake inhibitors (SSRIs), serotonin modulators, tricyclic antidepressants (TCAs), and miscellaneous agents. The agents which make up these subclasses differ with respect to their Food and drug Administration (FDA)-approved indications, mechanism of action, pharmacokinetics, adverse events, and drug interactions.

Monoamine oxidase is an enzyme that is distributed in various tissues throughout the body. This enzyme is responsible for the catabolism of monoamines ingested in food, as well as for the inactivation of neurotransmitters (e.g., serotonin, norepinephrine, and dopamine).[1,2] MAOIs increase the concentration of these neurotransmitters, which leads to their antidepressant activity. There are two types of monoamine oxidase, including MAO-A and MAO-B. The MAOIs differ with regards to selectivity for MAO receptor type and reversibility.[3-6] The SNRIs are potent inhibitors of neuronal norepinephrine and serotonin reuptake.[7-10] The SSRIs inhibit the neuronal uptake of serotonin and have minimal effects on norepinephrine or dopamine neuronal uptake.[11-20] The clinical efficacy of the SNRIs and SSRIs is thought to be related to the potentiation of neurotransmitter activity in the central nervous system. The exact mechanism of action of the serotonin modulators is unknown. Nefazodone inhibits neuronal uptake of serotonin and norepinephrine, and is a direct antagonist of serotonin ($5\text{-}HT_2$) receptors. Nefazodone and trazodone also block $alpha_1$-adrenergic receptors, which may be associated with postural hypotension.[1,2,21] Trazodone is thought to selectively inhibit serotonin uptake at the presynaptic neuronal membrane.[1,2] Vilazodone is a SSRI and partial serotonin $5\text{-}HT_{1A}$ receptor agonist.[22] Vortioxetine exhibits various serotonergic activities including the inhibition of the reuptake of serotonin, antagonistic effects at the $5\text{-}HT_3$, $5\text{-}HT_7$, and $5\text{-}HT_{1D}$ receptors, inhibition of the serotonin transporter, agonistic effects at $5\text{-}HT_{1A}$ receptors, and partial agonistic effects at $5\text{-}HT_{1B}$ receptors.[23] The TCAs interact with a wide variety of central nervous system receptor types, and as a result, cause many undesirable side effects. Clinically, they inhibit the reuptake of norepinephrine (secondary amines) and serotonin (tertiary amines) at the presynaptic neuron.[1,2,24-28] The miscellaneous antidepressants include bupropion and mirtazapine. Bupropion is a relatively weak inhibitor of the neuronal uptake of norepinephrine and dopamine; it does not inhibit monoamine oxidase or the reuptake of serotonin.[29-32] Mirtazapine is a tetracyclic compound, but is unrelated to the TCAs. It acts as an antagonist at central $alpha_2$-adrenergic receptors, which is thought to result in an increase in central noradrenergic and serotonergic activity.[33-34] Mirtazapine is also a potent antagonist of histamine receptors and is a moderate peripheral $alpha_1$-adrenergic receptor antagonist, which results in sedation and orthostatic hypotension.

The antidepressants that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. The majority of the products are available in a generic formulation, and there is at least one generic product available in each antidepressant subclass. This class was last reviewed in May 2014.

Table 1. Antidepressants Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Monoamine Oxidase Inhibitors			
Isocarboxazid	tablet	Marplan®	none
Phenelzine	tablet	Nardil®*	phenelzine
Selegiline	transdermal patch	Emsam®	none
Tranylcypromine	tablet	Parnate®*	tranylcypromine
Selective Serotonin- and Norepinephrine-reuptake Inhibitors			
Desvenlafaxine	extended-release tablet	Desvenlafaxine ER®, Pristiq®, Khedezla®*	desvenlafaxine
Duloxetine	delayed-release capsule	Cymbalta®*, Irenka®*	duloxetine
Levomilnacipran	extended-release capsule	Fetzima®	none
Venlafaxine	extended-release capsule, extended-release tablet, tablet	Effexor XR®*	venlafaxine
Selective Serotonin-reuptake Inhibitors			
Citalopram	solution, tablet	Celexa®*	citalopram
Escitalopram	solution, tablet	Lexapro®*	escitalopram
Fluoxetine	capsule, delayed-release capsule, solution, tablet	Prozac®*, Prozac Weekly®*, Sarafem®*	fluoxetine
Fluvoxamine	extended-release capsule, tablet	N/A	fluvoxamine
Paroxetine	capsule, extended-release tablet, suspension, tablet	Brisdelle®, Paxil®*, Paxil CR®*, Pexeva®	paroxetine
Sertraline	oral concentrate, tablet	Zoloft®*	sertraline
Serotonin Modulators			
Nefazodone	tablet	N/A	nefazodone
Trazodone	extended-release tablet, tablet	Oleptro®	trazodone
Vilazodone	tablet	Viibryd®	none
Vortioxetine	tablet	Brintellix®	none
Tricyclics and Other Norepinephrine-reuptake Inhibitors-Single Entity Agents			
Amitriptyline	tablet	N/A	amitriptyline
Amoxapine	tablet	N/A	amoxapine
Clomipramine	capsule	Anafranil®*	clomipramine
Desipramine	tablet	Norpramin®*	desipramine
Doxepin	capsule, oral concentrate, tablet	Silenor®	doxepin
Imipramine	capsule, tablet	Tofranil®*, Tofranil-PM®*	imipramine
Maprotiline	tablet	N/A	maprotiline
Nortriptyline	capsule, solution	Pamelor®*	nortriptyline
Protriptyline	tablet	N/A	protriptyline
Trimipramine	capsule	Surmontil®	trimipramine
Tricyclics and Other Norepinephrine-reuptake Inhibitors-Combination Products			
Amitriptyline and chlordiazepoxide	tablet	N/A	amitriptyline and chlordiazepoxide
Antidepressants, Miscellaneous			
Bupropion	extended-release tablet, sustained-release tablet, tablet	Aplenzin®, Forfivo XL®, Wellbutrin®*, Wellbutrin SR®*, Wellbutrin XL®*	bupropion
Mirtazapine	orally disintegrating tablet, tablet	Remeron®*	mirtazapine

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List.
N/A=Not available.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the antidepressants are summarized in Table 2.

Table 2. Treatment Guidelines Using the Antidepressants

Clinical Guideline	Recommendation(s)
American Psychiatric Association: **Practice Guideline for the Treatment of Patients with Major Depressive Disorder, Third Edition (2010)**[36]	Acute phase • Pharmacotherapy: o An antidepressant medication is recommended as an initial treatment choice for patients with mild to moderate major depressive disorder (MDD) and should be provided for those with severe MDD. o Due to the fact that the effectiveness of antidepressant medications is generally comparable between classes and within classes of medications, the initial selection of an antidepressant medication will largely be based on the anticipated side effects; the safety or tolerability of these side effects; pharmacological properties of the medication and additional factors such as medication response in prior episodes, cost and patient preference. o For the majority of patients, a selective serotonin reuptake inhibitor (SSRI), serotonin norepinephrine reuptake inhibitor (SNRI), bupropion or mirtazapine is optimal. o In general, the use of nonselective monoamine oxidase inhibitors (MAOIs) should be restricted to patients who do not respond to other treatments. o During the acute phase of treatment, patients should be carefully and systematically monitored on a regular basis to assess their response to pharmacotherapy. o If side effects do occur, an initial strategy is to lower the dose of the antidepressants or to change to an antidepressant that is not associated with those side effects. • Assessing the adequacy of treatment response: o It is important to establish that treatment has been administered for a sufficient duration and at a sufficient frequency or, in the case of medication, dose. o Generally, four to eight weeks of treatment are needed before concluding that a patient is partially responsive or unresponsive to a specific intervention. • Strategies to address non-response: o For individuals who have not responded fully to treatment, the acute phase of treatment should not be concluded prematurely, as an incomplete response to treatment is often associated with poor functional outcomes. o If at least a moderate improvement in symptoms is not observed within four to eight weeks of treatment initiation, the diagnosis should be reappraised, side effects assessed, complicating co-occurring conditions and psychosocial factors reviewed and the treatment plan adjusted. o It is important to assess the quality of the therapeutic alliance and treatment adherence. o If medications are prescribed, the psychiatrist should determine whether pharmacokinetic or pharmacodynamic factors suggest a need to adjust medication dose. o After an additional four to eight weeks of treatment, if the patient continues to show minimal or no improvement in symptoms, the psychiatrist should conduct another thorough review of possible contributory factors and make additional changes in the treatment plan.

Clinical Guideline	Recommendation(s)
	o There are a number of strategies available when a change in treatment seems necessary. ▪ For patients treated with an antidepressant, optimizing the medication dose is a reasonable first step if the side effect burden is tolerable and the upper limit of a medication dose has not been reached. ▪ In patients who have shown minimal improvement or experienced significant medication side effects, other options include augmenting the antidepressant with a depression-focused psychotherapy or with other agents or with changing to another non-MAOI antidepressant. ▪ Patients may be changed to an antidepressant from the same pharmacological class or to one from a different class. ▪ Patients who have not responded to an SSRI, may respond to SNRI. ▪ Augmentation of antidepressant medications can utilize another non-MAOI antidepressant, generally from a different pharmacological class, or a non-antidepressant medication, such as lithium, thyroid hormone or a second generation antipsychotic. <u>Continuation phase</u> • During the continuation phase of treatment, the patient should be carefully monitored for signs of possible relapse. • Systematic assessment of symptoms, side effects, adherence and functional status is essential and may be facilitated through the use of clinician- and/or patient-administered rating scales. • To reduce the risk of relapse, patients who have been treated successfully with antidepressant medications in the acute phase should continue treatment with these agents for four to nine months. • In general, the dose used in the acute phase should be used in the continuation phase. • To prevent a relapse of depression in the continuation phase, depression-focused psychotherapy is recommended, with the best evidence available for cognitive behavioral therapy (CBT). <u>Maintenance phase</u> • In order to reduce the risk of a recurrent depressive episode, patients who have had three or more prior MDD episodes or who have chronic MDD should proceed to the maintenance phase of treatment after completing the continuation phase. • Maintenance therapy should also be considered for patients with additional risk factors for recurrence. • Additional considerations that may play a role in the decision to use maintenance therapy include patient preference, the type of treatment received, the presence of side effects during continuation therapy, the probability of recurrence, the frequency and severity of prior depressive episodes, the persistence of depressive symptoms after recovery and the presence of co-occurring disorders. Such factors also contribute to decisions about the duration of the maintenance phase. • For many patients, some form of maintenance treatment will be required indefinitely. • An antidepressant medication that produced symptom remission during the acute phase and maintained remission during the continuation phase should be continued at a full therapeutic dose.

Clinical Guideline	Recommendation(s)
	• For patients whose depressive episodes have not previously responded to acute or continuation treatment with medications or a depression-focused psychotherapy but who have shown a response to electroconvulsive therapy (ECT), maintenance ECT may be considered. • Due to the risk of recurrence, patients should be monitored systematically and at regular intervals during the maintenance phase. <u>Discontinuation of treatment</u> • When pharmacotherapy is being discontinued, it is best to taper the medication over the course of at least several weeks. • To minimize the likelihood of discontinuation symptoms, patients should be advised not to stop medications abruptly and to take medications with them when they travel or are away from home. • A slow taper or temporary change to a longer half-life antidepressant may reduce the risk of discontinuation syndrome when discontinuing antidepressants or reducing antidepressant doses. • Before the discontinuation of active treatment, patients should be informed of the potential for a depressive relapse and a plan should be established for seeking treatment in the event of recurrent symptoms. • After discontinuation of medications, patients should continue to be monitored over the next several months and should receive another course of adequate acute phase treatment if symptoms recur.

National Institute for Health and Clinical Excellence: **Depression in Adults: recognition and management (2009)**[37]	<u>Persistent subthreshold depressive symptoms or mild to moderate depression</u>
	• Do not use antidepressants routinely to treat persistent subthreshold depressive symptoms or mild depression.
	• Consider antidepressants for the following people:
	  o A past history of moderate or severe depression.
	  o Initial presentation of subthreshold depressive symptoms that have been present for a long period (typically at least two years).
	  o Subthreshold depressive symptoms or mild depression that persist(s) after other interventions.
	
	<u>Persistent subthreshold depressive symptoms or mild to moderate depression with inadequate response to initial interventions, and moderate and severe depression</u>
	• For patients with persistent subthreshold depressive symptoms or mild to moderate depression who have not benefited from a low-intensity psychosocial intervention, discuss the relative merits of different interventions with the person and provide:
	  o An antidepressant (normally an SSRI) or a high intensity psychosocial intervention.
	• For people with moderate or severe depression, provide a combination of an antidepressant medication and a high intensity psychological intervention.
	• The choice of intervention should be influenced by the duration of the episodes of depression and the trajectory of symptoms, previous course of depression and response to treatment, likelihood of adherence to treatment and any potential adverse effects and the patient's treatment preference and priorities.
	
	<u>Antidepressant drugs</u>
	• Choice of antidepressant:
	  o Discuss the choice of antidepressant with the patient, including any anticipated adverse events and potential drug interactions, and their perception of the efficacy and tolerability of any antidepressant they have previously taken.
	  o When an antidepressant is used, it should normally be an SSRI in a generic form. The SSRIs are equally effective as other antidepressants

Clinical Guideline	Recommendation(s)
	and have a favorable risk-benefit ratio. Fluoxetine, fluvoxamine and paroxetine are associated with a higher propensity for drug interactions than other SSRIs, and paroxetine is associated with a higher incidence of discontinuation symptoms than other SSRIs. o Take into account toxicity in overdose when choosing an antidepressant for people at significant risk for suicide. Be aware that compared to other equally effective antidepressants routinely used in primary care, venlafaxine is associated with a greater risk of death from overdose, and tri-cyclic antidepressants (TCAs), except lofepramine, are associated with the greatest risk in overdose. o When prescribing drugs other than SSRIs, take the following into account: the increased likelihood of the person stopping treatment because of side effects with duloxetine, venlafaxine and TCAs, the specific cautions, contraindications and monitoring requirements for some drugs, that non-reversible MAOIs should normally be prescribed only by specialists. • Starting and initial phase of treatment: o When prescribing antidepressants, explore any concerns the patient has. Explain the gradual development of the full antidepressant effect, the importance of taking the medication as prescribed, the need to continue treatment after remission, potential side effects, the potential for interactions with other medications, the risk and nature of discontinuation symptoms with all antidepressants and how these symptoms can be minimized and the fact that addiction does not occur with antidepressants. o If side effects develop early in antidepressant treatment, provide appropriate information and consider one of the following strategies: monitor symptoms closely where side effects are mild and acceptable to the patient, stop the antidepressant, change to a different antidepressant if the person prefers or consider short term concomitant treatment with a benzodiazepine if anxiety, agitation and/or insomnia are problematic (this should usually be for no longer than two weeks in order to prevent the development of dependence). o Patients who start on low dose TCAs and who have clear clinical response can be maintained on that dose with careful monitoring. o If the patient's depression shows no improvement after two to four weeks with the first antidepressant, check that the drug has been taken regularly and in the prescribed dose. o If response is absent or minimal after three to four weeks of treatment with a therapeutic dose of an antidepressant, increase the level of support and consider increasing the dose in line with the summary of product characteristics if there are no significant side effects or switching to another antidepressant. • If the patient's depression shows some improvement by four weeks, continue treatment for another two to four weeks. Consider switching to another antidepressant if response is still not adequate, there are side effects or the person prefers to change treatment.
National Institute for Clinical Excellence: **Generalized Anxiety Disorder and Panic Disorder in Adults: management (2011)**[38]	<u>Stepped care for people with generalized anxiety disorder (GAD)</u> • If a person with GAD chooses drug treatment, offer an SSRI, specifically sertraline. • If sertraline is ineffective, offer an alternative SSRI or a SNRI, taking into account the following factors: o Tendency to produce a withdrawal syndrome (especially with paroxetine and venlafaxine). o The side-effect profile and the potential for drug interactions. o The risk of suicide and likelihood of toxicity in overdose (especially

Clinical Guideline	Recommendation(s)
	with venlafaxine). o The person's prior experience of treatment with individual drugs (particularly adherence, effectiveness, side effects, experience of withdrawal syndrome and the person's preference). • If the person cannot tolerate SSRIs or SNRIs, consider offering pregabalin. • Do not offer a benzodiazepine for the treatment of GAD in primary or secondary care except as a short-term measure during crises. • Do not offer an antipsychotic for the treatment of GAD in primary care. <u>Panic disorder general considerations</u> • Benzodiazepines are associated with a less effective outcome in the long term and should not be prescribed for panic disorder. • Sedating antihistamines or antipsychotics should not be prescribed for panic disorder. • Interventions with evidence for the longest duration of effect are listed in descending order, where preference of the patient should be taken into account: o Psychological therapy (i.e., cognitive behavioral therapy, structured problem solving, psychoeducation). o Pharmacological therapy (antidepressant therapy). o Self-help interventions (i.e., bibliotherapy, support groups, exercise, CBT via a computer interface). • Antidepressants should be the only pharmacologic intervention used in the longer term. • Two types of medication are considered in the guideline for the treatment of panic disorder; TCAs and SSRIs. • Unless otherwise indicated, an SSRI (e.g., paroxetine, fluvoxamine, citalopram) licensed for panic disorder should be offered. If an SSRI is not suitable or there is no improvement after a 12-week course and if further medication is appropriate, imipramine or clomipramine may be considered. • If the patient is showing improvement, the medication should be continued for at least six months after optimal dose is reached, after which the dose may be tapered slowly over an extended period to minimize the risk of discontinuation/withdrawal symptoms.
American Psychiatric Association: **Practice Guideline for the Treatment of Patients with Panic Disorder, Second Edition (2009)**[39]	• SSRIs, SNRIs, TCAs, and benzodiazepines have demonstrated efficacy in numerous controlled trials and are recommended for treatment of panic disorder. • Because SSRIs, SNRIs, TCAs, and benzodiazepines appear roughly comparable in their efficacy for panic disorder, selecting a medication involves considerations of side effects, pharmacological properties, potential drug interactions, prior treatment history, and comorbid medical and psychiatric conditions. • The relatively favorable safety and side effect profile of SSRIs and SNRIs makes them the best initial choice for many patients with panic disorder. • There is no evidence of differential efficacy between the SSRIs, although differences in the side-effect profile (e.g., potential for weight gain, discontinuation-related symptoms), half-life, propensity for drug interactions, and availability of generic formulations may be clinically relevant. They are safer than TCAs and monoamine oxidase inhibitors. They are rarely lethal in overdose and have few serious effects on cardiovascular function. • Venlafaxine extended release has been shown to be effective for panic disorder. It is generally well tolerated and has a side effect profile similar to the SSRIs. No systematic data are currently available supporting the use of duloxetine, in panic disorder, although its mechanism of action suggests it might be an effective agent. • Although TCAs are effective, the side effects and greater toxicity in overdose

Clinical Guideline	Recommendation(s)
	limit their acceptability to patients and clinical utility. Given the equivalency of TCAs in treating depression, there is little reason to expect other TCAs to work less well for panic disorder. TCAs that are more noradrenergic (e.g., desipramine, maprotiline) may be less effective than agents that are more serotonergic. • SSRIs, SNRIs, and TCAs are all preferable to benzodiazepines as monotherapies for patients with comorbid depression or substance use disorders. Benzodiazepines may be especially useful adjunctively with antidepressants to treat residual anxiety symptoms. • Benzodiazepines may be preferred for patients with very distressing or impairing symptoms in whom rapid symptom control is critical. The benefit of more rapid response to benzodiazepines must be balanced against the possibilities of troublesome side effects and physiological dependence that may lead to difficulty discontinuing the medication. • MAOIs appear effective for panic disorder but, because of their safety profile, they are generally reserved for patients who have failed to respond to several first-line treatments. • Neither trazodone nor nefazodone can be recommended as a first-line treatment for panic disorder. There is minimal support for the use of trazodone in panic disorder and it appears less effective than imipramine and alprazolam. There are a few small, uncontrolled studies showing benefits of nefazodone in some patients with panic disorder; however, its use has been limited by concerns about liver toxicity. • Bupropion was effective in one small trial and ineffective in another. It cannot be recommended as a first line treatment for panic disorder. • Other medications with less empirical data may be considered as monotherapies or adjunctive treatments for panic disorder when patients have failed to respond to several standard treatments or based on other individual circumstances.
American Academy of Child and Adolescent Psychiatry: **Practice Parameter for the Assessment and Treatment of Children and Adolescents With Obsessive-Compulsive Disorder (2012)**[40]	• The psychiatric assessment of children and adolescents should routinely screen for the presence of obsessions and/or compulsions or repetitive behaviors. • If screening suggests obsessive-compulsive symptoms, clinicians should fully evaluate the child using the DSM-IV-TR criteria and scalar assessment. • A complete psychiatric evaluation should be performed, including information from all available sources and compromising standard elements of history and a mental state examination, with attention to the presence of commonly occurring comorbid psychiatric disorders. • It is possible that three out of four children with obsessive-compulsive disorder (OCD) meet criteria for at least one comorbid diagnosis, and these children have lower response rates to CBT than children without comorbid diagnoses. • Identification of MDD and bipolar disorder is very important before initiating treatment with a SSRI. • Comorbid eating disorders are infrequent in younger children; however, comorbid eating disorders become more prevalent in adolescents. • A full medical, developmental, family and school history should be included with the psychiatric history and examination. • CBT is the first-line treatment for mild to moderate OCD in children, whenever possible. • For moderate to severe OCD, medication is indicated in addition to CBT. • Serotonin reuptake inhibitors (SRIs) are the first-line medications recommended for OCD in children, including clomipramine (a TCA) and certain SSRIs (fluoxetine, fluvoxamine, paroxetine and sertraline). • There is no SRI that is proven to be more efficacious over another. • The modality of assigned treatment should be guided by empirical evidence on the moderators and predictors of treatment response. • Multimodal treatment with CBT and medication is recommended if CBT fails

Clinical Guideline	Recommendation(s)
	to achieve a clinical response after several months or in more severe cases. • Medication augmentation strategies are reserved for treatment-resistant cases in which impairments are deemed moderate in at least one important domain of function despite adequate monotherapy. • Adding clomipramine to an SSRI is a useful medication augmentation strategy. • Augmenting with an atypical neuroleptic is also a strategy employed by experts (e.g. haloperidol and risperidone combined) based on studies in adults with OCD; however, controlled data for the use of atypical antipsychotics in children with OCD does not exist. • A minimum of two adequate SSRI trials or an SSRI and clomipramine trial is recommended before atypical augmentation. • Empirically validated medication and psychosocial treatments for comorbid disorders should be considered.
American Psychiatric Association: **Practice Guideline for the Treatment of Patients with Obsessive-Compulsive Disorder (2007)**[41]	General considerations • OCD is a chronic illness which typically waxes and wanes. • Patients who have symptoms interfering with daily functioning should be treated. • Clinical remission and recovery may not always occur and will not occur rapidly. • Goals of treatment include improving symptoms, patient functioning, and quality of life. Initial treatment options • The choice of treatment depends on the patient's ability to comply with therapy, whether psychotherapy, pharmacotherapy, or both. • First-line treatments include cognitive-behavioral therapy, SRIs, or a combination of the two. The choice depends on past treatment history, comorbid psychiatric conditions, severity of symptoms, and functional limitations. • Cognitive-behavioral therapy or SRI therapy may be used alone or in combination, and combination therapy may be considered in patients who do not respond fully to monotherapy, those with severe symptoms, those with comorbid psychiatric illnesses for which an SRI is indicated, or in patients who wish to limit SRI exposure. • All SRIs appear to be equally effective, though patients may respond to agents differently. • Prescribers should consider the safety, side effects, FDA warnings, drug interactions, past response to treatment, and comorbid medical conditions when choosing a medication for treatment. • Most patients do not experience a significant improvement until four to six weeks after treatment initiation, and some may ultimately respond after as many as 10 to 12 weeks. • Patients not responding after 10 to 12 weeks may respond to a higher dose of the same medication. Changing treatments and pursuing sequential treatment trials • Augmentation strategies may be preferred to switching strategies in patients who have a partial response to the initial treatment. • Augmentation of SRIs with trials of different antipsychotic medications or with cognitive-behavioral therapy or augmentation of cognitive-behavioral therapy with an SRI. • Patients who do not respond to their first SRI may have their medication switched to a different SRI. A switch to venlafaxine is less likely to produce an adequate response. • For patients who have not benefitted from their first SSRI trial, a switch to

Clinical Guideline	Recommendation(s)
	mirtazapine can be considered. • After first- and second-line treatments and well-supported augmentation strategies have been exhausted, less well-supported treatment strategies may be considered. These include augmenting SRIs with clomipramine, buspirone, pindolol, riluzole, or once- weekly oral morphine sulfate. • Evidence for beneficial effects of benzodiazepines as monotherapy for OCD is limited to case reports with clonazepam and alprazolam. Modest doses of benzodiazepines may relieve anxiety and distress in OCD without directly diminishing the frequency or duration of obsessions or compulsions. Given their limited evidence for efficacy, benzodiazepines cannot be recommended as monotherapy for OCD, except in those rare individuals who are unable or unwilling to take standard anti-OCD medications.
American Academy of Child and Adolescent Psychiatry: **Practice Parameter for the Assessment and Treatment of Children and Adolescents With Posttraumatic Stress Disorder (2010)**[42]	• The psychiatric evaluation of children and adolescents should routinely include questions about traumatic experiences and posttraumatic stress disorder (PTSD) symptoms. • If the evaluation indicates symptoms of PTSD, the clinician should formally determine if PTSD is present, the severity of PTSD symptoms and the degree of functional impairment. Caregivers should be included in the formal evaluation. • A differential diagnosis should be conducted in order to rule out diagnoses with symptoms that can mimic PTSD symptoms. • The treatment plan should be comprehensive in approach and should consider the severity of symptoms and impairment, as well as comorbid psychiatric conditions. • Trauma-focused psychotherapies should be considered first-line in children and adolescents with PTSD, including psychoanalytic, attachment and cognitive behavioral treatment models. • SSRIs can be considered for treatment of children and adolescents with PTSD. • The effect of SSRIs in children with PTSD may be more consistent with a placebo effect. • Other medications such as clonidine and propranolol may be useful in decreasing symptoms of hyperarousal, and anticonvulsants may beneficial in treating PTSD symptoms other than avoidance. • Benzodiazepines have not been found to be beneficial in treating PTSD symptoms. • School-based accommodations are recommended for children with PTSD, especially in children with school-based trauma, such as bullying. • The use of restrictive, “rebirthing,” binding or other coercive therapies are not recommended. • Screening for PTSD in the school or community should be conducted after traumatic events that affect significant numbers of children.
American Psychiatric Association: **Guideline Watch: Practice Guideline for the Treatment of Patients with Acute Stress Disorder and Posttraumatic Stress Disorder (2009)**[43]	• Meta-analyses and several randomized controlled trials published since 2004 support the greater efficacy of SSRIs and SNRIs over placebo for non-combat-related PTSD. • The evidence base for pharmacological intervention in combat-related PTSD has not been significantly augmented by recent studies. Studies suggest that SSRIs may not be recommended with the previous level of confidence for the treatment of PTSD in this particular population. Further research is needed to answer why these populations have been shown to have differential responses to SSRI treatment. • As described in the 2004 guideline, no significant differences among antidepressants, including the SSRIs, were found in the few head-to-head studies then available. Since that time, studies have been published comparing nefazodone and sertraline, venlafaxine and sertraline, the SNRI reboxetine and fluvoxamine, and fluoxetine, moclobemide, and tianeptine. These studies have generally demonstrated the greater efficacy of antidepressants to placebo but

<table>
<tr><th>Clinical Guideline</th><th>Recommendation(s)</th></tr>
<tr><td></td><td>have done little to clarify the relative utility of these different antidepressants.
• There is a relatively robust evidence basis for pharmacological treatment with antidepressant medications (particularly SSRIs and SNRIs for noncombat PTSD) as compared to other classes of medications.
• Comparison of other treatments with the SSRIs and SNRIs is complicated by methodological differences in the available studies. SSRIs and SNRIs have mostly been studied in rigorous trials compared to placebo; other agents have been studied against “treatment as usual” or as augmentation agents in patients with refractory illness.</td></tr>
<tr><td>American Psychiatric Association:
Practice Guideline for the Treatment of Patients with Acute Stress Disorder and Posttraumatic Stress Disorder (2004)[44]</td><td>• Goals of treatment for patients with PTSD and acute stress disorder (ASD) include lessening the severity of symptoms and preventing trauma-related comorbid conditions.
• Clinical trial data and randomized studies are limited and difficult to perform.
• Treatment includes pharmacotherapy, psychotherapy and supportive measures.
• SSRIs are first-line therapy for PTSD and ASD and if found effective, treatment should be continued in order to continue to see benefit.
• Second-line treatment agents include TCAs (specifically amitriptyline and imipramine, but not desipramine) and MAOIs.
• Benzodiazepines should not be used as monotherapy, but may be effective as sedatives and anxiolytics.
• Atypical antipsychotics may be necessary for patients experiencing psychotic symptoms.
• Anticonvulsants (divalproex, carbamazepine, topiramate and lamotrigine) have produced mixed results for treating PTSD and ASD but may prove to be beneficial.
• Limited data exists for the use of adrenergic inhibitors and their use is not part of the guideline at this time.
• An adequate trial of therapy requires a minimum of three months of treatment. If treatment is effective, it should be continued for up to 12 months or longer.</td></tr>
<tr><td>American College of Obstetricians and Gynecologists:
Practice Bulletin: Premenstrual Syndrome (2000)[45]</td><td>• SSRIs have been proven effective in treating premenstrual syndrome (PMS).
• Current evidence does not support the use of natural progesterone or primrose oil for the treatment of PMS.
• Gonadotropin-releasing hormone agonists and surgical oophorectomy have been shown to be effective, but side effects limit usefulness in most patients.
• Alprazolam may be useful in some patients, but side effects prevent it from being used as a first-line agent.
• Calcium supplements may be effective.
• Magnesium, vitamin B6, and vitamin E are minimally effective in treating PMS.</td></tr>
<tr><td>American Psychiatric Association:
Practice Guideline for the Treatment of Patients with Eating Disorders (2006)[46]</td><td>• Patients with eating disorders should be treated with nutritional rehabilitation.
• Psychosocial therapy should be used in the treatment of anorexia.
• SSRIs may be considered in the treatment of anorexia.
• Bupropion, TCAs, and MAOIs should be avoided in patients with eating disorders.
• Atypical antipsychotics may be used in patients with severe symptoms.
• SSRIs may be considered in patients with bulimia.</td></tr>
<tr><td>A Joint Clinical Practice Guideline from the American College of Physicians and the American Pain Society:
Diagnosis and Treatment of Low Back Pain (2007)[47]</td><td>• Treatment is based on initial workup, evaluation, additional studies (i.e. imaging or blood work) and duration of symptoms.
• The potential interventions for low back pain are outlined below:
<table>
<tr><th colspan="4">Interventions for the Management of Low Back Pain</th></tr>
<tr><th colspan="2">Intervention Type</th><th>Acute pain (duration <4 weeks)</th><th>Subacute or chronic pain (duration >4 weeks)</th></tr>
<tr><td>Self-care</td><td>Advice to remain active</td><td>Yes</td><td>Yes</td></tr>
</table></td></tr>
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Clinical Guideline	Recommendation(s)

	Application of superficial heat	Yes	No
	Book, handouts	Yes	Yes
Pharmaco-logic Therapy	Acetaminophen	Yes	Yes
	TCA	No	Yes
	Benzodiazepines	Yes	Yes
	NSAIDs	Yes	Yes
	Skeletal muscle relaxants	Yes	No
	Tramadol, opioids	Yes	Yes
Non-pharmaco-logic Therapy	Acupuncture	No	Yes
	Cognitive behavior therapy	No	Yes
	Exercise therapy	No	Yes
	Massage	No	Yes
	Progressive relaxation	No	Yes
	Spinal manipulation	Yes	Yes
	Yoga	No	Yes
	Intensive interdisciplinary rehabilitation	No	Yes

Adapted with permission from Chou R, et al. Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society [published correction appears in Ann Intern Med. 2008;148(3):247-8]. Ann Intern Med. 2007;147(7):482.

- Physicians should conduct a focused history and physical examination to classify patients into one of three categories: (1) nonspecific pain; (2) pain possibly associated with radiculopathy or spinal stenosis; and (3) pain from another specific spinal cause (e.g., neurologic deficits or underlying conditions, ankylosing spondylitis, vertebral compression fracture). Patient history should be assessed for psychosocial risk factors.
- In combination with information and self-care, the use of medications with proven benefits should be considered. Before beginning treatment, physicians should evaluate the severity of the patient's baseline pain and functional deficits and the potential benefits and risks of treatment, including the relative lack of long-term effectiveness and safety data. In most cases, acetaminophen or NSAIDs are the first line options.
- Acetaminophen is considered first-line, even though it is a weaker analgesic compared to NSAIDs, due to more favorable safety profile and low cost. Nonselective NSAIDs are more effective for pain relief but are associated with gastrointestinal and renovascular risks, therefore assessments need to be made before starting a regimen.
- Skeletal muscle relaxants are associated with central nervous system effects (primarily sedation).These agents should be used with caution.
- Benzodiazepines seem similar in efficacy as skeletal muscle relaxants for short term pain relief but are associated with risk of abuse and tolerance.
- Opioid analgesics and tramadol are options for patients with severe, disabling pain that is not controlled with acetaminophen or NSAIDs. Evidence is insufficient to recommend one opioid over another.
- Opioid analgesics and tramadol carry a risk for abuse and addiction especially with long-term use. These agents should be used with caution.

American College of Rheumatology: **American College of Rheumatology 2012 Recommendations for the Use of Nonpharmacologic**

<u>Nonpharmacologic recommendations for the management of hand osteoarthritis</u>

- It is recommended that health professionals should:
  - Evaluate the ability to perform activities of daily living.
  - Instruct in joint protection techniques.
  - Provide assistive devices, as needed, to help patients perform activities of daily living.
  - Instruct in use of thermal modalities.

Clinical Guideline	Recommendation(s)
and Pharmacologic Therapies in Osteoarthritis of the Hand, Hip, and Knee (2012)[48]	o Provide splints for patients with trapeziometacarpal joint osteoarthritis. <u>Pharmacologic recommendations for the initial management of hand osteoarthritis</u> • It is recommended that health professionals should use one or more of the following: o Topical capsaicin. o Topical NSAIDs, including trolamine salicylate. o Oral NSAIDs, including cyclooxgenase-2 selective inhibitors. o Tramadol. • It is conditionally recommend that health professionals should not use the following: o Intraarticular therapies. o Opioid analgesics. • It is conditionally recommend that: o In persons ≥75 years of age should use topical rather than oral NSAIDs. o In persons <75 years of age, no preference for using topical rather than oral NSAIDs is expressed in the guideline. <u>Nonpharmacologic recommendations for the management of knee osteoarthritis</u> • It is strongly recommend that patients with knee osteoarthritis do the following: o Participate in cardiovascular (aerobic) and/or resistance land-based exercise. o Participate in aquatic exercise. o Lose weight (for persons who are overweight). • It is conditionally recommend that patients with knee osteoarthritis do the following: o Participate in self-management programs. o Receive manual therapy in combination with supervised exercise. o Receive psychosocial interventions. o Use medially directed patellar taping. o Wear medially wedged insoles if they have lateral compartment osteoarthritis. o Wear laterally wedged subtalar strapped insoles if they have medial compartment osteoarthritis. o Be instructed in the use of thermal agents. o Receive walking aids, as needed. o Participate in tai chi programs. o Be treated with traditional Chinese acupuncture (conditionally recommended only when the patient with knee osteoarthritis has chronic moderate to severe pain and is a candidate for total knee arthroplasty but either is unwilling to undergo the procedure, has comorbid medical conditions, or is taking concomitant medications that lead to a relative or absolute contraindication to surgery or a decision by the surgeon not to recommend the procedure). o Be instructed in the use of transcutaneous electrical stimulation (conditionally recommended only when the patient with knee osteoarthritis has chronic moderate to severe pain and is a candidate for total knee arthroplasty but either is unwilling to undergo the procedure, has comorbid medical conditions, or is taking concomitant medications that lead to a relative or absolute contraindication to surgery or a decision by the surgeon not to recommend the procedure). • No recommendation is made regarding the following: o Participation in balance exercises, either alone or in combination with strengthening exercises. o Wearing laterally wedged insoles.

Clinical Guideline	Recommendation(s)
	o Receiving manual therapy alone. o Wearing knee braces. o Using laterally directed patellar taping. <u>Pharmacologic recommendations for the initial management of knee osteoarthritis</u> • It is conditionally recommend that patients with knee osteoarthritis use one of the following: o Acetaminophen. o Oral NSAIDs. o Topical NSAIDs. o Tramadol. o Intraarticular corticosteroid injections. • It is conditionally recommend that patients with knee osteoarthritis not use the following: o Chondroitin sulfate. o Glucosamine. o Topical capsaicin. • No recommendation is made regarding the use of intraarticular hyaluronates, duloxetine, and opioid analgesics. <u>Nonpharmacologic recommendations for the management of hip osteoarthritis</u> • It is strongly recommend that patients with hip osteoarthritis do the following: o Participate in cardiovascular and/or resistance land based exercise. o Participate in aquatic exercise. o Lose weight (for persons who are overweight). • It is conditionally recommend that patients with hip osteoarthritis do the following: o Participate in self-management programs. o Receive manual therapy in combination with supervised exercise. o Receive psychosocial interventions. o Be instructed in the use of thermal agents. o Receive walking aids, as needed. • No recommendation is made regarding the following: o Participation in balance exercises, either alone or in combination with strengthening exercises. o Participation in tai chi. o Receiving manual therapy alone. <u>Pharmacologic recommendations for the initial management of hip osteoarthritis</u> • It is conditionally recommend that patients with hip osteoarthritis use one of the following: o Acetaminophen. o Oral NSAIDs. o Tramadol. o Intraarticular corticosteroid injections. • It is conditionally recommend that patients with hip osteoarthritis not use the following: o Chondroitin sulfate. o Glucosamine. • No recommendation is made regarding the use of the following: o Topical NSAIDs. o Intraarticular hyaluronate injections. o Duloxetine. • Opioid analgesics.
American Academy of	• Conservative treatments

Clinical Guideline	Recommendation(s)
Orthopedic Surgeons: **Clinical Practice Guideline on Osteoarthritis of the Knee (2013)**[49]	o It is recommended that patients with symptomatic osteoarthritis of the knee participate in self-management programs, strengthening, low-impact aerobic exercises, and neuromuscular education; and engage in physical activity consistent with national guidelines. o Weight loss for patients with symptomatic osteoarthritis of the knee and a body mass index ≥25 is recommended. o The guideline cannot recommend acupuncture in patients with symptomatic osteoarthritis of the knee. o No recommendation can be made concerning the use of physical agents (including electrotherapeutic modalities) in patients with symptomatic osteoarthritis of the knee. o No recommendation can be made concerning manual therapy in patients with symptomatic osteoarthritis of the knee. o The guideline cannot suggest a valgus directing force brace (medial compartment unloader) for patients with symptomatic osteoarthritis of the knee. o No recommendation can be made concerning a lateral wedge insoles be used for patients with symptomatic medial compartment osteoarthritis of the knee. o The guideline cannot recommend using glucosamine and chondroitin for patients with symptomatic osteoarthritis of the knee. • Pharmacologic treatments o NSAIDs; oral or topical or tramadol for patients with symptomatic osteoarthritis of the knee are recommended. o No recommendation can be made concerning the use of acetaminophen, opioids, or pain patches for patients with symptomatic osteoarthritis of the knee. • Procedural treatments o No recommendation can be made concerning the use of intraarticular corticosteroids for patients with symptomatic osteoarthritis of the knee. o The guideline cannot recommend using hyaluronic acid for patients with symptomatic osteoarthritis of the knee. o No recommendation can be made concerning growth factor injections and/or platelet rich plasma for patients with symptomatic osteoarthritis of the knee. o The guideline cannot suggest that the practitioner use needle lavage for patients with symptomatic osteoarthritis of the knee. • Surgical treatments o The guideline cannot recommend performing arthroscopy with lavage and/or debridement in patients with a primary diagnosis of symptomatic osteoarthritis of the knee. o No recommendation can be made concerning arthroscopic partial meniscectomy in patients with osteoarthritis of the knee with a torn meniscus. o The practitioner might perform a valgus producing proximal tibial osteotomy in patients with symptomatic medial compartment osteoarthritis of the knee. • In the absence of reliable evidence, it is the opinion of the work group not to use the free-floating (un-fixed) interpositional device in patients with symptomatic medial compartment osteoarthritis of the knee.
European League Against Rheumatism: **Evidence-based Recommendations for the Management of**	• Tramadol is recommended for the management of pain in fibromyalgia. • Simple analgesics such as paracetamol and other weak opioids can also be considered in the treatment of fibromyalgia. • Corticosteroids and strong opioids are not recommended. • Amitriptyline, fluoxetine, duloxetine, milnacipran, moclobemide and pirlindole

Clinical Guideline	Recommendation(s)
Fibromyalgia Syndrome (2007)[50]	(not available in the United States), reduce pain and often improve function, therefore they are recommended for the treatment of fibromyalgia. • Tropisetron, pramipexole and pregabalin reduce pain and are recommended for the treatment of fibromyalgia.
American Academy of Neurology/American Association of Neuromuscular and Electrodiagnostic Medicine/American Academy of Physical Medicine and Rehabilitation: **Treatment of Painful Diabetic Neuropathy (2011)**[51]	Anticonvulsants • If clinically appropriate, pregabalin should be offered for treatment. • Gabapentin and sodium valproate should be considered for treatment. • There is insufficient evidence to support or refute the use of topiramate for treatment. • Oxcarbazepine, lamotrigine, and lacosamide should probably not be considered for treatment. Antidepressants • Amitriptyline, venlafaxine, and duloxetine should be considered for the treatment of painful diabetic neuropathy. Data are insufficient to recommend one of these agents over another. • Venlafaxine may be added to gabapentin for a better response. • There is insufficient evidence to support or refute the use of desipramine, imipramine, fluoxetine, or the combination of nortriptyline and fluphenazine in the treatment of painful diabetic neuropathy. Opioids • Dextromethorphan, morphine sulfate, tramadol, and oxycodone should be considered for treatment. Data are insufficient to recommend one agent over the other. Other pharmacologic options • Capsaicin and isosorbide dinitrate spray should be considered for treatment. • Clonidine, pentoxifylline, and mexiletine should probably not be considered for treatment. • Lidocaine patch may be considered for treatment. • There is insufficient evidence to support or refute the usefulness of vitamins and α-lipoic acid for treatment. Nonpharmacologic options • Percutaneous electrical nerve stimulation should be considered for treatment. • Electromagnetic field treatment, low-intensity laser treatment, and Reiki therapy should probably not be considered for treatment. • Evidence is insufficient to support or refute the use of amitriptyline plus electrotherapy for treatment.
European Federation of Neurological Societies: **Guidelines on the Pharmacological Treatment of Neuropathic Pain (2010)**[52]	Painful polyneuropathy • Diabetic and non-diabetic painful polyneuropathy are similar in symptomatology and with respect to treatment response, with the exception of human immunodeficiency virus (HIV)-induced neuropathy. • Recommended first-line treatments include tricyclic antidepressants (TCA), gabapentin, pregabalin, and SNRIs (duloxetine, venlafaxine). • Tramadol is recommended second line, except for patients with exacerbations of pain or those with predominant coexisting non-neuropathic pain. • Strong opioids are recommended third-line treatments due to concerns regarding long-term safety, including addiction potential and misuse. • In HIV-associated polyneuropathy, only lamotrigine (in patients receiving antiretroviral treatment), smoking cannabis, and capsaicin patches were found moderately useful. Post herpetic neuropathy

Clinical Guideline	Recommendation(s)
	• Recommended first-line treatments include a TCA, gabapentin, or pregabalin. • Topical lidocaine with its excellent tolerability may be considered first-line in the elderly, especially if there are concerns of adverse events of oral medications. • Strong opioids and capsaicin cream are recommended as second-line therapies.
American Association of Clinical Endocrinologists/ College Of Endocrinology: **Clinical Practice Guidelines for Developing a Diabetes Mellitus Comprehensive Care Plan (2015)**[53]	Diabetic neuropathy • Diabetic painful neuropathy is diagnosed clinically and must be differentiated from other neurologic conditions. • Interventions that reduce oxidative stress, improve glycemic control, and/or improve dyslipidemia and hypertension might have a beneficial effect on diabetic neuropathy. • Exercise and balance training may also be beneficial. • Tricyclic antidepressants, anticonvulsants, and serotonin and norepinephrine reuptake inhibitors are useful treatments. • Large-fiber neuropathies are managed with strength, gait, and balance training; pain management; orthotics to treat and prevent foot deformities; tendon lengthening for pes equinus from Achilles tendon shortening; and/or surgical reconstruction and full contact casting as needed. • Small-fiber neuropathies are managed with foot protection (e.g., padded socks), supportive shoes with orthotics if necessary, regular foot and shoe inspection, prevention of heat injury, and use of emollient creams; however, for pain management, the medications mentioned above must be used.
American Diabetes Association: **Diabetic Neuropathies (2005)**[54]	Algorithm for the management of symptoms diabetic polyneuropathy • Exclude nondiabetic etiologies, followed by, stabilize glycemic control (insulin not always required in type 2 diabetes), followed by, tricyclic antidepressants (e.g., amitriptyline 25 to 250 mg before bed), followed by, anticonvulsants (e.g., gabapentin, typical dose 1.8 g/day), followed by, opioid or opioid-like drugs (e.g., tramadol, oxycodone), followed by, consider pain clinical referral.
American Academy of Neurology: **Practice Parameter: Treatment of Postherpetic Neuralgia (2004)**[55] **(Reaffirmed 2008)**	• Tricyclic antidepressants (amitriptyline, nortriptyline, desipramine, maprotiline), gabapentin, pregabalin, opioids, and topical lidocaine patches are effective and should be used in the treatment of post herpetic neuropathy. • There is limited evidence to support nortriptyline over amitriptyline, and the data are insufficient to recommend one opioid over another. • Amitriptyline has significant cardiac effects in the elderly when compared to nortriptyline and desipramine. • Aspirin cream is possibly effective in the relief of pain in patients with postherpetic neuralgia, but the magnitude of benefit is low, as seen with capsaicin. • In countries with preservative-free intrathecal methylprednisolone available, it may be considered in the treatment of postherpetic neuralgia. • Acupuncture, benzydamine cream, dextromethorphan, indomethacin, epidural methylprednisolone, epidural morphine sulfate, iontophoresis of vincristine, lorazepam, vitamin E, and zimelidine are not of benefit. • The effectiveness of carbamazepine, nicardipine, biperiden, chlorprothixene, ketamine, He:Ne laser irradiation, intralesional triamcinolone, cryocautery, topical piroxicam, extract of *Ganoderma lucidum*, dorsal root entry zone lesions, and stellate ganglion block are unproven in the treatment of postherpetic neuralgia. • There is insufficient evidence to make any recommendations on the long-term effects of these treatments.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the antidepressants are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Antidepressants[1-34]

Generic Name(s)	Depression/ Major Depressive Disorder	Generalized Anxiety Disorder	Mixed Anxiety/ Depressive Disorder	Obsessive-Compulsive Disorder	Panic Disorder	Posttraumatic Stress Disorder	Premenstrual Dysphoric Disorder	Seasonal Affective Disorder	Social Anxiety Disorder	Other
Monoamine Oxidase Inhibitors										
Isocarboxazid	✔									
Phenelzine	✔									
Selegiline	✔									
Tranylcypromine	✔									
Selective Serotonin- and Norepinephrine-reuptake Inhibitors										
Desvenlafaxine	✔									
Duloxetine	✔	✔								Chronic musculoskeletal pain; fibromyalgia*; neuropathic pain associated with diabetic peripheral neuropathy
Levomilnacipran	✔									
Venlafaxine	✔	✔ ‡			✔ ‡				✔ ‡	
Selective Serotonin-reuptake Inhibitors										
Citalopram	✔									
Escitalopram	✔	✔								
Fluoxetine	✔			✔	✔		✔ ‡			Bulimia nervosa
Fluvoxamine				✔						
Paroxetine	✔	✔ §		✔ §	✔	✔ §	✔ *		✔	Moderate to severe vasomotor symptoms associated with menopause‖
Sertraline	✔			✔	✔	✔	✔		✔	
Serotonin Modulators										
Nefazodone	✔									
Trazodone	✔									
Vilazodone	✔									
Vortioxetine	✔									
Tricyclics and Other Norepinephrine-reuptake Inhibitors-Single Entity Agents										
Amitriptyline	✔									
Amoxapine	✔									
Clomipramine				✔						
Desipramine	✔									
Doxepin	✔		✔							Insomnia¶
Imipramine	✔									Pediatric nocturnal enuresis
Maprotiline	✔		✔							

Generic Name(s)	Depression/ Major Depressive Disorder	Generalized Anxiety Disorder	Mixed Anxiety/ Depressive Disorder	Obsessive-Compulsive Disorder	Panic Disorder	Posttraumatic Stress Disorder	Premenstrual Dysphoric Disorder	Seasonal Affective Disorder	Social Anxiety Disorder	Other
Nortriptyline	✔									
Protriptyline	✔									
Trimipramine	✔									
Tricyclics and Other Norepinephrine-reuptake Inhibitors-Combination Products										
Amitriptyline and chlordiazepoxide			✔							
Antidepressants, Miscellaneous										
Bupropion	✔							✔ ‡		Smoking cessation‡
Mirtazapine	✔									

*Excluding Irenka® formulation.
‡Extended-release formulation only.
‡Sarafem® formulation only; Sarafem® is not approved for other indications.
§Immediate-release formulation only.
‖Brisdelle® formulation only.
¶ Silenor® formulation only.

IV. Pharmacokinetics

The pharmacokinetic parameters of the antidepressants are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Antidepressants[1-34]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Monoamine Oxidase Inhibitors					
Isocarboxazid	Not reported	Not reported	Liver	Renal	Not reported
Phenelzine	Not reported	Not reported	Liver	Renal (79)	11
Selegiline	25 to 30	90	Liver	Renal (10) Feces (2)	18 to 25
Tranylcypromine	Not reported	Not reported	Not reported	Renal	1.5 to 3.5
Selective Serotonin- and Norepinephrine-reuptake Inhibitors					
Desvenlafaxine	80	30	Liver	Renal (45)	10 to 11
Duloxetine	30 to 80	>90	Liver	Renal (70) Feces (20)	8 to 17
Levomilnacipran	92	22	Liver	Renal (85)	12
Venlafaxine	12.6 to 45.0	27 to 30	Liver	Renal (87) Feces (2)	5
Selective Serotonin-reuptake Inhibitors					
Citalopram	80	80	Liver	Renal (20) Feces	24 to 48
Escitalopram	80	56	Liver	Renal (8)	22 to 32
Fluoxetine	100	95	Liver	Renal (60) Feces (12)	96 to 144
Fluvoxamine	53	80	Liver	Renal (94)	15 to 16
Paroxetine	Completely absorbed	93 to 95	Liver	Renal (64 to 67) Feces (36 to 37)	15 to 22
Sertraline	Not reported	99	Liver	Renal (40 to 45) Feces (40 to 45)	24
Serotonin Modulators					
Nefazodone	20	>99	Liver	Renal (55) Feces (20 to 30)	1.9 to 5.3
Trazodone	65	89 to 95	Liver	Renal (70 to 75) Feces (21)	7 to 8
Vilazodone	72	96 to 99	Liver	Renal (1) Feces (2)	25
Vortioxetine	75	98	Liver	Renal (59) Feces (26)	66
Tricyclics and Other Norepinephrine-reuptake Inhibitors-Single Entity Agents					
Amitriptyline	100	90 to 95	Liver	Renal (18)	9 to 27
Amoxapine	18 to 54	90	Liver	Renal (69) Feces (18)	8
Clomipramine	20 to 78	97	Liver	Renal (51 to 60) Feces (24 to 32)	19 to 37
Desipramine	Not reported	Not reported	Liver	Renal (70)	14.3 to 24.7
Doxepin	Not reported	79 to 84	Liver	Bile	16.8
Imipramine	94 to 96	89	Liver	Renal	6 to 18
Maprotiline	100	88	Liver	Renal (70) Feces (30)	27 to 53
Nortriptyline	60	93 to 95	Liver	Renal Feces	28 to 31
Protriptyline	Not reported	Not reported	Liver	Renal Feces	54 to 198

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Trimipramine	Not reported	95	Liver	Renal	23
Tricyclics and Other Norepinephrine-reuptake Inhibitors-Combination Products					
Amitriptyline and chlordiazepoxide	100	90 to 98	Liver	Renal (18)	9.0 to 27.0; 6.6 to 48.0
Antidepressants, Miscellaneous					
Bupropion	Not reported	84	Liver	Renal (87)	14 to 21
Mirtazapine	50	85	Liver	Renal (75) Feces (15)	20 to 40

V. Drug Interactions

Major drug interactions with the antidepressants are listed in Table 5.

Table 5. Major Drug Interactions with the Antidepressants[2]

Generic Name(s)	Interaction	Mechanism
MAOIs		
MAOIs	Central nervous system depressants (e.g., alcohol, barbiturates, narcotics)	Severe hypertension may occur. Concurrent use is contraindicated.
MAOIs	Central nervous system stimulants (e.g., amphetamines, cocaine, methylphenidate, dexmethylphenidate)	Hypertensive crisis may occur. Coadministration is contraindicated.
MAOIs	MAOIs	Do not administer MAOIs with other MAOIs because hypertensive crisis and convulsive seizures, coma, or circulatory collapse may occur.
MAOIs	Methylphenidates	Pharmacological effects of methylphenidates may be increased by MAOIs. Headache, gastrointestinal symptoms and hypertension may occur. Concomitant use of methylphenidates and MAOIs is contraindicated.
MAOIs	Norepinephrine reuptake inhibitors (including tapentadol)	Coadministration may increase risk of toxic effects. Serious and sometimes fatal reactions have occurred. Use of norepinephrine reuptake inhibitors within 14 days of MAOIs is contraindicated.
MAOIs	SNRIs and SSRIs	A serotonin syndrome may occur. Concomitant use is contraindicated. At least 14 days should elapse between discontinuation of a MAOI and the start of an SSRI or vice versa. Allow at least five weeks between discontinuation of fluoxetine and initiation of a MAOI and at least 14 days between discontinuation of a MAOI and initiation of fluoxetine.
MAOIs	Sympathomimetics	The MAOIs' potentiation of indirect- or mixed-acting sympathomimetic substances, including anorexiants, may result in severe headache, hypertension, high fever, and hyperpyrexia, possibly resulting in hypertensive crisis; avoid coadministration.
MAOIs	TCAs	Do not administer MAOIs with or immediately following TCAs. There have been reports of

Generic Name(s)	Interaction	Mechanism
		serious, sometimes fata, reactions. These reactions include hyperthermia, rigidity, myoclonus, autonomic instability with possible vital sign fluctuations, and mental status changes that can include extreme agitation and confusion progressing to delirium and coma.
MAOIs	Triptans	Prolonged vasospastic reaction is a possibility when triptans and MAOIs are coadministered. The potential for development of serotonin syndrome also exists. Coadministration is not recommended.
MAOIs	Apraclonidine	Coadministration of MAOIs and apraclonidine is contraindicated. MAOIs and apraclonidine should not be administered within 14 days of discontinuation of either agent.
MAOIs	Atomoxetine	Toxic effects may be increased with concurrent administration of atomoxetine and MAOIs. Serious and sometimes fatal reactions have occurred. Use of atomoxetine within 14 days of MAOIs is contraindicated.
MAOIs	Bupropion	Coadministration is contraindicated. Risk of acute bupropion toxicity may be increased. Allow at least 14 days to elapse between discontinuing an MAOI and starting bupropion.
MAOIs	Buspirone	The risk of hypertension induced by MAOIs may be increased by co-administration of buspirone. It should be noted for selegiline that only higher dosages participate in this interaction. Allow at least 10 days between discontinuation of isocarboxazid and institution of buspirone.
MAOIs	Cyclobenzaprine	Because cyclobenzaprine is structurally related to the TCAs, use with caution with MAOIs. It should be noted for selegiline that only higher doses participate in this interaction.
MAOIs	Dextromethorphan	Hyperpyrexia, abnormal muscle movement, psychosis, bizarre behavior, hypotension, coma, and death have been associated with this combination.
MAOIs	Levodopa	Hypertensive reactions occur if levodopa is given to patients receiving MAOIs.
MAOIs	Linezolid	Adverse effects may be increased with concurrent administration of linezolid and MAOIs.
MAOIs	Meperidine	Coadministration of these agents may result in agitation, seizures, diaphoresis, and fever with the potential to progress to coma, apnea, and death. Reactions may be delayed and occur several weeks following withdrawal of MAOIs. Avoid this combination. Administer other narcotic analgesics with caution.
MAOIs	Nefazodone	The combination of MAOIs and nefazodone is contraindicated. The combination may be useful for treating depression; however, unexpected toxicity may occur.
MAOIs	Tetrabenazine	The combination of MAOIs and tetrabenazine may produce severe unexpected toxicity. Coadministration is contraindicated.

Generic Name(s)	Interaction	Mechanism
MAOIs	Tramadol	Coadministration may enhance seizure risk, and/or cause a severe reaction potentially involving the respiratory, cardiac, and central nervous system. Avoid coadministration.
MAOIs	Trazodone	The potential for the development of serotonin syndrome exists with concurrent use of MAOIs and trazodone.
MAOIs	Vilazodone	Do not administer MAOIs and vilazodone within 14 days of one another. Serotonin syndrome may result from concurrent administration.
MAOIs	Vortioxetine	Coadministration of MAOI used to treat psychiatric disorders and vortioxetine is contraindicated in the official package labeling of vortioxetine. In addition, the initiation of vortioxetine in patients receiving linezolid is contraindicated. Serotonin syndrome (unexpected irritability, increased muscle tone, altered consciousness and myoclonus) may result from concurrent administration.
MAOIs (selegiline)	Methadone	A severe reaction potentially involving the respiratory, cardiac and central nervous systems may occur shortly after administering methadone to patients receiving selegiline. At least 14 days should elapse between discontinuation of selegiline and administration of methadone.
MAOIs	Insulins	The hypoglycemic effect of insulin may be increased by MAOIs.
MAOIs	Meglitinides	The hypoglycemic effects of meglitinides may be increased by MAOIs.
MAOIs	Sulfonylureas	MAOIs enhance the hypoglycemic action of sulfonylureas.
MAOIs	Carbamazepine	While the manufacturer's data states that carbamazepine is contraindicated with MAOIs, other conflicting data suggest safe coadministration. It should be noted that only higher doses of selegiline (e.g. antidepressant doses) participate in this interaction.
MAOIs	Ginseng	Use of MAOIs with ginseng may produce unexpected toxic effects.
MAOIs	Tryptophan	Coadministration may result in hyperreflexia, confusion, disorientation, shivering, myoclonic jerks, agitation, amnesia, delirium, hypomanic signs, ataxia, ocular oscillations, Babinski signs.
MAOIs (isocarboxazid, phenelzine, tranylcypromine)	COMT inhibitors	The combination of these MAOIs with COMT inhibitors may result in inhibition of the majority of pathways responsible for normal catecholamine metabolism. Excessive sympathetic stimulation may result. Coadministration of COMT inhibitors and non-selective MAOIs is not recommended.
MAOIs (isocarboxazid, phenelzine, tranylcypromine)	Narcotic analgesics	A severe reaction potentially involving the respiratory, cardiac and central nervous systems may occur shortly after administering narcotic analgesics to patients receiving these MAOIs. At least 14 days should elapse after discontinuation of an MAOI before initiation of treatment with a

Generic Name(s)	Interaction	Mechanism
		narcotic analgesic.
SNRIs		
SNRIs	MAOIs	Coadministration of SNRIs and MAOIs is contraindicated. Serious, sometimes fatal, reactions may occur, including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. It is recommended that SNRIs not be used within at least 14 days of discontinuing treatment with an MAOI.
SNRIs	Linezolid	Serotonin syndrome may occur, possibly due to excessive accumulation of serotonin. Initiation of an SNRI is contraindicated in patients receiving linezolid.
SNRIs	Methylene blue	Coadministration of methylene blue and desvenlafaxine may increase the risk of central nervous system toxicity, including serotonin syndrome.
SNRIs	Tramadol	Increased risk of seizures is a possibility when tramadol and SNRIs are coadministered. Serotonin syndrome is also a risk with this combination. Concomitant use is not recommended.
SNRIs (duloxetine)	Phenothiazines (thioridazine)	Plasma concentrations and pharmacologic effects of thioridazine may be increased by duloxetine. The possibility of serious ventricular dysrhythmias should be considered. Do not coadminister.
SNRIs (duloxetine)	Tamoxifen	Pharmacologic effects of Tamoxifen may be decreased by Duloxetine. Coadministration of Duloxetine with Tamoxifen may increase the risk of breast cancer recurrence.
SNRIs	Anticoagulants	The risk of bleeding with Anticoagulants may be potentiated with concomitant use of these SNRIs and patients are at an increased risk of bleeding. The mechanism of this interaction is unknown.
SNRIs	SSRIs	The development of serotonin syndrome is possible when the combination of SNRIs and serotonin reuptake blockers are coadministered. In addition, plasma concentrations of SNRIs may be increased by serotonin reuptake blockers.
SNRIs	Iobenguane	SNRIs may reduce uptake and diagnostic efficacy of Iobenguane. False-negative Iobenguane imaging tests may result.
SNRIs	L-Tryptophan	Coadministration may lead to the development of serotonin syndrome.
SNRIs (desvenlafaxine, venlafaxine)	NSAIDs	The toxic effects may be increased with concurrent administration of NSAIDs and desvenlafaxine/venlafaxine. The risk of upper gastrointestinal bleeding may be increased. Patients taking concurrent SNRIs and NSAIDs should be educated about the signs and symptoms of gastrointestinal bleeding.
SNRIs	Salicylates	The risk of upper gastrointestinal bleeding may

Generic Name(s)	Interaction	Mechanism
(desvenlafaxine, venlafaxine)		be increased with concurrent administration of salicylates and desvenlafaxine or venlafaxine. The mechanism is unknown. Prolonged use of desvenlafaxine or venlafaxine may lead to depletion of serotonin, which is thought to play an important role in hemostasis.
SNRIs (desvenlafaxine, venlafaxine)	Cyproheptadine	Decreased pharmacologic effects of venlafaxine may result. Since cyproheptadine is a serotonin antagonist, the interaction may occur at the receptor level.
SNRIs (desvenlafaxine, venlafaxine)	Lithium	Coadministration of lithium and desvenlafaxine or venlafaxine may cause central nervous system toxicity, including serotonin syndrome. Serum lithium concentrations may be increased due to increased serotonergic neurotransmission.
SNRIs (desvenlafaxine, venlafaxine)	St. John’s wort	Unexpected toxicity may occur when St. John's wort and desvenlafaxine/ venlafaxine are coadministered; the mechanism is unknown.
SNRIs (desvenlafaxine, venlafaxine)	Trazodone	Unexpected toxic effects may occur when trazodone is combined with desvenlafaxine or venlafaxine. The mechanism is unknown.
SNRIs (duloxetine)	TCAs	Plasma concentrations of TCAs may be increased by duloxetine. Inhibition of cytochrome CYP2D6 isoenzymes by duloxetine may decrease the metabolic elimination of TCAs.
SNRIs (duloxetine)	Ciprofloxacin	Plasma concentrations and pharmacologic effects of duloxetine may be increased when coadministered with ciprofloxacin. Inhibition of CYP1A2 by ciprofloxacin may decrease the metabolic elimination of duloxetine.
SNRIs (duloxetine)	Flecainide	Plasma concentrations of flecainide may be increased by duloxetine. Clinical outcome is unknown.
SNRIs (duloxetine)	Propafenone	Plasma concentrations of propafenone may be increased by duloxetine due to inhibition of CYP2D6 isoenzymes.
SNRIs (levomilnacipran)	Alcoholic beverages	Consumption of alcohol may interfere with the delayed release mechanism of levomilnacipran.
SNRIs (venlafaxine)	Bupropion	Unexpected adverse effects, including serotonin syndrome, may occur when Venlafaxine and Bupropion are coadministered. The mechanism of this interaction is unknown.
SNRIs (venlafaxine)	Terbinafine	Plasma concentrations and pharmacologic effects of venlafaxine may be increased when coadministered with terbinafine. The potential for adverse effects due to venlafaxine may be increased. Inhibition of CYP2D6-mediated metabolism of venlafaxine by terbinafine is suspected.
SSRIs		
SSRIs	Linezolid	Serotonin syndrome may occur as a result of excessive accumulation of serotonin. The coadministration of linezolid and SSRIs should be handled with caution.
SSRIs	Tramadol	Increased risk of seizures is possible when

Generic Name(s)	Interaction	Mechanism
		tramadol and SSRIs are coadministered. Serotonin syndrome is also a potential risk when tramadol and SSRIs are coadministered.
SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline)	Clozapine	These SSRIs may increase plasma concentrations and pharmacologic effects of clozapine. Severe toxicity may occur. Inhibition of cytochrome P450 1A2 isoenzymes by these SSRIs may decrease the metabolic elimination of clozapine.
SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, sertraline)	Pimozide	Plasma concentrations of pimozide may be increased by SSRIs. The risk of life-threatening cardiac arrhythmias, including torsades de pointes, may be increased. The mechanism is unknown.
SSRIs (fluoxetine, fluvoxamine paroxetine)	Phenothiazines (chlorpromazine, thioridazine)	Pharmacologic effects and plasma concentrations of phenothiazines may be increased by SSRIs. Neurologic toxicity, including extrapyramidal effects, and cardiac toxicity, including the potential for torsade de pointes, may occur.
SSRIs (fluoxetine, paroxetine sertraline)	Tamoxifen	Pharmacologic effects of tamoxifen may be decreased by certain SSRIs. Coadministration may increase the risk of breast cancer recurrence.
SSRIs (citalopram, escitalopram)	Cimetidine	Pharmacologic effects and plasma concentrations of citalopram may be increased by cimetidine. Cimetidine may inhibit the metabolic and/or renal elimination of citalopram.
SSRIs (citalopram, fluoxetine)	Nilotinib	Additive QT prolongation may occur during coadministration of vandetanib and certain SSRIs. The black box warning contained in the official package labeling for vandetanib states that the use of vandetanib with medications that prolong the QT interval should be avoided.
SSRIs (citalopram, fluoxetine)	Vandetanib	Additive QT prolongation may occur during coadministration of vandetanib and certain SSRIs. The black box warning contained in the official package labeling for vandetanib states that the use of vandetanib with medications that prolong the QT interval should be avoided.
SSRIs (fluvoxamine)	Ramelteon	Plasma concentrations of ramelteon may be increased by coadministration of fluvoxamine. Coadministration of fluvoxamine and ramelteon is contraindicated.
SSRIs (fluvoxamine)	Tizanidine	Tizanidine plasma concentrations and pharmacologic effects may be increased by fluvoxamine. Adverse effects associated with tizanidine, including significant hypotension, may be expected. Concomitant use is contraindicated.
SSRIs	Anticoagulants	The risk of bleeding with anticoagulants may be potentiated with concomitant use of SSRIs and patients are at an increased risk of bleeding.
SSRIs	NSAIDs	Toxic effects may be increased with concurrent administration of NSAIDs and SSRIs. The risk of upper gastrointestinal bleeding may be increased. Patients taking both SSRIs and NSAIDs should be educated about the signs and symptoms of gastrointestinal bleeding.

Generic Name(s)	Interaction	Mechanism
SSRIs	Salicylates	Toxic effects may be increased with concurrent administration of salicylates and SSRIs. The risk of upper gastrointestinal bleeding may be increased. Patients taking both salicylates and NSAIDs should be educated about the signs and symptoms of gastrointestinal bleeding.
SSRIs	SNRIs	Serotonin syndrome has been reported during coadministration of SSRIs and SNRIs. If coadministration is necessary, the patient should be closely monitored, especially when starting treatment of increasing doses. Plasma concentrations of duloxetine may be increased by CYP2D6 inhibitors, such as fluoxetine and paroxetine.
SSRIs	Cyproheptadine	Decreased pharmacologic effects of SSRIs may result. Since cyproheptadine is a serotonin antagonist, the interaction may occur at the receptor level.
SSRIs	L-tryptophan	Coadministration may lead to the development of serotonin syndrome.
SSRIs	St. John’s wort	Unexpected toxicity may occur when St. John's wort and SSRIs are coadministered.
SSRIs (citalopram, escitalopram, fluoxetine, paroxetine, sertraline)	Beta-blockers	Coadministration of SSRIs and beta-blockers may increase risk of bradycardia and hypotension.
SSRIs (fluoxetine, sertraline)	Bupropion	Unexpected adverse effects, including serotonin syndrome, may occur when these SSRIs and bupropion are coadministered. The mechanism of this interaction is unknown.
SSRIs (fluoxetine, sertraline)	Carbamazepine	Plasma concentrations and pharmacologic effects of carbamazepine may be increased by these SSRIs. Toxicity may occur. Toxic serotonin syndrome may also occur.
SSRIs (fluoxetine, paroxetine)	Iloperidone	Plasma concentrations and pharmacologic effects of iloperidone may be increased by these SSRIs. A modification of the iloperidone dose is recommended.
SSRIs (fluoxetine, paroxetine)	Risperidone	These SSRIs may increase plasma concentrations and pharmacologic effects of risperidone. Additionally, concomitant use has resulted in reported cases of serotonin syndrome. Worsening of obsessive-compulsive disorder has also been reported with combined use.
SSRIs (fluoxetine, paroxetine)	Tetrabenazine	Plasma concentrations and pharmacologic effects of tetrabenazine may be increased by these SSRIs. Dosage adjustment is recommended.
SSRIs (fluoxetine)	HIV protease inhibitors	HIV protease inhibitors may increase plasma concentrations of fluoxetine resulting in possible fluoxetine toxicity. Similarly, fluoxetine may increase plasma concentrations of HIV protease inhibitors.
SSRIs (fluoxetine)	Hydantoins	Serum hydantoin concentrations may be elevated. Close monitoring of hydantoin levels and observing patients for toxicity or loss of

Generic Name(s)	Interaction	Mechanism
		therapeutic activity if fluoxetine is started or stopped is advised. Fosphenytoin may enhance QTc-prolonging effect of fluoxetine.
SSRIs (fluvoxamine)	Theophyllines	Pharmacological effects of the theophyllines may be increased by fluvoxamine. Elevated theophylline concentrations and toxicity including nausea, vomiting, cardiovascular instability and seizures may occur.
SSRIs (paroxetine)	Abiraterone	Plasma concentrations and pharmacologic effects of paroxetine may be increased by abiraterone, due to the inhibition of CYP2D6 by abiraterone.
Serotonin Modulators		
Serotonin modulators	MAOIs	Coadministration of the Serotonin Modulators and MAOIs is contraindicated due to increased risk for serotonin syndrome.
Serotonin modulators	Linezolid	Coadministration of the Serotonin Modulators and linezolid is contraindicated due to risk of serotonin syndrome.
Serotonin modulators (vilazodone, vortioxetine)	Methylene blue	Coadministration of certain Serotonin Modulators may increase the risk of central nervous system toxicity, including serotonin syndrome. Initiation of certain Serotonin Modulators in patients receiving methylene blue is contraindicated.
Nefazodone	Statins	The risk of rhabdomyolysis and myositis may be increased with certain statins. Coadministration of nefazodone with lovastatin or simvastatin is contraindicated.
Nefazodone	Tyrosine kinase receptor inhibitors	Plasma concentrations and pharmacologic effects of tyrosine kinase receptor inhibitors may be increased by nefazodone due to the inhibition of CYP3A4 by nefazodone.
Nefazodone	Vasopressin receptor agonists	Plasma concentrations and pharmacologic effects of vasopressin receptor antagonists may be increased by nefazodone. Coadministration of nefazodone and conivaptan or tolvaptan is contraindicated.
Nefazodone	Colchicine	Plasma concentrations of colchicine may be increased by nefazodone and life-threatening and fatal colchicine toxicity may occur. Dosage adjustment of colchicine is required for coadministration of these agents. Coadministration is contraindicated in patients with renal or hepatic impairment.
Nefazodone	Docetaxel	Plasma concentrations and pharmacologic effects of docetaxel may be increased by nefazodone. Use of nefazodone with docetaxel may increase the risk and/or severity of docetaxel-related toxicity. Coadministration should be avoided.
Nefazodone	Dronedarone	Plasma concentrations and pharmacologic effects of dronedarone may be increased by nefazodone. Coadministration is contraindicated.
Nefazodone	Lurasidone	Plasma concentrations and pharmacologic effects of lurasidone may be increased by nefazodone. Coadministration is contraindicated.
Nefazodone	Pimozide	Pharmacologic effects of pimozide may be

Generic Name(s)	Interaction	Mechanism
		increased by nefazodone. Elevated plasma concentrations and cardiovascular toxicity may occur. Coadministration is contraindicated.
Nefazodone	Ranolazine	Plasma concentrations and pharmacologic effects of ranolazine may be increased when coadministered with nefazodone. Coadministration is contraindicated.
Nefazodone	Ticagrelor	Plasma concentrations and pharmacologic effects of ticagrelor may be increased by nefazodone. Coadministration of nefazodone and ticagrelor should be avoided according to official package labeling.
Nefazodone	Toremifene	Plasma concentrations and pharmacologic effects of toremifene may be increased by nefazodone. Toxicity, including QT prolongation may occur. Coadministration of nefazodone and toremifene should be avoided according to a black box warning in official package labeling.
Trazodone	Sodium oxybate	Concurrent use of sodium oxybate and trazodone may result in an increase in sleep duration and central nervous system depression. Coadministration is contraindicated.
Vilazodone	Tramadol	Increased risk of seizures is listed in the manufacturer's package labeling as a possibility when tramadol and vilazodone are coadministered. Serotonin syndrome is also a potential risk with this combination.
Serotonin modulators (nefazodone, vilazodone, vortioxetine)	Triptans	Coadministration of certain serotonin modulators and Triptans may cause central nervous system toxicity, and rarely, serotonin syndrome.
Serotonin modulators (nefazodone, vilazodone)	Narcotic analgesics	Plasma concentrations and pharmacologic effects of some narcotic analgesics may be increased by certain serotonin modulators. Toxic effects of vilazodone may be increased by fentanyl, resulting in the development of serotonin syndrome.
Serotonin modulators (trazodone, vilazodone)	HIV protease inhibitors	HIV protease inhibitors may increase the plasma concentration of trazodone and vilazodone.
Nefazodone	Benzodiazepines	Nefazodone may increase the pharmacologic effects of certain benzodiazepines. Impaired psychomotor performance and increased sedation may result from elevated benzodiazepine plasma concentrations.
Nefazodone	MTOR inhibitors	Pharmacologic effects of MTOR inhibitors may be increased by nefazodone. Official package labeling for MTOR inhibitors states that coadministration with strong CYP3A4 inhibitors, such as nefazodone, should be avoided.
Nefazodone	Muscarinic receptor antagonists	Plasma concentrations and pharmacologic effects of muscarinic receptor antagonists may be increased by nefazodone. Official package labeling recommends a reduced maximum dose of muscarinic receptor antagonists in patients receiving strong CYP3A4 inhibitors, such as

Generic Name(s)	Interaction	Mechanism
		nefazodone.
Nefazodone	Brentuximab	Plasma concentrations and pharmacologic effects of brentuximab may be increased by nefazodone. The inhibition of CYP3A4 by nefazodone may increase the plasma concentrations of monomethyl auristatin E, the microtubule disrupting agent in brentuximab.
Nefazodone	Budesonide	Plasma concentrations and pharmacologic effects of oral or inhaled budesonide may be increased by nefazodone. Corticosteroid toxicity and/or adrenal suppression may occur.
Nefazodone	Buspirone	Plasma concentrations and pharmacologic effects of buspirone may be increased by nefazodone. The risk of buspirone-induced adverse reactions may be increased. Inhibition of CYP3A4 isoenzymes by nefazodone may decrease the metabolic elimination of buspirone.
Nefazodone	Cabazitaxel	Plasma concentrations and pharmacologic effects cabazitaxel may be increased by nefazodone due to the inhibition of CYP3A4 by nefazodone.
Nefazodone	Cilostazol	Plasma concentration and pharmacologic effects of cilostazol may be increased by nefazodone due to the inhibition of CYP3A4 by nefazodone.
Nefazodone	Cyclosporine	Cyclosporine concentration and pharmacologic effects may be increased by nefazodone. Cyclosporine toxicity may occur.
Nefazodone	Eszopiclone	Plasma concentrations and the pharmacologic effects of eszopiclone may be increased by nefazodone.
Nefazodone	Iloperidone	Plasma concentrations and pharmacologic effects of iloperidone may be increased by nefazodone. A modification of the iloperidone dose is recommended.
Nefazodone	Ivacaftor	Plasma concentrations and pharmacologic effects of ivacaftor may be increased by nefazodone. A reduction in the ivacaftor dose is recommended in patients receiving both medications according to the official package labeling.
Nefazodone	Ixabepilone	The pharmacologic effects of epothilones may be increased by nefazodone. Strong CYP3A4 inhibitors, such as nefazodone, should be avoided in patients receiving ixabepilone.
Nefazodone	Maraviroc	The pharmacologic effects of maraviroc may be increased by nefazodone. A dosage adjustment is recommended for maraviroc during concomitant therapy with strong CYP3A4 inhibitors, such as nefazodone. Coadministration is contraindicated in patients with severe renal impairment.
Nefazodone	Mifepristone	Plasma concentrations and pharmacologic effects of mifepristone may be increased by nefazodone.
Nefazodone	Ruxolitinib	Plasma concentrations and pharmacologic effects of ruxolitinib may be increased by nefazodone. A dose reduction of ruxolitinib or avoidance of ruxolitinib is recommended in patients receiving nefazodone.

Generic Name(s)	Interaction	Mechanism
Nefazodone	Saxagliptin	Plasma concentrations and pharmacologic effects of saxagliptin may be increased by nefazodone.
Trazodone	SSRIs	Unexpected toxic effects may occur when trazodone and certain SSRIs are coadministered. The mechanism of this interaction is unknown.
Trazodone	Delavirdine	Plasma concentrations of trazodone may be increased when coadministered with delavirdine. Inhibition of CYP3A4 isoenzymes by delavirdine may decrease the metabolic elimination of trazodone.
Vilazodone	Cyproheptadine	Pharmacologic effects of may be decreased or reversed by cyproheptadine. Symptoms of depression may recur, because cyproheptadine may directly antagonize the serotonin receptor activity of vilazodone.
Vilazodone	Lithium	Coadministration of lithium and vilazodone may cause central nervous system toxicity, including serotonin syndrome. Serum lithium concentrations may be increased lithium and vilazodone may increase serotonergic neurotransmission.
Vilazodone	L-tryptophan	Both agents acutely increase central nervous system serotonin activity. Coadministration of these two agents could result in serotonin syndrome.
Vilazodone	NSAIDs	Toxic effects may be increased with concurrent administration of NSAIDs and vilazodone. The risk of upper gastrointestinal bleeding may be increased. The mechanism of this interaction is unknown.
Vilazodone	Salicylates	The risk of upper gastrointestinal bleeding may be increased with concurrent administration of salicylates and vilazodone. The mechanism of this interaction is unknown.
Vilazodone	SNRIs	The potential exists for the occurrence of additive serotonergic activity. Inhibition of cytochrome P450 2D6 isoenzymes by vilazodone may decrease the metabolic elimination of SNRIs. The development of serotonin syndrome is possible when the combination of SNRIs and vilazodone are coadministered. In addition, plasma concentrations of SNRIs may be increased by vilazodone.
Vilazodone	Strong CYP3A4 inhibitors	Strong CYP3A4 inhibitors may decrease the metabolic elimination of vilazodone, increasing the plasma concentrations and pharmacological effects of vilazodone.
Vilazodone	St. John’s wort	Unexpected toxicity may occur when St. John's wort and vilazodone are coadministered. The mechanism of this is unknown.
Vortioxetine	CYP2D6 inhibitors (e.g. bupropion, fluoxetine, paroxetine)	Pharmacologic effects of vortioxetine may be increased by CYP2D6 inhibitors.
Tricyclics and Other Norepinephrine-reuptake Inhibitors		
TCAs	MAOIs	Although the combination of MAOIs and TCAs may be useful for treating depression, severe,

Generic Name(s)	Interaction	Mechanism
		sometimes lethal, toxicity may occur. Mechanism of this interaction is unknown.
TCAs (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)	Mibefradil	Pharmacologic and toxic effects of certain TCAs may be enhanced by mibefradil due to its effect on oxidative metabolism of coadministered agents. Substantial dosage adjustment of TCA may be necessary during concurrent administration with mibefradil.
TCAs (amitriptyline, desipramine, imipramine, maprotiline)	Droperidol	Arrhythmias resulting from the potential for additive QT prolongation should be considered as a possibility when droperidol and certain TCAs are coadministered.
TCAs (doxepin, maprotiline, nortriptyline)	Arsenic	The rare occurrence of arrhythmias resulting from the potential for additive QT prolongation should be considered as a possibility when these TCAs and Arsenic are coadministered.
TCAs (amitriptyline, desipramine, imipramine)	Pimozide	Certain TCAs and pimozide may cause additive adverse effects when coadministered. Cardiovascular toxicity may occur due to additive QT-interval prolongation.
TCAs (doxepin, maprotiline, nortriptyline)	Toremifene	Prolongation of the QT interval with possible development of cardiac arrhythmias, including torsades de pointes, should be considered when toremifene is coadministered with these TCAs.
TCAs (doxepin, maprotiline, nortriptyline)	Vandetanib	Additive QT prolongation may occur during coadministration of vandetanib and these TCAs.
TCAs (amitriptyline-chlordiazepoxide)	Azole antifungals	Inhibition of cytochrome P450 3A4 isoenzymes by azole antifungals may decrease the metabolic elimination of chlordiazepoxide and amitriptyline, increasing the pharmacological effects and duration of action of chlordiazepoxide and amitriptyline.
TCAs (amitriptyline-chlordiazepoxide)	Clozapine	Delirium, sedation, sialorrhea, and ataxia may occur when amitriptyline-chlordiazepoxide and clozapine are coadministered. Severe orthostatic hypotension and respiratory depression may occur when clozapine combined with amitriptyline-chlordiazepoxide. The mechanism of this interaction is unknown. Clozapine and amitriptyline- chlordiazepoxide should not be started simultaneously.
TCAs (amitriptyline-chlordiazepoxide)	Sodium oxybate	Concurrent use of sodium oxybate and amitriptyline-chlordiazepoxide may result in an additive increase in sleep duration and central nervous system depression.
TCAs (clomipramine)	Methylene blue	Coadministration of clomipramine and methylene blue may increase the risk of central nervous system toxicity, including serotonin syndrome.
TCAs (maprotiline)	Class III antiarrhythmics	Additive QT prolongation may occur when class III antiarrhythmics and maprotiline are coadministered. Use of class III antiarrhythmics

Generic Name(s)	Interaction	Mechanism
		and maprotiline is not recommended.
TCAs (maprotiline)	Quinolones	The risk of life-threatening cardiac arrhythmias may be increased. The exact mechanism is unknown. Levofloxacin should be avoided, while gatifloxacin and moxifloxacin should be used with caution.
TCAs (maprotiline)	Furazolidone	Concomitant administration of maprotiline and furazolidone may enhance the sympathomimetic effects of maprotiline. The mechanism is unknown.
TCAs (maprotiline)	Halofantrine	Prolonged QT interval and cardiac arrhythmias are a potential when halofantrine and maprotiline are used concomitantly.
TCAs (maprotiline)	Nilotinib	Additive QT prolongation may occur during coadministration of nilotinib and maprotiline.
TCAs (nortriptyline)	Quinidine	Pharmacologic effects of nortriptyline may be increased by quinidine. Elevated plasma concentrations with toxicity characterized by QT prolongation including torsades de pointes may occur. Mechanism: Inhibition of CYP2D6 isoenzymes by quinidine may decrease the metabolic elimination of nortriptyline which may increase the risk for concentration-dependent prolongation of the QT interval.
TCAs	Tramadol	Increased risk of seizures may occur when tramadol and TCAs are coadministered.
TCAs (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)	Cimetidine	Therapeutic efficacy and frequency of side effects of TCAs may be altered by concurrent therapy with cimetidine.
TCAs (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)	Clonidine	The antihypertensive effects of clonidine may be decreased by TCAs. TCAs may worsen rebound reactions from abrupt clonidine withdrawal.
TCAs (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)	Fluconazole	Fluconazole may increase plasma concentrations and toxic effects of these TCAs.
TCAs (amitriptyline,	Fluoxetine	The pharmacologic and toxic effects of TCAs may be increased by fluoxetine, despite reports of

Generic Name(s)	Interaction	Mechanism
amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)		increased clinical efficacy.
TCAs (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)	Fluvoxamine	The pharmacologic and toxic effects of TCAs may be increased by fluvoxamine. Toxicity may result.
TCAs (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)	Guanfacine	The antihypertensive effect of guanfacine may be decreased by TCAs.
TCAs (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)	Iobenguane	TCAs may reduce uptake and diagnostic efficacy of iobenguane. False-negative iobenguane imaging tests may result.
TCAs (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)	Paroxetine	The pharmacologic/toxic effects and plasma concentrations of TCAs may be increased by paroxetine.
TCAs (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)	Rasagiline	The combination of rasagiline and these TCAs may precipitate symptoms of serotonin syndrome.
TCAs (amitriptyline, amoxapine, clomipramine, desipramine,	Sertraline	The pharmacologic and toxic effects of TCAs may be increased by sertraline.

Generic Name(s)	Interaction	Mechanism
doxepin, imipramine, protriptyline, trimipramine)		
TCAs (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline)	Phenothiazines	Plasma concentrations of phenothiazines and TCAs may be increased when coadministered. Risk of toxicity associated with TCAs and/or risk for potential additive QT prolongation is possible with some when some TCAs are coadministered with phenothiazines.
TCAs (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline)	Carbamazepine	Serum carbamazepine levels may be elevated, increasing pharmacologic and toxic effects, while TCA levels may be decreased. Carbamazepine may alter the parent drug-hydroxylated metabolite ratio, resulting in increased risk of toxicity or loss of efficacy of TCAs.
TCAs (amoxapine, clomipramine, desipramine, maprotiline, nortriptyline)	Abiraterone	Plasma concentrations and pharmacologic effects of these TCAs may be increased by abiraterone. Coadministration of these TCAs and abiraterone should be avoided.
TCAs (amitriptyline, desipramine, doxepin, imipramine, nortriptyline)	Duloxetine	Plasma concentrations of these TCAs may be increased by duloxetine. Serotonin syndrome is also a risk with this combination.
TCAs (amitriptyline, clomipramine, desipramine, imipramine, nortriptyline)	Terbinafine	The pharmacologic and toxic effects of TCAs may be increased by terbinafine. Toxic signs may occur.
TCAs (amitriptyline, clomipramine, nortriptyline)	Valproic acid and derivatives	Plasma concentrations and toxic effects of these TCAs may be increased by valproic acid and its derivatives.
TCAs (amitriptyline-chlordiazepoxide)	Hydantoins	Pharmacologic effects of hydantoins may be increased by amitriptyline-chlordiazepoxide. Elevated hydantoin plasma concentrations and toxicity may occur. Serum concentrations and pharmacologic effects of amitriptyline-chlordiazepoxide may be decreased by hydantoins.
TCAs (amitriptyline-chlordiazepoxide)	Rifamycins	Pharmacologic effects of chlordiazepoxide-amitriptyline may be decreased by rifamycins.
TCAs (amitriptyline-chlordiazepoxide)	Disulfiram	Pharmacologic and toxic effects of amitriptyline-chlordiazepoxide may be increased by disulfiram. Disulfiram may inhibit hepatic metabolism of amitriptyline- chlordiazepoxide.
TCAs (amitriptyline-chlordiazepoxide)	Nefazodone	Nefazodone may increase the pharmacologic effects of amitriptyline-chlordiazepoxide. Impaired psychomotor performance and increased sedation may result from elevated

Generic Name(s)	Interaction	Mechanism
		amitriptyline-chlordiazepoxide plasma concentrations.
Antidepressants, Miscellaneous		
Bupropion	MAOIs	The use of bupropion with MAOIs is contraindicated due to the potential for hypertensive crisis. Only very high doses of selegiline participate in this interaction.
Bupropion	Linezolid	Manufacturer's literature states that the use of bupropion with linezolid is contraindicated due to risk for hypertensive crisis.
Bupropion	Methylene blue	Coadministration of bupropion and methylene blue may increase the risk of hypertensive reactions. The official package labeling of bupropion contraindicates the initiation of bupropion in patients receiving methylene blue.
Bupropion	Pimozide	Plasma concentrations of pimozide may be increased by bupropion. Coadministration of pimozide with bupropion is contraindicated.
Bupropion	Tamoxifen	Pharmacologic effects of tamoxifen may be decreased by bupropion. Coadministration of bupropion with tamoxifen may increase the risk of breast cancer recurrence.
Mirtazapine	MAOIs	Concomitant administration of mirtazapine and MAOIs may enhance the sympathomimetic effects of mirtazapine. Concomitant use of mirtazapine and MAOIs is contraindicated. Only higher doses of selegiline participate in this interaction.
Mirtazapine	Furazolidone	Concomitant administration of mirtazapine and furazolidone may enhance the sympathomimetic effects of mirtazapine. The mechanism is unknown.
Mirtazapine	Linezolid	Coadministration of mirtazapine and linezolid may increase the risk of central nervous system toxicity, including serotonin syndrome. Coadministration of mirtazapine and linezolid is contraindicated. The initiation of mirtazapine is contraindicated in patients receiving linezolid according to the package labeling of mirtazapine.
Mirtazapine	Methylene blue	Coadministration of mirtazapine and methylene blue may increase the risk of central nervous system toxicity, including serotonin syndrome. The official package labeling of mirtazapine contraindicates the initiation of mirtazapine in patients receiving methylene blue.
Mirtazapine	Perampanel	The central nervous system effects of mirtazapine may be enhanced by perampanel. In addition, increased levels of confusion, depression, anger and aggression may occur.
Bupropion	Lopinavir/ritonavir	Plasma concentrations and pharmacologic effects of bupropion may be decreased by lopinavir/ritonavir.
Bupropion	Rifamycins	Bupropion plasma concentrations may be reduced secondary to increased metabolism of bupropion. In patients receiving bupropion, close monitoring of clinical efficacy is advised when rifamycins is

Generic Name(s)	Interaction	Mechanism
		coadministered.
Bupropion	Ritonavir	Plasma concentrations and pharmacologic effects of bupropion may be decreased by ritonavir.
Bupropion	Tiagabine	The potential exists for seizures to occur in patients receiving tiagabine who are also receiving drugs such as bupropion that are known to lower the seizure threshold.
Mirtazapine	Hydantoins	Mirtazapine plasma concentrations may be reduced by hydantoins.

COMT=catechol-O-methyltransferase, HIV=human immunodeficiency virus, MAOI=monoamine oxidase inhibitors, MTOR=mammalian target of rapamycin, NSAIDS=nonsteroidal anti-inflammatory drugs, SNRI=serotonin–norepinephrine reuptake inhibitors, SSRI=selective serotonin re-uptake inhibitors, TCA=tricyclic antidepressants

VI. Adverse Drug Events

The most common adverse drug events reported with the antidepressants are listed in Tables 6a to 6f. The boxed warnings for the antidepressants are listed in Tables 7 to 9.

Table 6a. Adverse Drug Events (%) Reported with the Monoamine Oxidase Inhibitors[1-34]

Adverse Events	Isocarboxazid	Phenelzine	Selegiline	Tranylcypromine
Cardiovascular				
Arrhythmia	-	-	<1	-
Atrial fibrillation	-	-	<1	-
Bradycardia	-	-	<1	-
Cardiovascular depression	-	✔	-	-
Chest pain	-	-	≥1	-
Hypertension	-	-	≥1	-
Hypotension	-	-	3 to 10	-
Myocardial infarct	-	-	<1	-
Orthostatic hypotension	4	✔	-	✔
Palpitation	2	-	<1	✔
Peripheral edema	-	-	≥1	-
Peripheral vascular disorder	-	-	<1	-
Postural hypotension	-	✔	-	-
Syncope	2	-	<1	-
Tachycardia	-	✔	<1	✔
Vasodilation	-	-	<1	-
Central Nervous System				
Abnormal thinking	-	-	>1	-
Agitation	-	-	>1	✔
Akathisia	✔	-	-	-
Akinesia	-	-	-	✔
Amnesia	-	-	>1	-
Anxiety	2	✔	-	✔
Ataxia	✔	✔	<1	✔
Behavior changes	-	-	>1	-
Bradykinesia	-	-	>1	-
Coma	✔	✔	-	-
Confusion	-	-	<1	✔
Convulsions	-	✔	-	-
Delirium	-	✔	-	-
Delusions	-	-	<1	-
Depersonalization	-	-	<1	-

Adverse Events	Isocarboxazid	Phenelzine	Selegiline	Tranylcypromine
Depression	-	-	<1	-
Disorientation	-	-	-	✔
Dizziness	15 to 29	✔	-	✔
Drowsiness	4	✔	-	✔
Emotional lability	-	-	<1	-
Euphoria	✔	✔	<1	-
Fatigue	-	✔	-	✔
Forgetfulness	2	-	-	-
Hallucinations	<1	-	-	-
Headache	6 to 15	✔	18	✔
Hostility	-	-	<1	-
Hyperactivity	2	-	-	-
Hyperesthesia	-	-	<1	-
Hyperkinesias	-	-	<1	-
Hyperreflexia	-	✔	-	✔
Hypersomnia	-	✔	-	-
Insomnia	4 to 6	✔	12	✔
Jitteriness	-	✔	-	-
Lethargy	2	-	-	-
Loss of balance	-	-	<1	-
Manic symptoms	-	✔	<1	✔
Migraine	-	-	<1	-
Neuritis	✔	-	-	-
Neurosis	-	-	<1	-
Numbness	-	-	-	✔
Palilalia	-	✔	-	-
Paranoid reaction	-	-	<1	-
Parasomnia	-	-	>1	-
Paresthesia	2	✔	>1	✔
Restlessness	-	-	-	✔
Schizophrenia precipitation	-	✔	-	-
Sedation	2	-	-	-
Seizure	-	✔	-	-
Sleep disturbance	2 to 5	✔	-	✔
Tremor	4	✔	<1	✔
Twitching	-	✔	<1	✔
Vertigo	-	-	<1	-
Weakness	-	✔	-	✔
Dermatological				
Acne	-	-	≥1	-
Alopecia	-	-	<1	✔
Application site reaction	-	-	24	-
Bruising	-	-	≥1	-
Cystic acne flare-up	-	-	-	✔
Maculopapular rash	-	-	<1	-
Photosensitivity	✔	-	<1	-
Pruritus	-	✔	≥1	✔
Rash	-	✔	4	✔
Scleroderma	-	-	-	✔
Skin benign neoplasm	-	-	<1	-
Skin hypertrophy	-	-	<1	-
Urticaria	-	-	<1	✔
Vesiculobullous rash	-	-	<1	-
Gastrointestinal				

Adverse Events	Isocarboxazid	Phenelzine	Selegiline	Tranylcypromine
Abdominal pain	-	-	-	✔
Anorexia	-	-	≥1	✔
Appetite increased	-	-	<1	-
Black tongue	✔	-	-	-
Colitis	-	-	<1	-
Constipation	4 to 7	✔	>11	✔
Dental caries	-	-	<1	-
Diarrhea	2	-	9	✔
Dyspepsia	-	-	4	-
Eructation	-	-	<1	-
Flatulence	≥1	-	≥1	-
Gastritis	<1	-	<1	-
Gastroenteritis	≥1	-	≥1	-
Gastrointestinal disturbances	-	✔	-	-
Melena	<1	-	<1	-
Nausea	4 to 6	✔	-	✔
Rectal hemorrhage	<1	-	<1	-
Salivation increased	-	-	<1	-
Taste perversion	-	-	≥1	-
Tongue edema	-	-	<1	-
Vomiting	≥1	✔	≥1	-
Weight gain	-	✔	-	-
Weight loss	-	-	5	-
Xerostomia	6 to 9	✔	8	✔
Genitourinary				
Anorgasmia	-	✔	-	-
Cystitis	-	-	<1	-
Dysmenorrhea	-	-	≤1	-
Dysuria	✔	-	<1	-
Ejaculation disturbances	-	✔	-	✔
Hematuria	-	-	<1	-
Impotence	2	✔	-	✔
Incontinence	✔	-	-	-
Kidney calculus	-	-	<1	-
Libido increased	-	-	<1	-
Menorrhagia	-	-	<1	-
Pelvic pain	-	-	<1	-
Polyuria	-	-	<1	-
Prostatic hyperplasia	-	-	<1	-
Sexual disturbances	✔	✔	≤1	-
Urinary frequency	2	-	<1	✔
Urinary hesitancy	1	-	-	-
Urinary retention	✔	✔	<1	✔
Urinary tract infection	-	-	≥1	-
Urinary urgency	-	-	<1	-
Urination impaired	-	-	<1	-
Vaginal hemorrhage	-	-	<1	-
Vaginal moniliasis	-	-	<1	-
Hematologic				
Agranulocytosis	-	-	-	✔
Anemia	-	-	<1	✔
Hematologic changes	✔	-	-	-
Leukocytosis	-	-	<1	-
Leukopenia	-	✔	<1	✔

Adverse Events	Isocarboxazid	Phenelzine	Selegiline	Tranylcypromine
Thrombocytopenia	-	-	-	✔
Hepatic				
Hepatitis	-	✔ -	-	✔
Jaundice	-	✔	-	-
Liver function tests abnormal	-	-	<1	-
Hepatocellular damage	-	✔	-	-
Transaminases increased	-	✔	-	-
Laboratory Test Abnormalities				
Alkaline phosphatase increased	-	-	<1	-
Hypercholesterolemia	-	-	<1	-
Hyperglycemia	-	-	<1	-
Hypernatremia	-	✔	-	-
Hypoglycemic reaction	-	-	<1	-
Hyponatremia	-	-	<1	✔
Lactate dehydrogenase increased	-	-	<1	-
Musculoskeletal				
Generalized spasm	-	-	<1	-
Heavy feeling	2	✔	-	-
Hypertonia	-	-	<1	-
Myalgia	-	-	≥1	-
Myasthenia	-	-	<1	-
Myoclonic jerks/movements	2	✔	<1	✔
Neck pain	-	-	≥1	-
Tenosynovitis	-	-	<1	-
Respiratory				
Asthma	-	-	<1	-
Bronchitis	-	-	≥1	-
Cough	-	-	≥1	-
Dyspnea	-	-	<1	-
Laryngismus	-	-	<1	-
Pharyngitis	-	-	3	-
Pneumonia	-	-	<1	-
Respiratory depression	-	✔	-	-
Sinusitis	-	-	3	-
Special Senses				
Blurred vision	✔	✔	-	✔
Glaucoma	-	✔	-	✔
Nystagmus	-	✔	-	-
Tinnitus	-	-	<1	✔
Visual field defect	-	-	<1	-
Toxic amblyopia	✔	-	-	-
Other				
Bacterial infection	-	-	<1	-
Bilirubinemia	-	-	<1	-
Breast Pain	-	-	<1	-
Chills	2	-	<1	✔
Circumoral paresthesia	-	-	<1	-
Dehydration	-	-	<1	-
Diaphoresis	2	✔	≥1	✔
Edema	-	✔	<1	✔
Edema of the glottis	-	✔	-	-
Epistaxis	-	-	<1	-
Facial edema	-	-	<1	-

Adverse Events	Isocarboxazid	Phenelzine	Selegiline	Tranylcypromine
Fever	-	✔	<1	-
Fungal infection	-	-	<1	-
Glossitis	-	-	<1	-
Heat stroke	-	-	<1	-
Hernia	-	-	<1	-
Hypermetabolic syndrome	-	✔	-	✔
Impaired water secretion	✔	-	-	✔
Lupus-like syndrome	-	✔	-	-
Lymphadenopathy	-	-	<1	-
Moniliasis	-	-	<1	-
Neoplasia	-	-	<1	-
Osteoporosis	-	-	<1	-
Otitis external	-	-	<1	-
Parasitic infection	-	-	<1	-
Periodontal abscess	-	-	<1	-
Syndrome of inappropriate antidiuretic hormone secretion	✔	✔	-	✔
Suicide attempt	-	-	<1	-
Sweating	2	✔	>1	-
Toxic delirium	-	✔	-	-
Viral infection	-	-	<1	-

✔ Percent not specified.
- Event not reported or incidence <1%.

Table 6b. Adverse Drug Events (%) Reported with the Selective Serotonin- and Norepinephrine-reuptake Inhibitors[1-34]

Adverse Events	Desvenlafaxine	Duloxetine	Levomilnacipran	Venlafaxine
Cardiovascular				
Aneurysm	-	-	-	<1
Angina pectoris	-	-	<2	<1
Arrhythmia	-	-	-	<1
Atrial fibrillation	-	<1	-	-
Atrioventricular block	-	-	-	<1
Bigeminy	-	-	-	<1
Blood pressure increase	1 to 2	-	3	-
Bradycardia	-	-	-	<1
Bundle branch block	-	<1	-	<1
Cardiovascular disorder	-	-	-	<1
Cerebral ischemia	-	-	-	<1
Chest pain	-	-	<2	2
Congestive heart failure	-	<1	-	<1
Coronary artery disease	-	-	-	<1
Edema	-	-	-	✔
Electrocardiogram abnormalities	-	-	-	<1
Extrasystoles	-	-	<2	<1
Heart arrest	-	-	-	<1
Heart rate increase	-	-	6	-
Hemorrhage	-	-	-	<1
Hypertension, dose related and dose independent	<1	-	3	3 to 13
Hypertensive crisis	-	<1	-	-
Hypotension	-	-	3	<1

Adverse Events	Desvenlafaxine	Duloxetine	Levomilnacipran	Venlafaxine
Myocardial infarct	<2	<1	-	<1
Myocardial ischemia	<1	-	-	-
Orthostatic hypotension	<2	<1	10 to 12	-
Palpitation	≤3	1 to 2	5	3
Peripheral edema	-	<1	-	-
Postural hypotension	-	-	-	1
Syncope	<2	<1	<2	<1
Tachycardia	<1	<1	6	2
Vasodilation	-	-	-	3 to 4
Central Nervous System				
Abnormal dreams	2 to 3	2 to 3	-	3 to 7
Abnormal thinking	-	-	-	2
Agitation	-	5 to 6	<2	2 to 4
Aggression	-	<1	<2	-
Amnesia	-	-	-	✔
Anger	-	-	<2	-
Anxiety	3 to 5	3	-	5 to 6
Ataxia	-	<1	-	<1
Blurred vision	-	4	-	4 to 6
Bradykinesia	-	-	-	<1
Chills	-	-	-	3
Concentration decreased	≤1	-	-	-
Confusion	-	-	-	2
Deafness	-	-	-	<1
Delusions	-	-	-	<1
Dementia	-	-	-	<1
Depersonalization	<2	-	-	1
Depression	-	-	-	1 to 3
Diplopia	-	<1	-	-
Disorientation	-	<1	-	-
Dizziness	10 to 13	6 to 17	-	11 to 20
Dystonia	-	-	-	<1
Extrapyramidal symptoms	<2	-	<2	-
Fatigue	7	2 to 15	-	-
Fever	-	1 to 3	-	✔
Guillain-Barre syndrome	-	-	-	<1
Hostility	-	-	-	<1
Hypoesthesia	-	1	-	-
Headache	-	13	-	25 to 38
Hypoesthesia	-	1	-	✔
Hypomania	<2	-	-	-
Insomnia	9 to 12	8 to 6	-	15 to 23
Irritability	2	1	-	-
Lethargy	-	1	-	-
Loss of consciousness	-	-	-	<1
Mania	-	<1	-	-
Migraine	-	-	<2	✔
Mood swings	-	<1	-	-
Nervousness	-	1	-	6 to 21
Neuropathy	-	-	-	<1
Neutropenia	-	-	-	<1
Nightmares	-	1	-	-
Panic attack	-	-	<2	-
Paresthesia	≤2	1	<2	2 to 3

Adverse Events	Desvenlafaxine	Duloxetine	Levomilnacipran	Venlafaxine
Parkinsonism	<1	-	-	-
Photopsia	-	<1	-	-
Photosensitivity	-	<1	-	-
Restlessness	-	1	-	-
Seizure	-	<1	-	<1
Sleep disorder	-	1	-	-
Somnolence	≤9	13 to 20	-	12 to 23
Tension	-	-	<2	-
Trismus	-	-	-	✔
Vertigo	-	1	-	✔
Yawning	-	1	<2	3 to 5
Dermatological				
Acne	-	<1	-	-
Alopecia	-	<1	-	-
Bruising	-	-	-	✔
Ecchymosis	-	<1	-	-
Eczema	-	<1	-	-
Erythema	-	<1	-	-
Erythema multiforme	-	-	-	<1
Exfoliative dermatitis	-	-	-	<1
Dry skin	-	-	<2	-
Hyperhidrosis	10 to 21	6 to 8	9	-
Maculopapular rash	-	-	-	<1
Miliaria	-	-	-	<1
Pruritus	-	3	<2	1
Rash	1	4	2	3
Skin atrophy	-	-	-	<1
Stevens-Johnson syndrome	-	<1	-	<1
Toxic epidermal necrolysis	-	-	-	<1
Urticaria	-	<1	<2	-
Endocrine and Metabolic				
Bilirubin increased	-	<1	-	<1
Blood urea nitrogen increased	-	-	-	<1
Cholesterol increased	3 to 4	<1	-	-
Creatinine increased	-	-	-	<1
Diabetes mellitus	-	-	-	<1
Dyslipidemia	-	<1	-	-
Electrolyte abnormalities	-	-	-	<1
Hepatic steatosis	-	<1	-	-
Hepatitis	-	<1	-	<1
Hot flushes	-	2	<2	-
Hypercalcinuria	-	-	-	<1
Hyperchlorhydria	-	-	-	<1
Hypercholesterolemia	-	<1	-	<15
Hyperglycemia	-	-	-	<1
Hyperkalemia	-	-	-	<1
Hyperlipidemia	-	<1	-	<1
Hyperphosphatemia	-	-	-	<1
Hyperthyroidism	-	-	-	<1
Hypertriglyceridemia	-	<1	-	-
Hyperuricemia	-	-	-	<1
Hypocholesterolemia	-	-	-	<1
Hypoglycemia	-	1	-	<1

Adverse Events	Desvenlafaxine	Duloxetine	Levomilnacipran	Venlafaxine
Hypokalemia	-	-	-	<1
Hyponatremia	-	<1	-	<1
Hypophosphatemia	-	-	-	<1
Hypothyroidism	-	-	-	<1
Increased blood cholesterol	-	-	<2	-
Increased liver function tests	-	-	<2	-
Jaundice	-	<1	-	<1
Kidney function abnormal	-	-	-	<1
Low-density lipoprotein increased	≤1	-	-	-
Liver enzymes increased	≤2	-1	-	<1
Syndrome of inappropriate antidiuretic hormone secretion	-	<1	-	<1
Transaminase elevation	-	1	-	-
Triglycerides increased	-	-	-	✔
Weight gain	-	<1	-	✔
Weight loss	≤2	1 to 2	-	1 to 4
Gastrointestinal				
Abdominal pain	-	<1	<2	6
Abnormal taste	-	-	-	2
Anorexia	5 to 8	3 to 5	-	8 to 20
Aphthous stomatitis	-	<1	-	-
Appetite decreased	-	3 to 11	3	-
Appetite increased	-	-	-	✔
Bloody stools	-	<1	-	-
Cholelithiasis	-	-	-	<1
Colitis	-	<1	-	-
Constipation	9 to 11	5 to 15	9	8 to 15
Diarrhea	9 to 11	7 to 13	-	6 to 8
Diverticulitis	-	<1	-	-
Dyspepsia	-	4 to 5	-	7
Dysphagia	-	<1	-	-
Eructation	-	<1	-	-
Esophageal stenosis	-	<1	-	-
Flatulence	-	-	<2	3 to 4
Gastric emptying impaired	-	<1	-	-
Gastric irritation	-	<1	-	-
Gastric ulcer	-	<1	-	<1
Gastritis	-	1	-	-
Hematemesis	-	-	-	<1
Intestinal obstruction	-	-	-	<1
Irritable bowel syndrome	-	<1	-	-
Loose stools	-	2 to 3	-	-
Melena	-	<1	-	-
Nausea	22 to 26	14 to 30	17	21 to 58
Vomiting	≤4	1 to 6	5	3 to 6
Xerostomia	11 to 17	5 to 18	-	12 to 22
Genitourinary				
Crystalluria	-	-	-	<1
Dysuria	-	1	-	-
Ejaculation abnormality	≤1	1 to 4	5	2 to 19
Erectile dysfunction	3 to 6	1 to 5	6	-
Hematuria	-	-	<2	-

Adverse Events	Desvenlafaxine	Duloxetine	Levomilnacipran	Venlafaxine
Impotence	-	-	-	4 to 10
Libido decreased	4 to 5	2 to 4	-	3 to 9
Menstrual abnormalities	-	-	-	<1
Micturition urgency	-	<1	-	-
Nocturia	-	<1	-	-
Pollakiuria	-	1 to 5	<2	-
Prostatic disorder	-	-	-	✔
Proteinuria	6 to 8	-	<2	-
Pyelonephritis	-	-	-	<1
Pyuria	-	-	-	<1
Testicular pain	-	-	4	-
Urinary frequency	-	-	-	3
Urinary hesitation	-	-	4	-
Urinary retention	-	<1	-	1
Urinary symptoms	≤1	1	-	-
Urination impaired	-	-	-	2
Hematologic				
Agranulocytosis	-	-	-	<1
Anemia	-	<1	-	-
Aplastic anemia	-	-	-	<1
Bleeding time increased	-	-	-	<1
Eosinophilia	-	-	-	<1
Hypoproteinemia	-	-	-	<1
Leukocytosis	-	-	-	<1
Leukoderma	-	-	-	<1
Leukopenia	-	<1	-	<1
Lymphadenopathy	-	<1	-	<1
Lymphocytosis	-	-	-	<1
Pancytopenia	-	-	-	<1
Thrombocytopenia	-	<1	-	<1
Thrombophlebitis	-	-	-	<1
Musculoskeletal				
Arthralgia	-	-	-	✔
Dysarthria	-	<1	-	-
Extrapyramidal symptoms	-	-	<2	<1
Hypertonia	-	-	-	3
Malaise	-	<1	-	-
Muscle cramp	-	4 to 5	-	-
Muscle pain	-	1 to 5	-	-
Muscle tightness	-	1	-	1 to 2
Muscle twitching	-	4	-	<1
Myalgia	-	1 to 3	-	-
Myasthenia	-	-	-	<1
Myopathy	-	-	-	<1
Neck pain/rigidity	-	-	-	✔
Neuroleptic malignant-like syndrome	-	-	-	<1
Osteoporosis	-	-	-	<1
Rhabdomyolysis	-	-	-	<1
Rheumatoid arthritis	-	-	-	<1
Rigors	-	1	-	-
Tendon rupture	-	-	-	<1
Tremor	≤3	3 to 4	-	4 to 10
Weakness	≤2	2 to 8	-	8 to 19

Adverse Events	Desvenlafaxine	Duloxetine	Levomilnacipran	Venlafaxine
Respiratory				
Asthma	-	-	-	<1
Atelectasis	-	-	-	<1
Cough	-	3 to 6	-	✔
Dyspnea	-	-	-	✔
Epistaxis	<2	-	-	-
Nasopharyngitis	-	7 to 9	-	-
Pharyngitis	-	-	-	7
Pharyngolaryngeal pain	-	1 to 6	-	-
Pleurisy	-	-	-	<1
Pneumonia	-	-	-	<1
Sinusitis	-	-	-	2
Upper respiratory infection	-	7	-	-
Other				
Anaphylactic reaction	-	<1	-	<1
Angioneurotic edema	-	<1	-	-
Arteritis	-	-	-	<1
Bacteremia	-	-	-	<1
Basophilia	-	-	-	<1
Blurred/abnormal vision	-	1 to 3	<2	4 to 6
Bruxism	-	<1	<2	-
Cataract	-	-	-	<1
Catatonia	-	-	-	<1
Cellulites	-	-	-	<1
Conjunctival hemorrhage	-	-	<2	-
Cyanosis	-	-	-	<1
Deep vein thrombosis	-	-	-	<1
Dehydration	-	<1	-	<1
Diaphoresis increased	10 to 14	6	-	10 to 14
Embolus	-	-	-	<1
Facial edema	-	<1	-	-
Facial paralysis	-	-	-	<1
Fasciitis	-	-	-	<1
Flu-like syndrome	-	<1	-	6
Gingivitis	-	<1	-	-
Glaucoma	-	<1	-	<1
Homicidal ideation	-	-	-	<1
Hot flushes	-	2 to 3	<2	-
Hyperacusis	-	-	-	<1
Hypersensitivity reaction	<2	-	-	-
Infection	-	-	-	6
Keratoconjunctivitis sicca	-	<1	-	-
Larynx edema	-	-	-	<1
Macular degeneration	-	<1	-	-
Maculopathy	-	<1	-	-
Moniliasis	-	-	-	<1
Multiple myeloma	-	-	-	<1
Mydriasis	2	-	-	2
Nephropathy	-	<1	-	-
Night sweats	-	1	-	-
Oropharyngeal edema	-	<1	-	-
Phlebitis	-	<1	-	-
Retinal detachment	-	<1	-	-
Serotonin syndrome	-	-	-	<1

Adverse Events	Desvenlafaxine	Duloxetine	Levomilnacipran	Venlafaxine
Stomatitis	-	<1	-	-
Suicidal ideation/attempt	-	<1	-	<1 to 2
Thirst	-	<1	<2	-
Tinnitus	2	-	-	2
Trauma	-	-	-	2
Trismus	-	-	-	✔
Visual disturbance	-	<1	-	-
Withdrawal syndrome	-	<1	-	<1

✔ Percent not specified.
- Event not reported or incidence <1%.

Table 6c. Adverse Drug Events (%) Reported with the Selective Serotonin-reuptake Inhibitors[1-34]

Adverse Events	Citalopram	Escitalopram	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline
Cardiovascular						
Angina	-	-	<1	<1	<1	-
Arrhythmia	-	-	<1	-	-	-
Atrial arrhythmia	-	-	-	-	<1	<1
Atrial fibrillation	-	<1	<1	-	-	-
Atrioventricular block	-	-	-	<1	-	<1
Bradycardia	1 to 10	<1	-	<1	<1	<1
Cardiomyopathy	-	-	-	<1	-	-
Cerebrovascular accident	-	<1	<1	<1	<1	-
Chest pain	<1	<1	>1	3	3	>1
Chest tightness	-	<1	-	-	<1	-
Congestive heart failure	-	-	<1	<1	<1	-
Coronary artery disease	-	-	-	<1	-	-
Electrocardiogram abnormal	-	<1	-	<1	-	-
Edema	<1	<1	<1	≤1	-	<1
Hemorrhage	-	-	✔	<1	-	-
Hypertension	<1	<1	>1	1 to 2	≥1	<1
Myocardial infarct	-	-	<1	<1	<1	-
Orthostatic hypotension	-	<1	-	≤1	<1	-
Palpitation	-	<1	>1	3	2 to 3	>1
Pericarditis	-	-	-	<1	-	-
Peripheral edema	-	-	<1	-	-	<1
Postural hypotension	1 to 10	-	<1	-	<1	<1
Pulmonary hypertension	-	-	<1	-	-	<1
QT_c prolongation	<1	<1	<1	-	-	<1
Supraventricular extrasystoles	-	-	-	<1	-	-
Syncope	-	<1	<1	≤1	<1	<1
Tachycardia	1 to 10	<1	<1	≤1	≥1	-
Vasculitis	-	<1	<1	<1	<1	<1
Vasodilation	-	-	1 to 5	2	2 to 4	-
Ventricular arrhythmia	<1	<1	-	-	<1	-
Ventricular tachycardia	<1	<1	<1	<1	<1	<1
Central Nervous System						
Abnormal dreams	-	3	1 to 5	3	3 to 4	<1
Abnormal gait	-	<1	<1	-	-	<1
Abnormal thinking	-	-	2	3	<1	-

Adverse Events	Citalopram	Escitalopram	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline
Aggression	-	<1	-	-	-	<1
Agitation	3 to 10	<1	>1	2 to 3	3 to 5	5
Akathisia	-	<1	<1	-	-	-
Akinesia	-	-	-	<1	<1	-
Amnesia	>1	<1	>1	✔	2	<1
Anxiety	4	<1	6 to 15	5 to 8	5	4
Apathy	>1	<1	<1	1 to 3	-	<1
Aphasia	-	-	-	-	<1	-
Asthenia	-	-	-	14	-	>1
Ataxia	-	-	<1	<1	<1	<1
Auditory hallucination	-	<1	-	-	-	-
Blindness	-	-	-	-	-	<1
Blurred vision	-	1 to 10	-	-	-	-
Chills	-	-	>1	2	<1	-
Central nervous system stimulation	-	-	<1	2	-	-
Concentration impaired	✔	1 to 10	-	-	3 to 4	<1
Confusion	>1	<1	>1	<1	1	<1
Deafness	-	-	-	-	<1	-
Delirium	<1	<1	-	-	<1	-
Depersonalization	-	<1	<1	-	≤3	-
Depression	>1	<1	>1	2	-	<1
Dizziness	-	5	9	11 to 15	6 to 14	12
Dyskinesias	<1	<1	<1	<1	<1	-
Dystonia	-	-	-	<1	<1	<1
Emotional lability	-	<1	>1	-	>1	<1
Euphoria	-	-	<1	-	<1	<1
Excitability	-	<1	-	-	-	-
Extrapyramidal symptoms	-	-	<1	<1	<1	<1
Fatigue	5	5 to 8	-	-	-	12
Fever	2	<1	2	-	-	-
Guillain-Barre syndrome	-	-	-	-	<1	-
Hallucinations	-	<1	<1	<1	<1	<1
Headache	-	24	21	22 to 35	17 to 18	25
Hiccup	-	-	<1	-	-	-
Hyperkinesia	-	-	<1	✔	-	<1
Hyperreflexia	-	<1	-	-	-	-
Hypertonia	-	-	<1	2	<1	>1

Adverse Events	Citalopram	Escitalopram	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline
Hypoesthesia	-	<1	-	-	-	1 to 10
Hypokinesia	-	-	-	✔	-	<1
Hypomania	-	-	-	<1	-	-
Insomnia	>10	9 to 12	10 to 33	21 to 35	11 to 24	21
Irritability	-	<1	-	-	-	-
Lethargy	-	3	-	-	-	-
Lightheadedness	-	<1	-	-	-	-
Malaise	-	<1	<1	✔	-	1 to 10
Mania	-	-	-	✔	-	-
Meningitis	-	-	-	-	<1	-
Migraine	>1	<1	<1	-	<1	<1
Nervousness	-	-	8 to 14	10 to 12	4 to 9	5
Neuralgia	-	-	<1	<1	-	-
Neuropathy	-	-	<1	<1	<1	-
Neurosis	-	-	<1	2	<1	-
Nystagmus	-	<1	-	-	-	<1
Optic neuritis	-	-	<1	-	-	<1
Panic reaction	-	<1	-	-	-	-
Paralysis	-	-	-	<1	<1	-
Paresthesia	>1	2	-	3	4	2
Parkinsonism	-	<1	-	-	-	-
Psychiatric disturbances	-	<1	-	✔	-	<1
Seizure	-	✔	-	<1	<1	-
Somnolence	>10	6 to 13	5 to 17	22 to 27	15 to 24	13
Tardive dyskinesia	-	<1	-	<1	-	-
Tetany	-	-	-	-	<1	-
Tremors	8	-	9	4	-	8
Vertigo	-	<1	<1	-	>1	<1
Yawning	<10	2	<11	2 to 5	2 to 4	>1
Dermatological						
Acne	-	-	<1	2	<1	<1
Alopecia	-	-	<1	<1	<1	<1
Angioedema	-	-	-	<1	<1	<1
Bruising	-	-	<1	4	<1	-
Bullous eruption	-	-	-	<1	-	-
Cellulitis	-	-	-	-	<1	-
Ecchymosis	-	-	<1	2	<1	<1

Adverse Events	Citalopram	Escitalopram	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline
Eczema	-	-	<1	<1	<1	<1
Epidermal necrolysis	<1	<1	<1	-	<1	-
Erythema multiforme	<1	<1	<1	-	<1	-
Erythema nodosum	>1	-	<1	-	-	-
Exfoliative dermatitis	>1	-	<1	-	<1	-
Photosensitivity	<1	-	<1	<1	<1	<1
Pruritus	✔	-	4	-	>1	<1
Rash	✔	<1	2 to 6	-	2 to 3	>10
Stevens-Johnson syndrome	-	-	<1	<1	-	<1
Urticaria	<1	-	-	<1	<1	<1
Endocrine and Metabolic						
Albuminuria	-	-	<1	-	-	-
Alkaline phosphatase increased	-	-	-	-	<1	-
Bilirubin increased	-	<1	-	-	<1	<1
Blood urea nitrogen increased	-	-	-	-	<1	-
Cholecystitis	-	-	-	<1	-	-
Cholelithiasis	-	-	<1	<1	<1	-
Cholestatic jaundice	-	-	<1	-	-	-
Diabetes mellitus	-	<1	-	-	<1	-
Galactorrhea	-	-	-	-	-	<1
Goiter	-	-	-	<1	<1	-
Gynecomastia	-	<1	<1	-	5	<1
Hepatic failure	-	-	<1	-	-	<1
Hepatic necrosis	<1	<1	<1	-	<1	-
Hepatitis	-	<1	-	<1	<1	<1
Hepatomegaly	-	-	-	-	-	<1
Hot flashes	-	<1	-	-	-	-
Hypercholesterolemia	-	<1	<1	<1	<1	-
Hyperglycemia	-	<1	-	<1	<1	<1
Hyperprolactinemia	-	-	<1	-	-	<1
Hyperthyroidism	-	-	-	-	<1	-
Hypoglycemia	-	<1	-	<1	<1	<1
Hypokalemia	-	<1	<1	<1	-	-
Hyponatremia	<1	-	<1	<1	-	-
Hypothyroidism	-	-	<1	<1	<1	<1
Jaundice	-	-	<1	<1	<1	<1
Syndrome of inappropriate antidiuretic hormone	<1	<1	-	-	-	<1

Adverse Events	Citalopram	Escitalopram	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline
Transaminase elevation	-	-	-	-	<1	<1
Weight gain	>1	<1	>1	<1	>1	>1
Weight loss	>1	<1	2	1 to 2	<1	-
Gastrointestinal						
Abdominal cramps	-	1 to 10	-	-	-	-
Abdominal pain	3	2	-	5	4	<1
Abnormal taste	✔	<1	✔	2 to 3	2	-
Anorexia	4	-	4 to 17	6 to 14	5 to 9	6
Aphthous stomatitis	-	-	<1	-	<1	<1
Appetite decreased	-	3	-	4	5 to 9	-
Appetite increased	>1	1 to 10	✔	-	2 to 4	>1
Carbohydrate craving	-	<1	-	-	-	-
Cholelithiasis	-	-	<1	-	-	-
Colitis	-	-	<1	<1	<1	-
Constipation	-	3 to 5	5	4 to 10	5 to 16	6
Diarrhea	8	8	8 to 18	11 to 18	9 to 12	20
Dyspepsia	5	-	6 to 10	8 to 10	2 to 5	8
Dysphagia	-	<1	<1	2	<1	<1
Esophagitis	-	-	<1	-	-	<1
Flatulence	>1	2	3	4	4	1 to 10
Gastritis	-	-	<1	-	<1	-
Gastroenteritis	-	<1	<1	-	<1	<1
Gastrointestinal bleeding	-	-	-	<1	-	-
Gastrointestinal ulcer	-	-	<1	-	<1	-
Gingivitis	-	-	-	2	<1	-
Glossitis	-	-	<1	-	<1	-
Heartburn	-	<1	-	-	-	-
Hematemesis	-	-	-	<1	<1	-
Indigestion	-	3	-	10	-	-
Intestinal obstruction	-	-	-	<1	<1	-
Melena	-	-	<1	-	-	-
Nausea	>10	15	12 to 29	34 to 40	19 to 26	25
Pancreatitis	<1	<1	<1	<1	<1	<1
Vomiting	4	1 to 10	3	4 to 6	2 to 3	4
Xerostomia	>10	6 to 9	4 to 12	10 to 14	9 to 18	>10
Genitourinary						
Acute renal failure	<1	<1	<1	<1	<1	<1

Adverse Events	Citalopram	Escitalopram	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline
Anorgasmia	-	2 to 6	2	2 to 5	2 to 9	-
Anuria	-	-	-	<1	-	-
Ejaculation disorder	6	9 to 14	<7	7 to 11	13 to 28	7 to 19
Hematuria	-	-	<1	<1	<1	<1
Impotence	3	2 to 3	<7	2	2 to 9	>1
Libido decreased	1 to 4	3 to 7	1 to 11	2 to 10	3 to 15	6
Menstrual cramps	-	1 to 10	-	-	-	-
Menstrual disorder	3	<1	<1 to 2	3	5	<1
Micturition disorders	✔	-	-	-	-	<1
Priapism	<1	<1	<1	-	-	<1
Sexual dysfunction	✔	-	-	2 to 4	-	>1
Urinary frequency	-	<1	✔	2 to 3	2 to 3	<1
Urinary incontinence	<1	-	<1	<1	<1	<1
Urinary retention	<1	-	<1	1	<1	<1
Urinary tract infection	-	<1	-	2	2	-
Hematologic						
Agranulocytosis	-	-	-	<1	-	<1
Anemia	-	<1	<1	<1	<1	-
Aplastic anemia	-	<1	<1	-	-	<1
Blood dyscrasias	-	-	-	-	<1	-
Hemolytic anemia	<1	<1	<1	-	-	-
Increased bleeding	-	-	-	-	<1	<1
Ketosis	-	-	-	-	<1	-
Leukocytosis	<1	-	-	<1	<1	-
Leukopenia	-	-	-	<1	<1	<1
Liver enzymes increased	<1	-	<1	1 to 2	<1	-
Lymphadenopathy	-	-	-	<1	<1	-
Pancytopenia	-	-	<1	-	<1	-
Platelet count abnormalities	-	-	-	-	<1	-
Porphyria	-	-	-	<1	-	-
Prothrombin decreased	-	<1	-	-	-	-
Purpura	<1	<1	<1	<1	-	>2
Thrombosis	-	<1	-	-	<1	-
Thrombocytopenia	-	<1	<1	<1	<1	<1
Thrombocytopenic purpura	-	-	<1	-	-	-
Musculoskeletal						
Arthralgia	2	<1	-	-	>1	<1

Adverse Events	Citalopram	Escitalopram	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline
Arthritis	-	-	<1	-	<1	-
Back pain	-	-	-	-	3	>1
Bursitis	-	-	<1	-	-	-
Choreoathetosis	-	<1	-	-	-	-
Limb pain	-	1 to 10	-	-	-	-
Muscle contractions	-	<1	-	2	-	-
Muscle cramp	-	<1	<1	-	-	<1
Myalgia	2	<1	-	5 to 8	2 to 4	>1
Myoclonus	<1	-	-	-	2 to 3	-
Neck/shoulder pain	-	1 to 10	-	-	<1	-
Neuroleptic malignant syndrome	<1	<1	<1	<1	<1	<1
Osteoporosis	-	-	-	-	<1	-
Rhabdomyolysis	<1	<1	-	-	-	-
Rigors	<1	-	-	-	-	-
Tics	-	<1	-	-	-	-
Tremor	8	1 to 10	3 to 13	5 to 8	4 to 11	-
Weakness	-	<1	7 to 21	14 to 26	12 to 22	<1
Respiratory						
Asthma	-	-	<1	<1	<1	-
Bronchitis	-	<1	-	2	<1	<1
Cough	>1	1 to 10	-	✔	-	<1
Dyspnea	-	-	<1	2	<1	<1
Eosinophilic pneumonia	-	-	<1	-	-	-
Epistaxis	-	-	≥2	2	<1	<1
Hemoptysis	-	-	-	<1	<1	<1
Hyperventilation	-	-	<1	-	<1	<1
Laryngeal edema	-	-	<1	-	-	-
Laryngitis	-	-	-	3	-	<1
Laryngospasm	-	-	<1	-	-	-
Nasal congestion	-	1 to 10	-	-	-	-
Pharyngitis	-	-	3 to 11	6	4	-
Pulmonary embolism	-	<1	<1	<1	<1	-
Pulmonary fibrosis	-	-	<1	-	<1	-
Pulmonary hypertension	-	-	<1	-	<1	-
Respiratory infection	5	-	-	9	7	<1
Rhinitis	5	5	-	-	3	>1
Sinus headache	-	<1	-	-	-	-

Adverse Events	Citalopram	Escitalopram	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline
Sinusitis	3	3	1 to 6	✔	4	<1
Other						
Allergic reaction	-	<1	-	<1	>1	<1
Allergy	-	<1	<1	-	<1	-
Amblyopia	-	-	-	2 to 3	-	-
Anaphylaxis	<1	<1	<1	<1	<1	<1
Angioedema	<1	<1	-	-	-	-
Blindness	-	-	-	-	-	<1
Blurred/abnormal vision	-	<1	✔	<1	2 to 4	3
Cataract	-	-	<1	-	<1	<1
Dehydration	-	-	<1	-	<1	-
Diaphoresis	>10	4 to 5	2 to 8	6 to 7	5 to 14	4 to 6
Ear ache	-	<1	✔	-	-	-
Flu-like syndrome	-	5	3 to 10	3	-	-
Gout	-	-	<1	-	-	-
Gum hyperplasia	-	-	-	-	-	<1
Infection	-	-	-	-	5 to 6	-
Lupus-like syndrome	-	-	<1	-	-	<1
Oculogyric crisis	-	-	-	-	-	<1
Pain	-	-	<1	10	-	1 to 10
Retinal detachment	-	-	-	<1	-	-
Sepsis	-	-	-	-	<1	-
Serotonin syndrome	<1	<1	<1	<1	<1	<1
Serum sickness	-	-	-	-	-	<1
Spontaneous abortion	-	<1	-	-	-	-
Suicidal tendency	✔	<1	-	<1	<1	<1
Thirst	<1	<1	≥2	-	-	-
Tinnitus	-	<1	>1	-	>1	>1
Tooth disorder	-	2	-	2 to 3	-	-
Vasculitis	-	-	<1	-	-	-
Visual difficulty	-	<1	2	-	2 to 4	<1
Withdrawal syndrome	<1	<1	-	-	-	<1

✔ Percent not specified.
- Event not reported or incidence <1%.

Table 6d. Adverse Drug Events (%) Reported with the Serotonin Modulators[1-34]

Adverse Events	Nefazodone	Trazodone	Vilazodone	Vortioxetine
Cardiovascular				
Atrioventricular block	<1	-	-	-
Bradycardia	1 to 10	<1	-	-
Edema	-	1 to 10	-	-
Hypertension	-	1 to 10	-	-
Hypotension	1 to 10	1 to 10	-	-
Palpitation	-	-	1 to 2	-
Peripheral edema	1 to 10	-	-	-
Postural hypotension	1 to 10	-	-	-
Syncope	-	1 to 10	-	-
Tachycardia	-	<1	-	-
Vasodilation	1 to 10	-	-	-
Ventricular extrasystoles	-	-	<1	-
Central Nervous System				
Abnormal dreams	1 to 10	-	3	<1 to 3
Agitation	>10	<1	-	-
Anxiety	-	<1	-	-
Ataxia	1 to 10	-	-	-
Chills	1 to 10	-	-	-
Concentration decreased	1 to 10	1 to 10	-	-
Confusion	1 to 10	1 to 10	-	-
Dizziness	>10	>10	6 to 8	6 to 9
Drowsiness	>10	-	4 to 5	-
Fatigue	-	1 to 10	4	-
Fever	1 to 10	-	-	-
Hallucinations	<1	-	✔	-
Headache	>10	>10	15	-
Incoordination	1 to 10	1 to 10	-	-
Insomnia	>10	-	6 to 7	-
Lightheadedness	1 to 10	-	-	-
Mania	-	-	<1	-
Memory impairment	1 to 10	-	-	-
Panic attacks	-	-	<1	-
Paresthesia	1 to 10	-	3	-
Psychomotor retardation	1 to 10	-	-	-
Restlessness	-	-	3	-
Sedation	-	>10	>1	-
Seizure	<1	<1	-	-
Speech impairment	-	<1	-	-
Dermatological				
Alopecia	-	<1	-	-
Hyperhidrosis	-	-	≤1	-
Photosensitivity	<1	-	-	-
Pruritus	1 to 10	-	-	1 to 3
Rash	1 to 10	<1	✔	-
Stevens-Johnson syndrome	<1	-	-	-
Endocrine and Metabolic				
Galactorrhea	<1	-	-	-
Gynecomastia	<1	-	-	-
Hepatic failure	<1	-	-	-
Hepatic necrosis	<1	-	-	-
Hepatitis	<1	-	-	-
Hyponatremia	<1	-	✔	-

Adverse Events	Nefazodone	Trazodone	Vilazodone	Vortioxetine
Liver function tests abnormal	<1	-	-	-
Prolactin increased	<1	-	-	-
Weight gain	-	1 to 10	-	-
Weight loss	-	1 to 10	-	-
Gastrointestinal				
Abnormal taste	1 to 10	-	-	-
Appetite decreased	-	-	1 to 10	-
Appetite increased	1 to 10	-	2	-
Constipation	>10	1 to 10	-	3 to 6
Diarrhea	1 to 10	1 to 10	26 to 29	7 to 10
Dry mouth	-	-	-	6 to 8
Dyspepsia	1 to 10	-	3	-
Flatulence	-	-	3	1 to 3
Gastroenteritis	1 to 10	-	2	-
Nausea	>10	>10	22 to 24	21 to 32
Vomiting	1 to 10	-	4 to 5	3 to 6
Xerostomia	>10	>10	7 to 8	7 to 8
Genitourinary				
Ejaculation delayed	-	-	1 to 2	-
Erectile dysfunction	-	-	2	-
Impotence	1 to 10	-	-	-
Libido decreased	1 to 10	-	3 to 5	-
Orgasm abnormal	-	-	2 to 4	-
Priapism	<1	<1	-	-
Sexual dysfunction	-	-	<2	-
Urinary frequency	1 to 10	-	-	-
Urinary retention	1 to 10	<1	-	-
Hematologic				
Hematocrit decreased	1 to 10	-	-	-
Leukopenia	<1	-	-	-
Thrombocytopenia	<1	-	-	-
Musculoskeletal				
Arthralgia	1 to 10	-	2	-
Extrapyramidal symptoms	-	<1	-	-
Hypertonia	1 to 10	-	-	-
Jittery	-	-	2	-
Myalgia	-	1 to 10	-	-
Neck rigidity	1 to 10	-	-	-
Rhabdomyolysis	<1	-	-	-
Tremor	1 to 10	1 to 10	2	-
Weakness	>10	-	-	-
Respiratory				
Bronchitis	1 to 10	-	-	-
Cough	1 to 10	-	-	-
Dyspnea	1 to 10	-	-	-
Nasal congestion	-	1 to 10	-	-
Pharyngitis	1 to 10	-	-	-
Other				
Abnormal feeling	-	-	<1	-
Abnormal taste	-	-	<1	-
Allergic reaction	<1	<1	-	-
Angioedema	<1	-	-	-
Blurred/abnormal vision	7 to 9	>10	≤1	-
Breast pain	1 to 10	-	-	-

Adverse Events	Nefazodone	Trazodone	Vilazodone	Vortioxetine
Cataracts	-	-	<1	-
Eye pain	1 to 10	-	-	-
Flu syndrome	1 to 10	-	-	-
Infection	1 to 10	-	-	-
Night sweats	-	-	≤1	-
Serotonin syndrome	<1	-	-	-
Thirst	1 to 10	-	-	-
Tinnitus	1 to 10	-	-	-
Visual field defect	1 to 10	-	-	-

✔ Percent not specified.
- Event not reported or incidence <1%.

Table 6e. Adverse Drug Events (%) Reported with the Tricyclics and Other Norepinephrine-reuptake Inhibitors[1-34]

Adverse Events	Single Entity Agents										Combination Products
	Amitrip-tyline	Amox-apine	Clomip-ramine	Desip-ramine	Dox-epin	Imip-ramine	Mapro-tiline	Nortrip-tyline	Protrip-tyline	Trimip-ramine	Amitriptyline-Chlordiazepoxide
Cardiovascular											
Aneurysm	-	-	<1	-	-	-	-	-	-	-	-
Arrhythmia	✔	✔	<1	✔	-	✔	✔	✔	✔	✔	✔
Atrial flutter	-	-	<1	-	-	-	-	-	-	-	-
Atrioventricular conduction changes	✔	-	-	-	-	-	-	-	-	-	✔
Bradycardia	-	-	<1	-	-	-	-	-	-	-	-
Bundle branch block	-	-	<1	-	-	-	-	-	-	-	-
Cardiac arrest	-	-	<1	-	-	-	-	-	-	-	-
Cardiomyopathy	✔	-	-	-	-	-	-	-	-	-	✔
Cerebral hemorrhage	-	-	<1	-	-	-	-	-	-	-	-
Chest pain	-	-	4	-	-	-	-	-	-	-	-
Chills	-	-	2	-	-	-	-	-	-	-	-
Congestive heart failure	-	-	-	-	-	✔	-	-	-	-	-
Cyanosis	-	-	<1	-	-	-	-	-	-	-	-
Electrocardiogram changes	✔	1 to 7	<1	-	-	✔	-	-	-	-	✔
Edema	✔	1 to 7	3	✔	✔	-	-	✔	-	-	-
Encephalopathy	-	-	<1	-	-	-	-	-	-	-	-
Extrasystole	-	-	<1	-	-	-	-	-	-	-	-
Heart block	✔	✔	<1	-	-	✔	✔	✔	✔	✔	✔
Hypertension	✔	<1	-	✔	✔	✔	✔	✔	✔	✔	✔
Hypotension	✔	<1	1 to 10	✔	✔	-	✔	✔	✔	✔	✔
Myocardial infarction	✔	✔	<1	✔	-	✔	-	✔	✔	✔	✔
Myocardial ischemia	-	-	<1	-	-	-	-	-	-	-	-
Orthostatic hypotension	✔	-	20	-	-	✔	-	✔	-	-	✔
Palpitations	✔	1 to 7	4	✔	-	✔	-	✔	✔	✔	✔
Peripheral ischemia	-	-	<1	-	-	-	-	-	-	-	-
Stroke	✔	✔	-	✔	-	✔	-	✔	✔	✔	✔
Syncope	✔	<1	>1	-	-	-	✔	✔	-	-	✔
Tachycardia	✔	<1	4	✔	✔	✔	-	✔	✔	✔	✔
Vasospasm	-	-	<1	-	-	-	-	-	-	-	-
Central Nervous System											
Abnormal dreaming	-	-	3	-	-	-	-	-	-	-	-
Aggressiveness	-	-	2	-	-	-	-	-	-	-	-
Agitation	-	-	3	✔	-	✔	1 to 10	✔	✔	✔	-
Akathisia	-	-	-	-	-	-	<1	-	-	-	1 to 10
Anxiety	✔	1 to 7	9	✔	-	✔	1 to 10	✔	✔	✔	✔
Aphasia	-	-	<1	-	-	-	-	-	-	-	-
Apraxia	-	-	<1	-	-	-	-	-	-	-	-
Ataxia	✔	1 to 7	<1	✔	✔	-	<1	✔	✔	-	>10
Catalepsy	-	-	<1	-	-	-	-	-	-	-	-
Confusion	-	1 to 7	3	-	✔	-	-	✔	✔	-	1 to 10
Cognitive function (impaired)	✔	-	-	-	-	-	-	-	-	-	✔
Coma	✔	-	<1	-	-	-	-	-	-	-	✔

Adverse Events	Single Entity Agents										Combination Products
	Amitrip-tyline	Amox-apine	Clomip-ramine	Desip-ramine	Dox-epin	Imip-ramine	Mapro-tiline	Nortrip-tyline	Protrip-tyline	Trimip-ramine	Amitriptyline-Chlordiazepoxide
Confusion	✔	>1	3	✔	✔	✔	✔	✔	-	✔	✔
Coordination impairment	✔	<1	5	✔	-	✔	-	✔	✔	✔	✔
Deafness	-	-	<1	-	-	-	-	-	-	-	-
Delirium	-	-	<1	✔	-	-	-	✔	✔	✔	-
Delusions	✔	✔	<1	-	-	✔	✔	✔	✔	✔	✔
Depersonalization	-	-	2	-	-	-	-	-	-	-	-
Depression	-	-	5	-	<1	-	-	✔	-	-	-
Disinhibition	-	-	-	-	-	-	-	-	-	-	1 to 10
Disorientation	✔	<1	-	✔	✔	✔	✔	✔	-	✔	✔
Dizziness	✔	1 to 7	54	✔	>1	✔	-	✔	✔	✔	✔
Drowsiness	✔	14	46 to 54	✔	✔	✔	16	✔	✔	✔	✔
Dysarthria	✔	-	-	-	-	-	✔	-	-	-	>10
Dyskinesia	-	-	<1	-	-	-	-	-	-	-	-
Dysphagia	-	-	-	-	-	-	<1	-	-	-	-
Dysphonia	-	-	<1	-	-	-	-	-	-	-	-
Dystonia	-	-	<1	-	-	-	-	-	-	-	-
Emotional lability	-	-	2	-	-	-	-	-	-	-	-
Euphoria	✔	-	-	-	-	-	-	-	-	-	✔
Excitement	✔	1 to 7	-	-	-	-	-	-	-	-	✔
Extrapyramidal symptoms	✔	<1	<1	✔	✔	✔	✔	✔	✔	✔	✔
Fatigue	✔	1 to 7	35 to 39	✔	<1	✔	4	✔	✔	✔	✔
Fever	✔	<1	4	✔	-	-	-	✔	-	-	✔
Flushing	-	-	8	✔	<1	-	-	✔	-	✔	-
Hallucinations	✔	-	<1	✔	✔	✔	✔	✔	✔	✔	✔
Hangover effect	-	-	-	-	-	-	-	-	✔	-	-
Headache	✔	1 to 7	52	✔	✔	✔	4	✔	-	✔	✔
Hemiparesis	-	-	<1	-	-	-	-	-	-	-	-
Hostility	-	-	<1	-	-	-	-	-	-	-	-
Hyperesthesia	-	-	<1	-	-	-	-	-	-	-	-
Hyperkinesia	-	-	<1	-	-	-	-	-	-	-	-
Hyperreflexia	-	-	<1	-	-	-	-	-	-	-	-
Hypertonia	-	-	4	-	-	-	-	-	-	-	-
Hypoesthesia	-	-	<1	-	-	-	-	-	-	-	-
Hypokinesia	-	-	<1	-	-	-	-	-	-	-	-
Hypomania	-	-	-	✔	-	-	-	✔	✔	-	-
Ideation	-	-	<1	-	-	-	-	-	-	-	-
Insomnia	✔	1 to 7	25	✔	-	✔	2	✔	✔	✔	✔
Irritability	-	-	2	-	-	-	-	-	-	-	-
Malaise	✔	-	>1	-	-	-	-	✔	-	✔	✔
Mania	-	-	<1	-	-	-	✔	-	-	-	-
Memory impairment	-	-	9	-	-	-	✔	-	-	-	-
Migraine	-	-	3	-	-	-	-	-	-	-	-
Nervousness	-	1 to 7	18	✔	-	-	6	-	-	✔	-
Neuralgia	-	-	<1	-	-	-	-	-	-	-	-

Adverse Events	Single Entity Agents										Combination Products
	Amitrip-tyline	Amox-apine	Clomip-ramine	Desip-ramine	Dox-epin	Imip-ramine	Mapro-tiline	Nortrip-tyline	Protrip-tyline	Trimip-ramine	Amitriptyline-Chlordiazepoxide
Neuropathy	-	-	<1	-	-	-	-	-	-	-	-
Nightmares	✔	1 to 7	-	-	-	✔	✔	✔	✔	✔	✔
Oculogyric crisis	-	-	<1	-	-	-	-	-	-	-	-
Oculomotor nerve paralysis	-	-	<1	-	-	-	-	-	-	-	-
Panic	-	-	1	-	-	-	-	✔	✔	-	-
Paranoia	-	-	<1	-	-	-	-	-	-	-	-
Paresis	-	-	9	-	-	-	-	-	-	-	-
Paresthesia	-	-	2	-	-	-	-	-	-	-	-
Parkinsonian syndrome	-	-	-	✔	-	-	-	-	-	-	-
Psychosis exacerbation	-	-	<1	✔	-	✔	-	✔	✔	✔	-
Psychosomatic disorder	-	-	3	-	-	-	-	-	-	-	-
Restlessness	✔	1 to 7	-	✔	-	✔	-	✔	✔	✔	✔
Sedation	✔	-	-	-	-	-	-	-	-	-	✔
Sensory disturbance	-	-	<1	-	-	-	-	-	-	-	-
Seizure	✔	<1	<1	✔	✔	✔	<1	✔	✔	✔	✔
Somnolence	✔	-	-	-	-	-	-	-	-	-	✔
Sleep Disorder	-	-	4	-	-	-	-	-	-	-	-
Speech disorder	-	-	3	-	-	-	-	-	-	-	-
Stupor	-	-	<1	-	-	-	-	-	-	-	-
Syncope	-	<1	-	-	-	-	<1	-	-	-	-
Twitching	-	-	7	-	-	-	-	-	-	-	-
Yawning	-	-	3	-	-	-	-	-	-	-	-
Dermatological											
Acne	-	-	2	-	-	-	-	-	-	-	-
Alopecia	✔	-	<1	✔	✔	<1	-	✔	✔	✔	✔
Cellulitis	-	-	<1	-	-	-	-	-	-	-	-
Cheilitis	-	-	<1	-	-	-	-	-	-	-	-
Dermatitis	-	-	2	-	-	-	-	-	-	-	-
Dry skin	-	-	2	-	-	-	-	-	-	-	-
Petechiae	-	-	-	✔	-	<1	-	✔	✔	✔	-
Photosensitivity	✔	<1	<1	✔	✔	<1	<1	✔	✔	✔	✔
Pruritus	-	<1	6	✔	✔	<1	-	✔	✔	✔	✔
Rash	✔	1 to 7	8	✔	✔	<1	<1	✔	✔	✔	✔
Skin discoloration	-	-	<1	-	-	-	-	-	-	-	-
Skin ulceration	-	-	<1	-	-	-	-	-	-	-	-
Urticaria	✔	<1	1	✔	-	<1	-	✔	✔	✔	✔
Endocrine and Metabolic											
Breast enlargement	✔	-	2	✔	✔	✔	-	✔	✔	✔	✔
Breast pain	-	-	1	-	-	-	-	-	-	-	-
Diabetes mellitus	-	-	<1	-	-	-	-	-	-	-	-
Galactorrhea	✔	<1	<1	✔	✔	✔	-	✔	✔	✔	✔
Goiter	-	-	<1	-	-	-	-	-	-	-	-
Glycosuria	-	-	<1	-	-	-	-	-	-	-	-
Gynecomastia	✔	-	<1	-	-	✔	-	✔	✔	-	✔

Adverse Events	Single Entity Agents										Combination Products
	Amitrip-tyline	Amox-apine	Clomip-ramine	Desip-ramine	Dox-epin	Imip-ramine	Mapro-tiline	Nortrip-tyline	Protrip-tyline	Trimip-ramine	Amitriptyline-Chlordiazepoxide
Hyperglycemia	✔	-	<1	✔	✔	✔	-	✔	-	✔	✔
Hypoglycemia	✔	-	-	✔	✔	✔	-	-	-	✔	✔
Lactation	-	-	4	-	-	-	-	-	-	-	-
Prolactin levels increased	-	1 to 7	-	-	-	-	-	-	-	-	-
Syndrome of inappropriate antidiuretic hormone secretion	✔	<1	<1	✔	✔	✔	-	✔	✔	✔	✔
Thirst	-	-	2	-	-	-	-	-	-	-	-
Gastrointestinal											
Abdominal pain/cramps	-	<1	11	✔	<1	✔	-	✔	-	✔	-
Anorexia	✔	-	12	✔	✔	✔	-	✔	✔	✔	✔
Appetite decreased	-	-	11	-	<1	-	-	✔	-	-	✔
Appetite increased	-	1 to 7	11	-	<1	-	-	✔	✔	✔	✔
Black tongue	✔	✔	-	✔	-	✔	-	✔	-	✔	✔
Blood in stool	-	-	<1	-	-	-	-	-	-	-	-
Chronic enteritis	-	-	<1	-	-	-	-	-	-	-	-
Constipation	✔	12	47	✔	<1	✔	6	✔	✔	✔	✔
Diarrhea	✔	<1	13	✔	✔	✔	-	✔	✔	✔	✔
Dysphagia	-	-	2	-	-	-	-	-	-	-	-
Dyspepsia	-	-	22	✔	<1	-	-	✔	-	-	-
Eructation	-	-	>1	-	-	-	-	-	-	-	-
Esophageal sphincter tone decrease	-	-	-	✔	✔	-	-	-	✔	✔	-
Esophagitis	-	-	1	-	-	-	-	-	-	-	-
Flatulence	-	<1	6	-	-	-	-	-	-	-	-
Gastric/peptic ulcer	-	-	<1	-	-	-	-	-	-	-	-
Indigestion	-	-	-	-	✔	-	-	-	✔	✔	-
Intestinal obstruction	-	-	<1	-	-	-	-	-	-	-	-
Irritable bowel syndrome	-	-	<1	-	-	-	-	-	-	-	-
Nausea	✔	1 to 7	33	✔	✔	✔	2	✔	✔	✔	✔
Paralytic ileus	✔	✔	<1	✔	-	✔	-	-	-	✔	✔
Reflux	-	-	<1	-	<1	-	-	✔	-	-	-
Salivation decreased	-	-	-	-	-	-	✔	-	-	-	✔
Salivation increased	-	-	<1	-	-	-	-	-	-	-	✔
Stomatitis	✔	✔	>1	✔	✔	✔	-	-	-	✔	✔
Taste changes	✔	<1	8	✔	✔	✔	-	✔	✔	✔	✔
Tongue ulceration	-	-	<1	-	-	-	-	-	-	-	-
Vomiting	✔	<1	7	✔	<1	✔	<1	✔	✔	✔	✔
Weight gain	✔	<1	18	✔	✔	✔	-	✔	✔	✔	✔
Weight loss	✔	<1	>1	✔	-	✔	-	✔	✔	✔	✔
Xerostomia	✔	14	84	✔	✔	✔	22	✔	✔	✔	✔
Genitourinary											
Albuminuria	-	-	<1	-	-	-	-	-	-	-	-
Cervical dysplasia	-	-	<1	-	-	-	-	-	-	-	-
Cystitis	-	-	2	-	-	-	-	-	-	-	-
Dysmenorrhea	-	-	12	-	-	-	-	-	-	-	-

Adverse Events	Single Entity Agents										Combination Products
	Amitrip-tyline	Amox-apine	Clomip-ramine	Desip-ramine	Dox-epin	Imip-ramine	Mapro-tiline	Nortrip-tyline	Protrip-tyline	Trimip-ramine	Amitriptyline-Chlordiazepoxide
Dysuria	-	-	2	-	-	-	-	-	-	-	-
Ejaculation failure	-	-	42	-	-	-	-	-	-	-	-
Epididymitis	-	-	<1	-	-	-	-	-	-	-	-
Hematuria	-	-	<1	-	-	-	-	-	-	-	-
Impotence	✔	<1	20	✔	-	✔	<1	✔	✔	✔	✔
Incontinence	-	-	<1	-	-	-	-	-	-	-	✔
Leucorrhea	-	-	2	-	-	-	-	-	-	-	-
Menstrual Disorder	-	-	4	-	-	-	-	-	-	-	-
Micturition disorder/difficulty	-	-	4 to 14	-	-	-	<1	✔	✔	-	>10
Micturition frequency	-	-	5	-	-	-	-	-	-	-	-
Polyuria	-	-	-	✔	-	-	-	-	-	-	-
Pyelonephritis	-	-	<1	-	-	-	-	-	-	-	-
Renal calculus	-	-	<1	-	-	-	-	-	-	-	-
Renal cyst	-	-	<1	-	-	-	-	-	-	-	-
Sexual dysfunction	-	-	-	✔	-	-	-	✔	-	✔	✔
Testicular edema	✔	<1	-	✔	✔	✔	-	✔	✔	✔	-
Urinary retention	✔	<1	2	✔	✔	✔	<1	✔	✔	✔	✔
Urinary tract infection	-	-	6	-	-	-	-	<1	-	-	-
Vaginal hemorrhage	-	-	<1	-	-	-	-	-	-	-	-
Vaginitis	-	-	2	-	-	-	-	-	-	-	-
Hematologic											
Agranulocytosis	✔	<1	-	✔	✔	<1	-	✔	✔	✔	✔
Aphasia	-	-	<1	-	-	-	-	-	-	-	-
Aphasia	-	-	<1	-	-	-	-	<1	-	-	-
Bone marrow depression	✔	-	<1	-	✔	-	-	✔	-	✔	✔
Eosinophilia	✔	-	-	✔	✔	<1	-	✔	✔	✔	✔
Hemoptysis	-	-	<1	-	-	-	-	-	-	-	-
Leukemoid reaction	-	-	<1	-	-	-	-	-	-	-	-
Leukopenia	✔	<1	-	-	✔	-	-	-	✔	-	✔
Lymphadenopathy	-	-	<1	-	-	-	-	-	-	-	-
Lymphoma-like disorder	-	-	<1	-	-	-	-	-	-	-	-
Purpura	✔	-	3	✔	✔	<1	-	✔	✔	✔	✔
Thrombocytopenia	-	-	-	✔	✔	<1	-	✔	✔	✔	-
Thrombophlebitis	-	-	<1	-	-	-	-	-	-	-	-
Hepatic											
Cholestatic jaundice	✔	-	-	✔	-	<1	-	✔	✔	✔	✔
Hepatitis	✔	<1	<1	✔	-	-	-	-	-	-	✔
Liver enzymes increased	✔	<1	-	✔	-	<1	-	✔	✔	✔	✔
Neuromuscular and skeletal											
Arthralgia	-	-	3	-	-	-	-	<1	-	-	-
Back pain	-	-	6	-	-	-	-	<1	-	-	-
Choreoathetosis	-	-	<1	-	-	-	-	-	-	-	-
Myalgia	-	-	13	-	-	-	-	<1	-	-	-
Myoclonus	-	-	13	-	-	-	-	-	-	-	-

Adverse Events	Single Entity Agents										Combination Products
	Amitrip-tyline	Amox-apine	Clomip-ramine	Desip-ramine	Dox-epin	Imip-ramine	Mapro-tiline	Nortrip-tyline	Protrip-tyline	Trimip-ramine	Amitriptyline-Chlordiazepoxide
Myositis	-	-	<1	-	-	-	-	-	-	-	-
Neuroleptic malignant syndrome	✔	<1	-	-	-	-	-	-	-	-	✔
Numbness	✔	<1	-	✔	✔	✔	✔	✔	✔	✔	✔
Paresthesia	✔	<1	1 to 10	✔	✔	✔	-	✔	-	✔	✔
Peripheral neuropathy	✔	-	-	✔	-	✔	-	✔	-	✔	✔
Tardive dyskinesia	✔	<1	-	-	✔	-	-	-	-	-	✔
Tingling	✔	<1	-	✔	-	✔	✔	✔	✔	✔	✔
Torticollis	-	-	<1	-	-	-	-	-	-	-	-
Tremor	✔	1 to 7	54	✔	✔	✔	3	✔	✔	✔	✔
Weakness	✔	1 to 7	1	✔	✔	✔	1 to 10	-	✔	✔	✔
Ocular											
Abnormal Vision	-	-	18	-	-	-	-	-	-	-	-
Accommodation disturbances	✔	<1	<1	✔	-	✔	<1	✔	-	✔	✔
Anisocoria	-	-	>1	-	-	-	-	-	-	-	-
Blepharitis	-	-	<1	-	-	-	-	-	-	-	-
Blepharospasm	-	-	>1	-	-	-	-	-	-	-	-
Blurred vision	✔	7	1 to 10	✔	<1	✔	4	✔	✔	✔	✔
Conjunctival hemorrhage	-	-	<1	-	-	-	-	-	-	-	-
Conjunctivitis	-	-	1	-	-	-	-	-	-	-	-
Exophthalmos	-	-	<1	-	-	-	-	-	-	-	-
Eye pain	-	-	1 to 10	-	-	-	-	✔	✔	✔	-
Glaucoma,	-	-	<1	-	-	-	-	-	-	-	-
Intraocular pressure increased	✔	<1	-	✔	-	-	-	-	✔	✔	✔
Keratitis	-	-	<1	-	-	-	-	-	-	-	-
Lacrimation abnormal	-	-	3	-	-	-	-	-	-	-	-
Mydriasis	✔	<1	2	✔	-	✔	-	✔	-	✔	✔
Ocular Allergy	-	-	>1	-	-	-	-	-	-	-	-
Scleritis	-	-	<1	-	-	-	-	-	-	-	-
Strabismus	-	-	<1	-	-	-	-	-	-	-	-
Otic											
Hyperacusis	-	-	<1	-	-	-	-	-	-	-	-
Tinnitus	✔	<1	6	✔	✔	✔	<1	✔	✔	✔	1 to 10
Respiratory											
Bronchitis	-	-	<1	-	-	-	-	-	-	-	-
Bronchospasm	-	-	2	-	-	-	-	-	-	-	-
Cough	-	-	6	-	-	-	-	✔	-	-	-
Dyspnea	-	-	>1	-	-	-	-	-	-	-	-
Hypo/hyperventilation	-	-	<1	-	-	-	-	-	-	-	-
Epistaxis	-	-	2	-	-	-	-	-	-	-	-
Laryngitis	-	-	>1	-	-	-	-	-	-	-	-
Nasal congestion	-	<1	-	-	-	-	-	✔	-	-	✔
Pharyngitis	-	-	14	-	-	-	-	-	-	-	-
Pneumonia	-	-	<1	-	-	-	-	-	-	-	-
Rhinitis	-	-	12	-	-	-	-	-	-	-	-

Adverse Events	Single Entity Agents										Combination Products
	Amitrip-tyline	Amox-apine	Clomip-ramine	Desip-ramine	Dox-epin	Imip-ramine	Mapro-tiline	Nortrip-tyline	Protrip-tyline	Trimip-ramine	Amitriptyline-Chlordiazepoxide
Sinusitis	-	-	6	-	-	-	-	✔	-	-	-
Other											
Allergic reactions	-	<1	3	✔	✔	-	-	✔	✔	✔	-
Dehydration	-	-	<1	-	-	-	-	-	-	-	-
Diaphoresis	✔	1 to 7	29	✔	✔	✔	-	✔	✔	-	✔
Diplopia	✔	-	<1	-	-	-	-	✔	-	-	✔
Endometrial hyperplasia	-	-	<1	-	-	-	-	-	-	-	-
Endometriosis	-	-	<1	-	-	-	-	-	-	-	-
Halitosis	-	-	>1	-	-	-	-	-	-	-	-
Ovarian cyst	-	-	<1	-	-	-	-	-	-	-	-
Pain	-	-	3	-	-	-	-	-	-	-	-
Parosmia	-	-	<1	-	-	-	-	-	-	-	-
Polyarteritis nodosa	-	-	<1	-	-	-	-	-	-	-	-
Serotonin syndrome	✔	-	-	-	-	-	-	-	-	-	✔
Suicide ideation/attempt	✔	-	<1	-	-	-	-	-	-	-	✔
Tooth caries	-	-	<1	-	-	-	-	-	-	-	-
Tooth disorder	-	-	5	-	-	-	-	-	-	-	-
Uterine hemorrhage	-	-	<1	-	-	-	-	-	-	-	-
Uterine inflammation	-	-	<1	-	-	-	-	-	-	-	-
Visual field defect	-	-	<1	-	-	-	-	-	-	-	-
Withdrawal reactions	✔	-	<1	-	-	-	-	-	-	-	✔

✔ Percent not specified.
- Event not reported or incidence <1%.

Table 6f. Adverse Drug Events (%) Reported with the Antidepressants, Miscellaneous[1-34]

Adverse Events	Bupropion	Mirtazapine
Cardiovascular		
Arrhythmias	5	-
Atrioventricular block	✔	-
Chest pain	3 to 4	-
Electrocardiogram abnormality	✔	-
Extrasystoles	✔	-
Hypertension	2 to 4	2
Hypotension	3	-
Myocardial infarct	✔	<1
Orthostatic hypotension	-	<1
Palpitation	2 to 6	-
Peripheral edema	<1	2
Postural hypotension	✔	-
Stroke	✔	-
Syncope	✔	<1
Tachycardia	11	-
Vasodilation	✔	2
Central Nervous System		
Abnormal dreams	3	4
Abnormal thinking	-	3
Aggression	✔	-
Agitation	2 to 32	>
Akathisia	2	-
Akinesia	✔	-
Amnesia	✔	>1
Anxiety	5 to 7	>1
Aphasia	✔	-
Ataxia	✔	<1
Blurred vision	2 to 3	-
Central nervous system stimulation	1 to 2	-
Chills	<1	<1
Coma	✔	-
Confusion	8	2
Delirium	✔	<1
Delusions	✔	<1
Depersonalization	✔	<1
Depression	✔	-
Derealization	✔	-
Diplopia	✔	<1
Dizziness	6 to 22	7
Drowsiness	-	54
Dyskinesia	✔	-
Dysphoria	✔	-
Dystonia	✔	<1
Emotional lability	✔	<1
Euphoria	✔	-
Fever	1 to 2	<1
Hallucinations	✔	<1
Headache	25 to 34	-
Hostility	6	<1
Hyperkinesia	✔	<1
Hypertonia	✔	-
Hypoesthesia	✔	-

Adverse Events	Bupropion	Mirtazapine
Hypokinesia	✔	<1
Hypomania	✔	-
Incoordination	✔	-
Insomnia	11 to 20	-
Irritability	2 to 3	-
Malaise	✔	✔
Manic reaction	✔	<1
Memory decreased	<3	-
Migraine	1 to 4	<1
Nervousness	3 to 5	-
Neuropathy	✔	-
Pain	2 to 3	-
Paranoia	✔	<1
Paresthesia	1 to 2	<1
Restlessness	✔	-
Seizure	✔	-
Sensory disturbance	4	-
Sleep disturbance	4	-
Somnolence	2 to 3	54
Vertigo	✔	-
Dermatological		
Maculopapular rash	✔	-
Photosensitivity	<1	<1
Pruritus	2 to 4	>1
Rash	1 to 5	>1
Urticaria	1 to 2	<1
Endocrine and Metabolic		
Appetite increased	4	17
Glycosuria	✔	-
Gynecomastia	✔	-
Hepatic damage	✔	-
Hepatitis	✔	-
Hypercholesterolemia	-	✔
Hyperglycemia	✔	-
Hypertriglyceridemia	-	✔
Hypoglycemia	✔	-
Hot flashes	1 to 3	-
Jaundice	<1	-
Liver function abnormal	<1	<1
Syndrome of inappropriate antidiuretic hormone	✔	-
Weight gain	-	12
Weight loss	14 to 23	<1
Gastrointestinal		
Abdominal pain	2 to 9	>1
Abnormal taste	2 to 4	-
Anorexia	3 to 5	>1
Colitis	✔	<1
Constipation	5 to 26	13
Diarrhea	5 to 7	-
Dysphagia	<2	-
Dyspepsia	3	-
Flatulence	6	-
Gastric reflux	<1	-

Adverse Events	Bupropion	Mirtazapine
Gastrointestinal hemorrhage	✔	-
Intestinal perforation	✔	-
Nausea	1 to 18	<1
Pancreatitis	✔	-
Stomach ulcer	✔	<1
Vomiting	2 to 4	>1
Xerostomia	17 to 28	25
Genitourinary		
Cystitis	✔	-
Dyspareunia	✔	-
Ejaculation abnormality	✔	-
Impotence	<1	<1
Libido decreased	3	-
Libido increased	✔	-
Menopause	✔	-
Menstrual complaints	2 to 5	<1
Painful erection	✔	-
Prostate disorder	✔	-
Salpingitis	✔	-
Urinary frequency	2 to 5	2
Urinary incontinence	✔	<1
Urinary retention	✔	<1
Urinary tract infection	<1	>1
Urinary urgency	<2	-
Vaginal hemorrhage	<2	-
Vaginitis	✔	>1
Hematologic		
Agranulocytosis	-	<1
Anemia	✔	-
Leukocytosis	✔	-
Leukopenia	✔	-
Neutropenia	-	<1
Pancytopenia	✔	-
Thrombocytopenia	✔	-
Musculoskeletal		
Arthralgia	1 to 4	2
Arthritis	2	-
Back pain	-	2
Dysarthria	✔	-
Extrapyramidal syndrome	✔	-
Musculoskeletal chest pain	✔	-
Myalgia	2 to 6	2
Neck pain	✔	<1
Rhabdomyolysis	✔	-
Rigidity	✔	-
Tardive dyskinesia	✔	-
Tremor	3 to 21	2
Twitching	1 to 2	<1
Weakness	2 to 4	8
Respiratory		
Bronchospasm	✔	-
Cough	1 to 4	-
Dyspnea	-	1
Pharyngitis	3 to 13	-

Adverse Events	Bupropion	Mirtazapine
Pneumonia	✔	-
Pulmonary embolism	✔	-
Sinusitis	1 to 5	-
Upper respiratory infection	9	-
Other		
Accommodation abnormality	<1	<1
Allergic reaction	✔	-
Amblyopia	2	-
Angioedema	✔	-
Auditory disturbance	5	-
Bruxism	✔	-
Deafness	✔	<1
Dehydration	-	<1
Diaphoresis	5 to 22	-
Dry eye	✔	-
Ecchymosis	✔	-
Edema	-	1
Esophagitis	✔	-
Facial edema	✔	-
Flu-like syndrome	-	1
Gingivitis	✔	-
Glossitis	✔	-
Gum hemorrhage	✔	-
Hirsutism	✔	-
Hypersensitivity reactions	✔	-
Infection	8 to 9	-
Intraocular pressure increased	✔	-
Leg cramps	<1	-
Lymphadenopathy	✔	<1
Mouth ulcers	✔	-
Mydriasis	✔	-
Phlebitis	✔	-
Salivation increased	<1	<1
Sciatica	✔	-
Stomatitis	✔	-
Suicidal ideation	✔	-
Thirst	<1	>1
Tinnitus	3 to 6	-
Tongue edema	✔	-

✔ Percent not specified.
- Event not reported or incidence <1%.

Table 7. Boxed Warning for the Antidepressants[1]

WARNING
Suicidality and antidepressant drugs: Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder and other psychiatric disorders. Anyone considering the use of antidepressants in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults older than 24 years of age; there was a reduction in risk with antidepressants compared to placebo in adults 65 years of age and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Monitor patients of all ages who are started on antidepressant therapy appropriately and observe them closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be

WARNING
advised of the need for close observation and communication with the prescriber. Amitriptyline, amoxapine, bupropion, citalopram, desipramine, desvenlafaxine, doxepin, duloxetine, fluvoxamine (extended-release capsules), isocarboxazid, levomilnacipran, maprotiline, mirtazapine, nefazodone, nortriptyline, paroxetine, phenelzine, protriptyline, tranylcypromine, trazodone, trimipramine, venlafaxine, vilazodone and vortioxetine are not approved for use in pediatric patients. Clomipramine, fluvoxamine, and sertraline are not approved for use in pediatric patients, except for patients with obsessive compulsive disorder. Escitalopram is not approved for use in children younger than 12 years of age. Fluoxetine (except Sarafem®) is approved for use in children with major depressive disorder and obsessive-compulsive disorder. Imipramine is not approved for use in pediatric patients, except for patients with nocturnal enuresis. Selegiline is not approved for use in pediatric patients. Furthermore, selegiline at any dose should not be used in children younger than 12 years of age, even when administered with dietary modifications.

Table 8. Boxed Warning for Bupropion[1]

WARNING
Use in Smoking Cessation Treatment: Budeprion SR®, Forfivo XL®, Wellbutrin®, Wellbutrin SR®, and Wellbutrin XL® are not approved for smoking cessation treatment, but bupropion under the names Buproban® or Zyban® are approved for this use. Serious neuropsychiatric events, including but not limited to depression, suicidal ideation, suicide attempt, and completed suicide have been reported in patients taking bupropion for smoking cessation. Some cases may have been complicated by the symptoms of nicotine withdrawal in patients who stopped smoking. Depressed mood may be a symptom of nicotine withdrawal. Depression, rarely including suicidal ideation, has been reported in smokers undergoing a smoking cessation attempt without medication. However, some of these symptoms have occurred in patients taking bupropion who continued to smoke. All patients being treated with bupropion for smoking cessation treatment should be observed for neuropsychiatric symptoms including changes in behavior, hostility, agitation, depressed mood, and suicide-related events, including ideation, behavior, and attempted suicide. These symptoms, as well as worsening of pre-existing psychiatric illness and completed suicide have been reported in some patients attempting to quit smoking while taking bupropion in the postmarketing experience. When symptoms were reported, most were during treatment with bupropion, but some were following discontinuation of treatment with bupropion. These events have occurred in patients with and without pre-existing psychiatric disease; some have experienced worsening of their psychiatric illnesses. Patients with serious psychiatric illness such as schizophrenia, bipolar disorder, and major depressive disorder did not participate in the premarketing studies of bupropion. Advise patients and caregivers that the patient using bupropion for smoking cessation should stop taking bupropion and contact a healthcare provider immediately if agitation, hostility, depressed mood, or changes in thinking or behavior that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behavior. In many postmarketing cases, resolution of symptoms after discontinuation of bupropion was reported, although in some cases the symptoms persisted; therefore, ongoing monitoring and supportive care should be provided until symptoms resolve. The risks of using bupropion for smoking cessation should be weighed against the benefits of its use. Bupropion has been demonstrated to increase the likelihood of abstinence from smoking for as long as six months compared to treatment with placebo. The health benefits of quitting smoking are immediate and substantial.

Table 9. Boxed Warning for Nefazodone[1]

WARNING
Cases of life-threatening hepatic failure have been reported in patients treated with nefazodone. The reported rate in the United States is approximately one case of liver failure resulting in death or transplant per 250,000 to 300,000 patient-years of nefazodone treatment. The total patient-years is a summation of each patient's duration of exposure expressed in years. For example, one patient-year is equal to two patients each treated for six

WARNING

months, three patients each treated for four months, etc. Ordinarily, treatment with nefazodone should not be initiated in individuals with active liver disease or with elevated baseline serum transaminases. There is no evidence that preexisting liver disease increases the likelihood of developing liver failure; however, baseline abnormalities can complicate patient monitoring. Advise patients to be alert for signs and symptoms of liver dysfunction (e.g., jaundice, anorexia, gastrointestinal complaints, malaise) and to report them to their health care provider immediately if they occur. Discontinue nefazodone if clinical signs or symptoms suggest liver failure. If nefazodone-treated patients develop evidence of hepatocellular injury such as increased serum aspartate aminotransferase or serum alanine aminotransferase levels greater than or equal to three times the upper limit of normal, withdraw the drug. These patients should be presumed to be at increased risk for liver injury if nefazodone is reintroduced. Accordingly, do not consider such patients for retreatment.

VII. Dosing and Administration

The usual dosing regimens for the antidepressants are listed in Table 10.

Table 10. Usual Dosing Regimens for the Antidepressants[1-34]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Monoamine Oxidase Inhibitors			
Isocarboxazid	Depression: Tablet: 10 mg twice per day; maximum, 60 mg/day; reduce dose to 10 to 20 mg/day when condition improves	Safety and efficacy in children have not been established.	Tablet: 10 mg
Phenelzine	Depression: Tablet: 15 mg three times per day; may increase to 60 to 90 mg/day during the early phase of treatment, then reduce dose for maintenance therapy slowly after maximum benefit is obtained	Safety and efficacy in children have not been established.	Tablet: 15 mg
Selegiline	Depression: Transdermal patch: initial, 6 mg/24 hours once daily; may titrate based on clinical response in increments of 3 mg/day every two weeks up to a maximum of 12 mg/24 hours	Safety and efficacy in children have not been established.	Transdermal patch: 6 mg/24 hours 9 mg/24 hours 12 mg/24 hours
Tranylcypromine	Depression: Tablet: 10 mg twice daily; increase by 10 mg increments at one to three week intervals; maximum, 60 mg/day; usual effective dose, 30 mg/day	Safety and efficacy in children have not been established.	Tablet: 10 mg
Selective Serotonin- and Norepinephrine-reuptake Inhibitors			
Desvenlafaxine	Major depressive disorder: Extended-release tablet: 50 mg once-daily	Safety and efficacy in children have not been established.	Extended-release tablet: 25 mg 50 mg 100 mg
Duloxetine	Chronic musculoskeletal pain: Delayed-release capsule: initial, 30 mg/day; maintenance, 60 mg once- daily; maximum, 60 mg/day	Generalized anxiety disorder in patients 7 to 17 years of age: Delayed-release capsule: initial, 30 mg/day; maintenance,	Delayed-release capsule: 20 mg 30 mg 40 mg 60 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Fibromyalgia: Delayed-release capsule: initial, 30 mg/day; maintenance, 60 mg once daily; maximum, 60 mg/day Neuropathic pain associated with diabetic peripheral neuropathy: Delayed-release capsule: 60 mg once-daily Generalized anxiety disorder: Delayed-release capsule: initial, 60 mg/day; maintenance, 60 mg once-daily; maximum, 120 mg/day Major depressive disorder: Delayed-release capsule: initial, 40 to 60 mg/day; maintenance (acute treatment), 40 (20 mg twice-daily) to 60 mg/day (once-daily or 30 mg twice-daily); maintenance, 60 mg/day; maximum, 120 mg/day	30 to 60 mg once daily; maximum, 120 mg/day	
Levomilnacipran	Major depressive disorder: Extended-release capsule: initial, 20 mg once daily for two days, then increase to 40 mg once daily; maintenance, 40 to 120 mg once daily; maximum, 120 mg once daily	Safety and efficacy in children have not been established.	Extended-release capsules: 20 mg 40 mg 80 mg 120 mg Extended-release capsule dose pack: 20 mg (2 capsules), 40 mg (26 tablets)
Venlafaxine	Generalized anxiety disorder: Extended-release capsule: initial, 75 mg once-daily; maximum, 225 mg/day Major depressive disorder: Extended-release capsule: initial, 75 mg once-daily; maximum, 225 mg/day Extended-release tablet: initial, 75 mg/day; maintenance, 75 to 225 mg/day; maximum, 225 mg/day Tablet: initial, 37.5 to 75 mg/day administered in two or three divided doses; maintenance, 75 to 225 mg/day; maximum, 375 mg/day	Safety and efficacy in children have not been established.	Extended-release capsule: 37.5 mg 75 mg 150 mg Extended-release tablet: 37.5 mg 75 mg 150 mg 225 mg Tablet: 25 mg 37.5 mg 50 mg 75 mg 100 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Treatment of panic disorder, with or without agoraphobia: Extended-release capsule: initial, 37.5 mg once-daily for one week; maintenance, 75 to 225 mg/day; maximum, 225 mg/day Treatment of social anxiety disorder: Extended-release capsule, extended-release tablet: 75 mg once-daily		
Selective Serotonin-reuptake Inhibitors			
Citalopram	Depression: Solution, tablet: initial, 20 mg/day; increase dose in 20 mg increments at intervals of no less than one week; maximum dose, 40 mg/day	Safety and efficacy in children have not been established.	Solution: 10 mg/5 mL Tablet: 10 mg 20 mg 40 mg
Escitalopram	Depression: Solution, tablet: initial, 10 mg/day; dose may be increased to 20 mg/day after at least one week Generalized anxiety disorder: Solution, tablet: Initial, 10 mg/day; dose may be increased to 20 mg/day after at least one week	Depression ≥12 years of age: Solution, tablet: initial, 10 mg/day; dose may be increased to 20 mg/day after at least three weeks	Solution: 5 mg/5 mL Tablet: 5 mg 10 mg 20 mg
Fluoxetine	Bulimia nervosa: Immediate release capsule and tablet, solution: 20 mg once daily; usual dose: 60 mg/day; maximum, 60 mg/day; doses >20 mg may be given once daily or divided twice daily Depression: Immediate release capsule and tablet, solution: 20 mg once daily; usual dose, 20 to 40 mg/day; maximum, 80 mg/day; doses >20 mg may be given once daily or divided twice daily Delayed release capsule: patients maintained on fluoxetine immediate release 20 mg/day may be changed to fluoxetine delayed release capsule 90 mg/week, starting dose seven days after the last 20 mg/day	Depression eight to 18 years of age: Immediate release capsule and tablet, solution: 10 to 20 mg/day; lower-weight children may be started on 10 mg/day; may increase to 20 mg/day after one week if needed Obsessive-compulsive disorder seven to 18 years of age: Immediate release capsule and tablet, solution: 10 mg/day; in adolescents and higher-weight children, dose may be increased to 20 mg/day after two weeks; range, 10 to 60	Delayed release capsule: 90 mg Immediate release capsule: 10 mg 20 mg 40 mg Immediate release tablet: 10 mg 20 mg 60 mg Solution: 20 mg/5 mL

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	dose Obsessive-compulsive disorder: Immediate release capsule and tablet, solution: 20 mg once daily; usual dose: 40 to 80 mg/day; maximum, 80 mg/day; doses >20 mg may be given once daily or divided twice daily Delayed release capsule: patients maintained on fluoxetine immediate release 20 mg/day may be changed to fluoxetine delayed release capsule 90 mg/week, starting dose seven days after the last 20 mg/day dose Panic disorder: Immediate release capsule and tablet, solution: initial, 10 mg/day; after one1 week, increase to 20 mg/day; may increase after several weeks; doses >60 mg/day have not been evaluated Delayed release capsule: patients maintained on fluoxetine immediate release 20 mg/day may be changed to fluoxetine delayed release capsule 90 mg/week, starting dose seven days after the last 20 mg/day dose Premenstrual dysphoric disorder: Immediate release tablet (Sarafem®): 20 mg/day continuously or 20 mg/day starting 14 days prior to menstruation and through first full day of menses (repeat with each cycle)	mg/day	
Fluvoxamine	Obsessive-compulsive disorder: Immediate release tablet: initial, 50 mg at bedtime; adjust dose in 50 mg increments every four to seven days; usual dose, 100 to 300 mg/day; divide total daily dose into two doses; administer larger portion at bedtime; when total daily dose exceeds 100 mg, the dose should be given in two divided doses	Obsessive-compulsive disorder eight to 17 years of age: Immediate release tablet: initial, 25 mg at bedtime; adjust in 25 mg increments at four to seven day intervals; range, 50 to 200 mg/day	Extended release capsule: 100 mg 150 mg Immediate release tablet: 25 mg 50 mg 100 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Extended release capsule: initial, 100 mg at bedtime; may be increased in 50 mg increments at intervals of at least one week; usual dose range, 100 to 300 mg/day		
Paroxetine	Depression: Immediate release tablet, suspension: initial, 20 mg once daily; increase by 10 mg/day increments at intervals of at least one week; maximum dose, 50 mg/day Extended release tablet: initial, 25 mg once daily; increase if needed by 12.5 mg/day increments at intervals of at least one week; maximum dose, 62.5 mg/day Generalized anxiety disorder: Immediate release tablet, suspension: initial, 20 mg once daily; increase if needed by 10 mg/day increments at intervals of at least one week; doses of 20 to 50 mg/day were used in clinical trials; however, no greater benefit was seen with doses >20 mg Obsessive-compulsive disorder: Immediate release tablet, suspension: initial, 20 mg once daily; increase if needed by 10 mg/day increments at intervals of at least one week; recommended dose, 40 mg/day; range, 20 to 60 mg/day Moderate to severe vasomotor symptoms associated with menopause: Immediate release capsule: 7.5 mg once daily at bedtime Panic disorder: Immediate release tablet, suspension: initial, 10 mg once daily; increase if needed by 10 mg/day increments at intervals of at least one week; recommended dose, 40 mg/day; range, 10 to 60 mg/day	Safety and efficacy in children have not been established.	Extended release tablet: 12.5 mg 25 mg 37.5 mg Immediate release capsule: 7.5 mg Suspension: 10 mg/5 mL Immediate release tablet: 10 mg 20 mg 30 mg 40 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Extended release tablet: initial, 12.5 mg once daily in the morning; increase if needed by 12.5 mg/day increments at intervals of at least one week; maximum dose, 75 mg/day Premenstrual dysphoric disorder: Extended release tablet: initial, 12.5 mg once daily in the morning; dose may be increased to 25 mg/day; dosing changes should occur at intervals of at least one week; may be given daily throughout the menstrual cycle or limited to the luteal phase Posttraumatic stress disorder: Immediate release tablet, suspension: initial, 20 mg once daily; increase if needed by 10 mg/day increments at intervals of at least one week; range, 20 to 50 mg; limited data suggest doses of 40 mg/day were not more efficacious than 20 mg/day Social anxiety disorder: Immediate release tablet, suspension: initial, 20 mg once daily, preferably in the morning; recommended dose, 20 mg/day; range, 20 to 60 mg/day; doses >20 mg/day may not have additional benefit Extended release tablet: initial, 12.5 mg once daily; increase if needed by 12.5 mg/day increments at intervals of at least one week; maximum dose, 37.5 mg/day		
Sertraline	Depression: Oral concentrate, tablet: initial, 50 mg/day; may increase daily dose, at intervals of not less than one week; maximum, 200 mg/day; if somnolence is noted, give at bedtime Obsessive-compulsive disorder: Oral concentrate, tablet: initial, 50 mg/day; may increase daily dose, at intervals of not less than	Obsessive-compulsive disorder six to 12 years of age: Oral concentrate, tablet: initial, 25 mg once daily Obsessive-compulsive disorder 13 to 17 years of age: Oral concentrate, tablet: initial, 50 mg once	Oral concentrate: 20 mg/mL Tablet: 25 mg 50 mg 100 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	one week; maximum, 200 mg/day; if somnolence is noted, give at bedtime Panic disorder: Oral concentrate, tablet: initial, 25 mg once daily; increased after one week to 50 mg once daily Posttraumatic stress disorder: Oral concentrate, tablet: initial, 25 mg once daily; increased after one week to 50 mg once daily Premenstrual dysphoric disorder: Oral concentrate, tablet: 50 mg daily throughout menstrual cycle or limited to the luteal phase of menstrual cycle; patients not responding to 50 mg/day may benefit from dose increases (50 mg increments per menstrual cycle) up to 150 mg/day when dosing throughout menstrual cycle or up to 100 mg/day when dosing during luteal phase only Social anxiety disorder: Oral concentrate, tablet: initial, 25 mg once daily; increased after one week to 50 mg once daily; range, 50 to 200 mg/day	daily May increase daily dose, at intervals of not less than one week; maximum, 200 mg/day; if somnolence is noted, give at bedtime	
Serotonin Modulators			
Nefazodone	Depression: Tablet: 200 mg/day divided in two doses initially, with a range of 300 to 600 mg/day in two divided doses thereafter	Safety and efficacy in children have not been established.	Tablet: 50 mg 100 mg 150 mg 200 mg 250 mg
Trazodone	Major depressive disorder: Extended-release tablet: initial, 150 mg once daily; maintenance, may increase by 75 mg/day every three days; maximum, 375 mg/day Tablet: initial, 150 mg/day in three divided doses; maintenance, dose may be increased by 50 mg/day every three to seven days; maximum, 400 (outpatients) and 600 (inpatients) mg/day	Safety and efficacy in children have not been established.	Extended release tablet: 150 mg 300 mg Immediate release tablet: 50 mg 100 mg 150 mg 300 mg
Vilazodone	Major depressive disorder: Tablet: Initial, 10 mg once daily for seven days, then increase to	Safety and efficacy in children have not been established.	Tablet: 10 mg 20 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	20 mg once daily for seven days, then to recommended dose of 40 mg daily		40 mg Tablet dose pack: 10 mg (7 tablets), 20 mg (23 tablets) 10 mg (7 tablets), 20 mg (7 tablets), 40 mg (16 tablets)
Vortioxetine	Major depressive disorder: Tablet: initial, 10 mg once daily; maintenance, increase to 20 mg once daily, as tolerated; maximum, 20 mg once daily	Safety and efficacy in children have not been established.	Tablet: 5 mg 10 mg 20 mg
Tricyclics and Other Norepinephrine-reuptake Inhibitors-Single Entity Agents			
Amitriptyline	Depression: Tablet: 25 to 15 mg/day as a single dose at bedtime or in divided doses; dose may be gradually increased up to 300 mg/day	Depression >12 years of age: Tablet: 10 mg three times per day and 20 mg at bedtime	Tablet: 10 mg 25 mg 50 mg 75 mg 100 mg 150 mg
Amoxapine	Depression: Tablet: initial, 25 mg two to three times/day; if tolerated, dosage may be increased to 100 mg two to three times/day; may be given in a single bedtime dose when dosage <300 mg/day; maximum daily dose, 600 mg (inpatients) and 400 mg (outpatients)	Safety and efficacy in children have not been established.	Tablet: 25 mg 50 mg 100 mg 150 mg
Clomipramine	Obsessive-compulsive disorder: Capsule: initial, 25 mg/day and gradually increase, as tolerated, to 100 mg/day the first two weeks; maximum, 250 mg/day	Obsessive-compulsive disorder >10 years of age: Capsule: initial, 25 mg/day and gradually increase, as tolerated; maximum, 3 mg/kg/day or 200 mg/day, whichever is smaller	Capsule: 25 mg 50 mg 75 mg
Desipramine	Depression: Tablet: initial, 25 to 50 mg/day; increase gradually to 100 to 200 mg/day in divided or single dose; maximum, 300 mg/day	Depression >12 years of age: Tablet: initial, 25 to 50 mg/day; gradually increase to 100 mg/day in single or divided doses; maximum, 150 mg/day	Tablet: 10 mg 25 mg 50 mg 75 mg 100 mg 150 mg
Doxepin	Anxiety: Capsule, oral concentrate: initial, 25 to 75 mg/day at bedtime or in two to three divided doses; may gradually increase up to 300 mg/day; single dose should not exceed 150 mg; select patients may respond to 25 to 50 mg/day	Safety and efficacy in children have not been established.	Capsule: 10 mg 25 mg 50 mg 75 mg 100 mg 150 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Depression: Capsule, oral concentrate: initial, 25 to 75 mg/day at bedtime or in two to three divided doses; may gradually increase up to 300 mg/day; single dose should not exceed 150 mg; select patients may respond to 25 to 50 mg/day Insomnia: Tablet: 3 to 6 mg once daily at bedtime; maximum, 6 mg/day		Oral concentrate: 10 mg/mL Tablet: 3 mg 6 mg
Imipramine	Depression: Capsule: initial, 75 mg/day; dosage may be increased to 150 to 200 mg/day; doses >75 mg/day may be administered once daily; in some patients, it may be necessary to employ a divided-dose schedule Tablet: initial, 25 mg three to four times/day; increase dose gradually, total dose may be given at bedtime; maximum, 300 mg/day	Depression (adolescents): Tablet: initial, 30 to 40 mg/day; increase gradually; maximum, 100 mg/day in single or divided doses Pediatric nocturnal enuresis >6 years of age: Tablet: initial, 25 mg one hour before bedtime; if inadequate response after one week of therapy, increase by 25 mg/day; dose should not exceed 2.5 mg/kg/day or 50 mg at bedtime (if 6 to 12 years of age) or 75 mg at bedtime (if ≥12 years of age)	Capsule: 75 mg 100 mg 125 mg 150 mg Tablet: 10 mg 25 mg 50 mg
Maprotiline	Depression (mild to moderate): Tablet: initial, 25 to 75 mg/day for two weeks; increase by 25 mg as tolerated up to 150 mg/day; given in divided doses or in a single daily dose Depression (severe): Tablet: initial, 100 to 150 mg/day for 2 weeks; increase by 25 mg as tolerated up to 225 mg/day; given in divided doses or in a single daily dose	Safety and efficacy in children have not been established.	Tablet: 25 mg 50 mg 75 mg
Nortriptyline	Depression: Capsule, solution: 25 mg three to four times daily, up to 150 mg/day	Safety and efficacy in children have not been established.	Capsule: 10 mg 25 mg 50 mg 75 mg Solution:

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
			10 mg/5 mL
Protriptyline	Depression: Tablet: 15 to 60 mg/day in three to four divided doses	Depression (adolescents): Tablet: 15 to 20 mg/day in three divided doses	Tablet: 5 mg 10 mg
Trimipramine	Depression: Capsule: 50 to 150 mg/day as a single bedtime dose; maximum, 200 mg/day for outpatients and 300 mg/day for inpatients	Depression (adolescents): Capsule: initial, 50 mg/day, with gradual increments up to 100 mg/day	Capsule: 25 mg 50 mg 100 mg
Tricyclics and Other Norepinephrine-reuptake Inhibitors-Combination Products			
Amitriptyline and chlordiazepoxide	Mixed anxiety/depressive disorder: Tablet: initial, three to four tablets in divided doses; may be increased to six tablets per day as required; some patients respond to smaller doses and can be maintained on two tablets	Safety and efficacy in children have not been established.	Tablet: 12.5-5 mg 25-10 mg
Antidepressants, Miscellaneous			
Bupropion	Depression: Extended release tablet: initial, 150 mg/day in the morning; may increase as early as day four of dosing to 300 mg/day; maximum dose: 450 mg/day Extended release tablet: initial, 174 mg/day in the morning; may increase as early as day four to 348 mg/day; maximum dose: 522 mg/day Immediate release tablet: initial, 100 mg twice daily; maximum, 450 mg/day Sustained release tablet: initial, 150 mg/day; may increase to 150 mg twice daily by day four if tolerated; target dose, 150 mg twice daily; maximum dose, 400 mg/day Seasonal affective disorder: Sustained release tablet: initial, 150 mg/day in the morning; if tolerated, may increase after one week to 300 mg/day Smoking cessation: Immediate release tablet: initial, 150 mg once daily for three days; increase to 150 mg twice daily; treatment should continue	Safety and efficacy in children have not been established.	Extended release tablet: 150 mg (Wellbutrin XL®) 174 mg (Aplenzin®) 300 mg (Wellbutrin XL®) 348 mg (Aplenzin®) 450 mg (Forfivo®) 522 mg (Aplenzin®) Immediate release tablet (Wellbutrin®): 75 mg 100 mg Sustained release tablet (Wellbutrin SR®): 100 mg 150 mg 200 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	for seven to twelve weeks		
Mirtazapine	Depression: Orally disintegrating tablet, tablet: initial, 15 mg at bedtime; titrate up to 15 to 45 mg/day with dose increases made no more frequently than every one to two weeks	Safety and efficacy in children have not been established.	Orally disintegrating tablet: 15 mg 30 mg 45 mg Tablet: 7.5 mg 15 mg 30 mg 45 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the antidepressants are summarized in Table 11.

Table 11. Comparative Clinical Trials with the Antidepressants

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Depression				
Koshino et al.[56] (2013) Bupropion SR 150 mg daily vs bupropion SR 150 mg BID vs placebo	DB, MC, PC, RCT Patients 18 to 64 years of age with MDD in Japan or South Korea	N=569 8 weeks	Primary: Mean change from baseline in MADRS total score at week eight Secondary: Comparison of change from baseline for each group in MADRS total scores and IDS-SR total scores at weeks one, two, four, six and eight; MADRS total scores stratified by location at week eight for each group	Primary: The mean change from baseline in MADRS total scores was decreased for bupropion SR 150 mg daily, bupropion 150 mg BID and placebo; however no significant difference from placebo (-14.4; P=0.853, -12.9; P value not reported, -13.9; P value not reported, respectively). Secondary: Both MADRS and IDS-SR total scores consistently decreased (weeks one, two, four, six and eight) throughout the study for all groups, including placebo; however, neither bupropion treatment group significantly differed from placebo in either MADRS or IDS-SR in total scores. When MADRS results were stratified by location (Japan or South Korea), no significant differences were observed in change from baseline in MADRS total score at week eight.
Clayton et al.[57] (2006) Bupropion ER 300 to 450 mg daily vs escitalopram 10 to 20 mg daily	DB, PC, RCT Adult outpatients with moderate-to-severe MDD with normal sexual function	N=830 8 weeks	Primary: Orgasm dysfunction at eight weeks and incidence of worsened sexual functioning; CSFQ, HAM-D_{17} Secondary:	Primary: The incidence of worsened sexual functioning at the end of the treatment period was statically significantly lower with bupropion ER than with escitalopram (P<0.05), not statistically different between bupropion ER and placebo (P>0.067), and statistically significantly higher with escitalopram than with placebo (P<0.001). The percentages of patient with orgasm dysfunction at week eight were 15% with bupropion ER, 30% with escitalopram, and 15% with placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo			Not reported	The mean change in CSFQ sores for all domains at week eight was statistically significantly worse for escitalopram compared to bupropion ER (P<0.05). Bupropion did not statistically differ from escitalopram with respect to mean change in HAM-D_{17} total score, response or remission rates. Secondary: Not reported
Hewett et al.[58] (2009) Bupropion ER 150 mg/day for 4 weeks, then 300 mg/day vs venlafaxine ER 75 mg/day for 4 weeks, then 150 mg/day vs placebo	DB, MC, PC, RCT Patients 18 to 64 years of age with MDD	N=576 8 weeks	Primary: Mean change from baseline at week eight in the MADRS total score (LOCF) Secondary: MADRS total score (observed cases), MADRS subscore, percentage of MADRS responders and remitters at week eight; CGI-I score at week eight; CGI-S score and HAMA total score at weeks one, two, four, six and eight	Primary: The mean changes from baseline at week eight (LOCF) in MADRS total score were greater for patients receiving bupropion ER and venlafaxine ER compared to patients receiving placebo: -16.0 for bupropion ER (P=0.006 vs placebo), -17.1 for venlafaxine ER (P<0.001 vs placebo) and -13.5 for placebo. There was no significant difference between the bupropion ER group and the venlafaxine ER group (95% CI, -0.7 to 2.9). Secondary: The mean changes from baseline to week eight (observed cases) in MADRS total scores were significantly greater for bupropion ER and venlafaxine ER patients compared to the placebo group: -18.2 for bupropion ER (P=0.003), -18.5 for venlafaxine ER (P<0.001) and -15.8 for placebo. Significant improvements from baseline in MADRS sadness and concentration difficulties scores were observed for bupropion ER (-2.2; P<0.001 and -1.8; P=0.004, respectively) and venlafaxine ER (-2.3; P<0.001 and -1.9; P<0.001, respectively) compared to placebo at week eight (-1.7 and -1.4, respectively). Significant improvements in MADRS lassitude score were found for venlafaxine ER compared to placebo (-1.8 vs -1.5; P=0.009), but not for bupropion ER (-1.7 vs -1.5; P=0.140). A larger proportion of patients in the bupropion ER and venlafaxine ER groups were classified as MADRS responders (≥50% reduction in MADRS total score) and remitters (MADRS total score ≤11) at week eight

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				compared to the placebo group. Response rates were 57% for bupropion ER (P=0.033), 65% for venlafaxine ER (P<0.001), and 46% for placebo. Remission rates were 47% for bupropion ER (P=0.004), 51% for venlafaxine ER (P<0.001), and 32% for placebo. CGI-I response rates for both active treatment groups were significantly better than placebo with 68% of bupropion ER patients (P<0.001) and 65% of venlafaxine ER patients (P=0.009) rated 'much improved' or 'very much improved' at week eight compared to 53% of placebo patients. Significantly greater mean decreases from baseline in SDS total scores were observed for bupropion ER (-8.4; P=0.003) and venlafaxine ER (-9.0; P<0.001) compared to placebo (-6.2). The mean change from baseline in patient satisfaction with study medication was significantly greater for bupropion ER (4.9; P=0.005) and venlafaxine ER (5.2; P<0.001) than placebo (4.4).
Weihs et al.[59] (2000) Bupropion SR 100 to 300 mg/day vs paroxetine 10 to 40 mg/day	DB, MC, RCT Patients ≥60 years of age with MDD	N=100 6 weeks	Primary: HAM-D, HAMA, CGI-I, CGI-S scores Secondary: Adverse effects	Primary: Measurements of efficacy were similar between the treatment groups, with both showing improved scores on all depression rating scales. Secondary: Somnolence and diarrhea were more common in paroxetine-treated patients (P<0.05). Headache, insomnia, dry mouth, agitation, dizziness, and nausea occurred in >10% of patients in both groups.
Kavoussi et al.[60] (1997) Bupropion SR 100 to 300 mg/day vs sertraline 50 to 200 mg/day	DB, PG, RCT Outpatients with moderate-to-severe MDD	N=248 16 weeks	Primary: HAM-D, HAMA, CGI-I, CGI-S Secondary: Adverse effects	Primary: Mean HAM-D, HAMA, CGI-I, and CGI-S scores improved over the course of treatment in both the bupropion SR group and the sertraline group; no between-group differences were observed on any of the scales. Secondary: Orgasm dysfunction was significantly (P<0.001) more common in sertraline-treated patients compared to bupropion SR-treated patients. Adverse events (nausea, diarrhea, somnolence, and sweating) were

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				experienced more frequently (P<0.05) in sertraline-treated patients. No differences were noted between the treatments for vital signs and weight.
Rocca et al.[61] (2005) Citalopram 20 mg/day vs sertraline 50 mg/day	DB, RCT Patients >65 years of age with minor depressive disorder or subsyndromal depressive symptomatology	N=138 8 weeks	Primary: Change in depressive symptoms and remission rates (HAM-D) Secondary; Not reported	Primary: Both treatments induced notable improvement of depressive symptoms. No statistically significant differences were found between the two treatments in decreases from baseline HAM-D scores. At the end of the trial, the mean total HAM-D score had fallen 55.0% in the citalopram group and 52.7% in the sertraline group. No significant differences in remission rates were observed between the two agents. For one month, three month, and end follow-up periods, P=0.3466, 0.7570, and 0.2537, respectively. Secondary; Not reported
Clayton et al.[62] (2013) Desvenlafaxine 50 mg/day vs placebo	DB Adult outpatients with MDD	N=422 12 weeks	Primary: Mean change from baseline Arizona Sexual Experiences Scale scores Secondary: Not reported	Primary: Among women (desvenlafaxine, n=184; placebo, n=92), baseline scores were 20.0 (5.2) and 20.5 (5.3) for desvenlafaxine and placebo, respectively; mean changes at week 12 were -1.93 (0.37) and -1.03 (0.54), respectively (mean difference: 0.90 [-0.38 to 2.18]; P=0.169). Among men (desvenlafaxine, n=97; placebo, n=49), baseline scores were 16.4 (4.9) and 15.9 (4.8) for desvenlafaxine and placebo, respectively; mean changes at week 12 were -1.13 (0.47) and -1.06 (0.70), respectively (mean difference: 0.07 [-1.59 to 1.74]; P=0.932). Significantly greater orgasmic dysfunction at week 12 was observed in the subgroup of men without baseline sexual dysfunction treated with desvenlafaxine relative to placebo. Conversely, women without baseline sexual dysfunction experienced poorer overall sexual functioning and orgasm satisfaction at week 12 with placebo relative to desvenlafaxine treatment. Subgroup analyses of treatment responders and nonresponders found no difference in the proportion of men or women that developed or had resolution of sexual dysfunction in the desvenlafaxine and placebo groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Rosenthal et al.[63] (2013) Desvenlafaxine 50 mg/day vs placebo	DB, MC, PC, RCT Adult outpatients age >18 years of age with MDD (DSM-IV criteria) and a HDRS17 total score >20 at screening and baseline	N=874 11 months	Primary: Time to relapse (HDRS17 total score >16, discontinuation for unsatisfactory response, hospitalization for depression, suicide attempt, or suicide) Secondary: Safety and tolerability	Primary: Time to relapse was significantly shorter for placebo vs desvenlafaxine (P<0.001). At the end of the six-month DB treatment, the estimated probability of relapse was 30.2% for placebo vs 14.3% for desvenlafaxine 50 mg/day. Secondary: Safety and tolerability results were generally consistent with those in short-term studies of desvenlafaxine 50 mg/day.
Dunlop et al.[64] (2011) Desvenlafaxine 50 mg/day vs placebo	DB, PC, RCT Gainfully employed (≥20 hours/week) outpatients with MDD	N=427 12 weeks	Primary: HAM-D-17 total score Secondary: SDS, safety	Primary: Desvenlafaxine demonstrated superiority over placebo beginning at week two, which continued through week 12. Adjusted mean endpoint scores with desvenlafaxine and placebo were 9.33 and 11.45, respectively. Mean change scores were -12.61±0.45 and -10.50±0.60 with desvenlafaxine and placebo, respectively. The adjusted mean difference in change from baseline between desvenlafaxine and placebo at week 12 was 2.12 (95% CI, 0.78 to 3.46; P=0.002). Secondary: The adjusted mean difference in change from baseline score on the SDS between the desvenlafaxine and placebo at week 12 was 1.33 (95% CI, -0.09 to 2.76), which narrowly missed significance (P=0.067). There were six serious adverse events (no deaths) that occurred in four and two desvenlafaxine- and placebo-treated patients. None of these events were considered non-treatment related. No new safety concerns about desvenlafaxine were identified from safety analyses.
Kornstein et al.[65] (2010) Desvenlafaxine 100 or 200 mg/day	DB, MC, PC, RCT Perimenopausal and post-menopausal women 40 to 70	N=387 8 weeks	Primary: HAM-D-17 total score Secondary:	Primary: Baseline reductions in HAM-D-17 total scores were significantly greater with desvenlafaxine (adjusted mean change, -12.64) compared to placebo (-8.33; P<0.01). Significant differences between treatments were observed at week one (P=0.044) and were sustained though week eight (week two;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	years of age with MDD, single or recurrent episode		CGI-I, CGI-S, MADRS, HAMA, QIDS-SR, MRS, EQ-5D, VAS-PI, safety	P=0.013, weeks three to eight; P<0.001). Both perimenopausal (adjusted mean change, -10.96; P=0.003) and postmenopausal (-11.09; P<0.001) subgroups achieved significant reductions in HAM-D-17 total scores with desvenlafaxine compared to placebo. The treatment effect (adjusted mean difference from placebo) in these two populations were -4.07 (95% CI, -6.77 to -1.37) and -2.37 (95% CI, -5.07 to -1.47). HAM-D-17 based response (58.6%) and remission (38.2%) rates were significantly higher with desvenlafaxine compared to placebo (31.6 and 22.4%; P<0.001 and P=0.008, respectively). Secondary: Desvenlafaxine achieved significant improvement compared to placebo on all secondary outcomes. Desvenlafaxine-treated patients had significantly lower CGI-I scores at week eight compared to placebo-treated patients (2.00 vs 2.82; P<0.001); a significantly higher percentage of patients receiving desvenlafaxine had scored 1 (very much improved) or 2 (much improved) compared to patients receiving placebo (67.7 vs 41.2%; P<0.001). In total, 7.4 and 3.2% of desvenlafaxine- and placebo-treated patients discontinued study medication due to an adverse event. The event cited most commonly by patients discontinuing due to an adverse event was hypertension (five vs zero patients). Treatment-emergent adverse events were reported by 85.2 and 75.2% of desvenlafaxine- and placebo-treated patients. Most events were mild or moderate in severity. The most common treatment-emergent adverse events were dry mouth (24 vs 10%), somnolence (15 vs 7%), constipation (14 vs 6%), hypertension (7 vs 2%), sweating (7 vs 2%), dyspepsia (6 vs 2%), and anorexia (6 vs <1%). Serious adverse events were reported by three patients receiving desvenlafaxine (chest pain and hypertension, medication error and psychotic depression, and infection) and two patients receiving placebo (cerebrovascular disorder and skin carcinoma). No deaths were reported during the study or within 30 days after its conclusion.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Rickels et al.[66] (2010) Desvenlafaxine 200 to 400 mg/day vs placebo After 12 weeks of OL treatment with desvenlafaxine, patients with HAM-D-17 total score ≤11 were randomized to continue desvenlafaxine or be switched to placebo.	DB, PC, RCT Patients 18 to 75 years of age with MDD, single or recurrent episode, without psychotic features	N=374 (DB phase) N=575 (OL phase) 12 weeks of OL treatment, followed by a 6 month, DB phase	Primary: Time until relapse (HAMD-D-17 total score ≥16 at any visit, CGI-I score ≥6 at any visit, or discontinuation due to unsatisfactory response) Secondary: HAM-D-17 total score, CGI-I, CGI-S, HAM-D-6, Covi Anxiety score, safety	Primary: Patients receiving desvenlafaxine experienced significantly longer times to relapse of MDD compared to patients receiving placebo during DB treatment (P<0.0001). The proportions of patients relapsing were 42 and 24% of patients receiving placebo and desvenlafaxine, respectively (P<0.001). Secondary: A significant difference in HAM-D-17 total scores in favor of desvenlafaxine was observed from DB week three onward (P<0.001). At the final evaluation, adjusted mean changes were 0.85 and 5.03 for desvenlafaxine and placebo, respectively. Desvenlafaxine was also associated with significant differences compared to placebo on CGI-I, CGI-S, HAM-D-6, and Covi Anxiety scores. The most common primary reason cited for discontinuation of treatment during the OL phase was adverse events (19%), which consisted of nausea, dizziness, and insomnia. A total of 101 (55%) and 58 (31%) patients receiving placebo and desvenlafaxine discontinued treatment during the DB phase. The most frequent adverse event reported as the reason for discontinuation during the DB phase was depression (14 patients receiving placebo vs seven patients receiving desvenlafaxine). During the OL phase the most commonly reported adverse events with desvenlafaxine were nausea (42%), dry mouth (32%), headache (26%), dizziness (23%), hyperhidrosis (21%), insomnia (20%), constipation (15%), decreased appetite (12%), fatigue (12%), somnolence (11%), diarrhea (10%), tremor (10%), vomiting (8%), sedation (5%), and blurred vision (5%). During the DB phase, treatment-emergent adverse events were reported by 73 and 82% of patients receiving desvenlafaxine and placebo, respectively. The most commonly reported events with desvenlafaxine were headache (24%), dizziness (15%), nausea (14%), fatigue (13%), hyperhidrosis (13%), diarrhea (9%), abnormal dreams (9%), depression (8%), insomnia (8%), influenza (7%), irritability (7%) , back pain (6%), upper respiratory tract infection (6%), abdominal pain (5%), anxiety (5%), muscle spasms (5%), nasopharyngitis (5%), tremor

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(5%), delayed ejaculation (5% in men), erectile dysfunction (5% in men), vomiting (4%), vertigo (3%), myalgia (2%), paresthesia (2%), and altered mood (1%).
Clayton et al.[67] (abstract) (2009) Desvenlafaxine 50 to 400 mg/day vs placebo	DB, PC, RCTs (integrated analysis of short-term 9 trials) Adult outpatients with MDD	N=2,950 8 weeks	Primary: Treatment-emergent adverse events, laboratory values, vital signs, discontinuation symptoms Secondary: Not reported	Primary: The most common treatment-emergent adverse event was transient nausea that was generally mild to moderate. The most common sexual dysfunction associated with desvenlafaxine treatment was erectile dysfunction in men (7 vs 1%) and anorgasmia in women (1 vs 0%). One patient receiving desvenlafaxine died of a completed suicide; there were four suicide attempts (three vs one patient[s]) and eight cases of suicidal ideation (five vs three patients) during the on-therapy period. Desvenlafaxine was associated with small but significant mean changes in laboratory assessments, particularly lipid and liver enzyme elevations, and ECGs; few cases of these changes were clinically relevant. Small but significant changes in mean blood pressure occurred with all desvenlafaxine doses; clinically meaningful changes were observed in 1 and 2% of placebo- and desvenlafaxine-treated patients. In the overall population, adverse events resulted in discontinuations in 3 and 12% of placebo- and desvenlafaxine-treated patients; in the subset of fixed-dose trials, the rates were 4 and 4 to 18% with placebo and desvenlafaxine. Secondary: Not reported
Feiger et al.[68] (2009) Desvenlafaxine 200 to 400 mg/day vs placebo	DB, MC, PC, PG, RCT Outpatients ≥18 years of age with MDD	N=235 8 weeks (plus a 2 week tapering phase)	Primary: HAM-D-17 Secondary: CGI-I, CGI-S, MADRS, HAM-D-6, safety	Primary: No significant difference was observed in the adjusted mean change from baseline in the HAM-D-17 total score between desvenlafaxine and placebo at the final evaluation (difference in adjusted means, 1.6; 95% CI, -0.2 to 3.4). No significant differences were observed between desvenlafaxine and placebo groups for HAM-D-17 clinical response rates at the final evaluation; the logistic regression analysis demonstrated adjusted ORs of 1.456 (95% CI, 0.85 to 2.50; P=0.175) for HAM-D-17 response. No

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				significant difference in HAM-D-17 remission rates was observed between desvenlafaxine and placebo groups at final evaluation; the logistic regression analysis showed an adjusted OR of 1.158 (95% CI, 0.60 to 2.22; P=0.66). Secondary: At final evaluation, significant differences between desvenlafaxine and placebo were observed for the CGI-I (difference in adjusted means: 0.3; 95% CI, 0.0 to 0.6), CGI-S (0.3; 95% CI, 0.0 to 0.6), MADRS (2.9; 95% CI, 0.3 to 5.4), and HAM-D-6 (1.5; 95% CI, 0.5 to 2.6). A significant difference was observed between desvenlafaxine and placebo groups for MADRS clinical response rates; the logistic regression analysis demonstrated an adjusted OR of 1.754 (95% CI, 1.03 to 3.00; P=0.04). Treatment-emergent adverse events were reported by 112 patients (96%) and 101 patients (86%) receiving desvenlafaxine and placebo. Treatment-emergent adverse events reported by ≥5% of patients receiving desvenlafaxine and at a frequency at least twice that of the placebo group included nausea, dry mouth, hyperhidrosis, insomnia, somnolence, decreased appetite, tremor, blurred vision, yawning, sedation, vomiting, mydriasis, middle insomnia, initial insomnia, erectile dysfunction, constipation, feeling jittery, and dyspepsia. Nausea, the most frequently reported adverse event in patients receiving desvenlafaxine (36%), was mild to moderate in the majority of cases (88%). Treatment-emergent adverse events resulted in reduction in dose of study medication for six (5%) and two (2%) patients receiving desvenlafaxine and placebo. Taper/post-study-emergent adverse events were consistent with what has been seen in pervious trials of desvenlafaxine and with the SNRIs. Significantly more patients receiving desvenlafaxine (12%) discontinued the study because of treatment-emergent adverse events compared to patients receiving placebo (3%; P=0.008). No deaths or serious adverse events occurred during the study.
Thase et al.[69] (2009)	MA (9 trials) Outpatients ≥18	N=3,023 8 weeks	Primary: HAM-D-17 total score	Primary: Significantly greater improvement with desvenlafaxine vs placebo on HAM-D-17 total scores was observed for the full data set (difference in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Desvenlafaxine 50 to 400 mg/day vs placebo	years of age with MDD		Secondary: MADRS, HAM-D-6, CGI-I, CGI-S, remission and response rates, safety	adjusted means, -1.9; P<0.001). Significance was observed in all fixed-dose (P<0.001 for all) and flexible-dose trials (P=0.24). Secondary: For the overall desvenlafaxine group significant improvement from baseline was observed on all secondary outcome measures at the final evaluation. Overall, desvenlafaxine had a significantly greater change from baseline compared to placebo on the CGI-I, CGI-S, and MADRS total scores from week two onward and in the core symptoms of depression (HAM-D-6 total score) from week one onward. Overall rates of HAM-D-17 response (53 vs 41%) and remission (32 vs 23%) were significantly greater with desvenlafaxine vs placebo (P<0.001 for all). Discontinuation rates due to adverse events increased with desvenlafaxine dose (4 to 18 vs 3%). The most common treatment-emergent adverse events in the overall data set were nausea, dry mouth, hyperhidrosis, dizziness, and constipation.
Clayton et al.[70] (2015) Desvenlafaxine 50 and 100 mg/day vs placebo	DB, PC, RCT Outpatients ≥18 years of age with MDD, depressive symptoms for ≥30 days before screening and baseline HAM-D-17 total score ≥20; HAM-D-17 item 1 (depressed mood) score ≥2; and CGI-S ≥4	N=909 8 weeks	Primary: HDRS-17 total score Secondary: CGI-I, CGI-S, ASEX	Primary: A statistically significantly greater change from baseline in HDRS-17 total score was observed for both desvenlafaxine groups compared with placebo after adjusting for multiplicity (desvenlafaxine 50 mg, P=0.006; desvenlafaxine 100 mg, P<0.001). Secondary: Statistically significant improvement from baseline in CGI-S scores was observed at week eight for both desvenlafaxine dose groups compared with placebo. The adjusted mean difference versus placebo was 0.20 (95% CI, 0.05 to 0.34; P=0.009) for the desvenlafaxine 50-mg group and 0.28 (95% CI, 0.13 to 0.43; P<0.001) for the desvenlafaxine 100-mg group. Pairwise comparisons of CGI-I scores for each desvenlafaxine group versus placebo were statistically significant (desvenlafaxine 50 mg, P=0.029; desvenlafaxine 100 mg, P<0.001, without adjustment for multiplicity). At week eight (LOCF), ASEX total and individual item scores were

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				comparable for both 50 and 100 mg doses of desvenlafaxine and placebo, with widely overlapping confidence intervals.
Boyer et al.[71] (2008) Desvenlafaxine 50 and 100 mg/day vs placebo	DB, MC, PC, PG, RCT Outpatients ≥18 years of age with MDD, depressive symptoms for ≥30 days before screening and baseline HAM-D-17 total score ≥20; HAM-D-17 item 1 (depressed mood) score ≥2; and CGI-S ≥4	N=438 8 weeks (plus a 1 week taper phase)	Primary: HAM-D-17 total score Secondary: CGI-I, MADRS, CGI-S, VAS-PI, Covi Anxiety Scale total scores, remission rates, responder rates, safety	Primary: In a LOCF analysis, adjusted mean baseline changes in HAM-D-17 total scores were significantly greater with desvenlafaxine 50 (-13.2; P=0.002) and 100 mg/day (-13.7; P<0.001) compared to placebo (-10.7). Secondary: Significant differences on CGI-I scores were observed with desvenlafaxine 50 (P=0.002) and 100 mg/day (P<0.001) compared to placebo. For MADRS total score, the between-group difference vs placebo in adjusted mean was 3.1 (95% CI, 1.0 to 5.2) with desvenlafaxine 50 mg/day and 4.2 (95% CI, 2.1 to 6.3) with desvenlafaxine 100 mg/day. Adjusted mean changes from baseline were significantly greater with desvenlafaxine compared to placebo starting at week four (P=0.036 and P=0.004, respectively), and were sustained until the final evaluation (P=0.004 and P<0.001, respectively). For CGI-S score at final evaluation, adjusted mean changes from baseline were significantly greater than placebo for desvenlafaxine 50 (P=0.003) and 100 mg/day (P<0.001). Significant separation from placebo was observed beginning at week six and four for desvenlafaxine 50 (P=0.002) and 100 mg/day (P=0.027), and both groups remained significantly different through the final evaluation. Results of the VAS-PI are not reported because of the heterogeneity of the format of the translated scale; it was impossible to properly analyze the corresponding data. For Covi Anxiety Scale total score at final evaluation, adjusted mean changes from baseline were significantly greater than placebo for desvenlafaxine 50 (P=0.001) and 100 mg/day (P=0.004). The adjusted OR for response relative to placebo was 1.943 (95% CI, 1.24 to 3.05) and 1.798 (95% CI, 1.14 to 2.83) with desvenlafaxine 50 and 100

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				mg/day (P=0.004 and P=0.011). For remission rates, the adjusted OR for remission relative to placebo was 1.488 (95% CI, 0.93 to 2.38) and 2.117 (95% CI, 1.32 to 3.39) with desvenlafaxine 50 and 100 mg/day (P=0.099 and P=0.002). Responder rates were significantly higher with desvenlafaxine 50 (65%) and 100 mg/day (63%) compared to placebo (50%; P=0.005 and P=0.018, respectively; NNT, 6.5 and 7.4). Significantly more patients receiving desvenlafaxine 100 mg/day achieved remission compared to patients receiving placebo (45 vs 29%, respectively; P=0.003; NNT, 6.1). Most of the treatment-emergent adverse events were mild or moderate in severity. The most common treatment-emergent adverse events were nausea, dizziness, insomnia, constipation, fatigue, anxiety, and decreased appetite.
Liebowitz et al.[72] (abstract) (2008) Desvenlafaxine 50 or 100 mg/day vs placebo	DB, MC, PC, PG, RCT Patients 18 to 75 years of age with a primary diagnosis of MDD, depressive symptoms ≥30 days prior to screening, HAM-D-17 total score ≥20, and CGI-S score ≥4	N=447 8 weeks (plus a 1 week taper)	Primary: Change from baseline to final on-therapy evaluation on HAM-D-17score Secondary: Change from baseline in CGI-I, CGI-S, MADRS, VAS-PI, HAM-D-17 rate of response (percentage of patients with a HAM-D-17 score decrease of ≥50%), HAM-D-17 rate of remission (percentage of patients with a HAM-D-17score decrease to ≤7%),	Primary: There was a significant decrease in the HAM-D-17 score from baseline in the desvenlafaxine 50 mg group (-11.5; P=0.018) but not for the desvenlafaxine 100 mg group (-11; P=0.065) compared to the placebo group (-9.53). Secondary: The decrease from baseline in the CGI-I score was not considered significant for the desvenlafaxine 50 mg group (P=0.085) and the 100 mg group (P=0.076) compared to the placebo group. The decrease from baseline in CGI-S scores were not significantly different than the desvenlafaxine 50 mg (P=0.074) and 100 mg groups (P=0.208) compared to the placebo group. There was a significant decrease from baseline in MADRS scores in the desvenlafaxine 50 mg group (P=0.022) but not the 100 mg group (P=0.095). VAS-PI overall pain score showed significant improvement compared to baseline in the 100 mg group (P=0.041) but not for the 50 mg group (P=0.223). There was no significant difference between the desvenlafaxine 50 and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			SDS, WHO-5, safety	100 mg groups compared to the placebo group in terms of HAM-D-17 rates of response (P=0.133, P=0.246, respectively) and remission (P=0.075, P=0.194, respectively). The desvenlafaxine 50 mg group showed significant improvements from baseline in SDS score (-8.96; P=0.012) and WHO-5 score (6.68; P=0.020) compared to the placebo group. There were no significant differences from baseline in the 100 mg group compared to the placebo group in SDS or WHO-5 score. The most common adverse events seen (incidence ≥10% and at twice the rate in the placebo group) with desvenlafaxine treatment included: dry mouth, constipation, insomnia, decreased appetite, hyperhidrosis and dizziness (P values not reported).
Liebowitz et al.[73] (2007) Desvenlafaxine 100 mg/day for days 1 to 14, increasing to 200 mg/day vs placebo	DB, MC, PC, PG, RCT Patients 18 to 75 years of age with a primary diagnosis of MDD, depressive symptoms ≥30 days prior to screening, HAM-D-17 total score ≥20, a HAM-D item 1 (depressed mood) score ≥2 and CGI-S score ≥4	N=247 8 weeks	Primary: Change from baseline to final on-therapy evaluation on HAM-D-17 score Secondary: Change from baseline in CGI-I, MADRS, CGI-S, VAS-PI, vital signs, safety	Primary: There was no significant difference in the reduction of HAM-D-17 score from baseline between the desvenlafaxine and placebo group (14.1 vs 15.1 respectively; P=0.277). Secondary: There was no significant difference between CGI-I scores between the desvenlafaxine and the placebo group compared to baseline (2.5 vs 2.7 respectively; P value not reported). The CGI-S showed no difference from baseline between the desvenlafaxine and placebo groups (3.1 vs 3.3 respectively; P value not reported). Improvement was demonstrated at final evaluation between desvenlafaxine and placebo on the MADRS scale (16.8 vs 19.5 respectively; P=0.047), the VAS-PI overall pain scale (15.6 vs 11.6 respectively; P=0.008), the VAS-PI back pain scale (13.1 vs 20.5 respectively; P=0.006) and the VAS-PI arm, leg or joint pain scale (13.3 vs 21.6 respectively; P<0.001). There was a significant increase from baseline in supine SBP (3.76 vs -1.59; P<0.001, respectively) and supine DBP (1.85 vs -0.91; P=0.003

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				respectively) in the desvenlafaxine group compared to the placebo group. There was a significant decrease in body weight seen in the desvenlafaxine group compared to the placebo group (-0.74 vs 0.36 kg; P<0.001). There was an increase in heart rate from baseline observed in the desvenlafaxine group (4.27 beats per minute; P<0.01) and a decrease from baseline in the placebo group (-2.27 beats per minute; P<0.01). A decrease in the QT interval was observed in the desvenlafaxine group from baseline (-4.27 ms; P value not significant) and an increase in QT interval from baseline was observed in the placebo group (4.90; P<0.05). The difference in these values was considered to be statistically significant (P=0.01). Anorexia (P<0.001), constipation (P<0.05), dry mouth (P<0.01), nausea (P<0.001), tremor (P<0.01) and yawning (P<0.01) were seen more commonly in the desvenlafaxine group compared to the placebo group.
Demartinis et al.[74] (2007) Desvenlafaxine 100, 200, or 400 mg/day vs placebo	DB, MC, PC, PG, RCT Patients 18 to 75 years of age with a primary diagnosis of MDD, depressive symptoms ≥30 days prior to screening, HAM-D-17 total score ≥20, a Ham-D item 1 (depressed mood) score ≥2 and CGI-S score ≥4	N=461 8 weeks (plus a 2 week taper)	Primary: Change from baseline to final on-therapy evaluation on HAM-D-17 score Secondary: Change from baseline in CGI-I, CGI-S, MADRS, VAS-PI, HAM-D-17 rate of response (percentage of patients with a HAM-D-17 score decrease ≥50%), HAM-D-17 rate of remission (percentage of patients with a	Primary: Decrease in HAM-D-17 score from baseline was significantly greater at final on-therapy evaluation in the 100 mg (-10.60; P=0.0038) and 400 mg (-10.75; P=0.0023) groups compared to the placebo group (-7.65). However, the decrease in HAM-D-17 score from baseline in the 200 mg group was not significant (-9.63; P=0.0764) compared to the placebo group. Secondary: There were significant decreases in CGI-I score from baseline for the 100 mg (2.3; P=0.008), 200 mg (2.5; P=0.0462) and 400 mg (2.4; P=0.0129) groups compared to the placebo treated group (2.8). There were significant decreases in CGI-S scores from baseline in the 100 mg (-1.5; 95% CI, 0.2 to 0.8; P=0.002) and 400 mg (-1.5; 95% CI, 0.2 to 0.9; P<0.001) groups compared to the placebo group (-1.0). The CGI-S score difference observed in the 200 mg group was not significant (-1.13; 95% CI, 0.0 to 0.6; P=0.056). The decrease from baseline in MADRS score was significant for the 100 mg group (-13.6; 95% CI, 1.3 to 6.4; P=0.004), the 200 mg group (-13.5;

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			HAM-D-17 score decrease to ≤7%), SDS, WHO-5, vital signs, safety	95% CI, 1.3 to 6.2; P=0.005), and the 400 mg group (-15.2; 95% CI, 3.1 to 8.3; P<0.001) compared to the placebo group (-9.9). Patients in the desvenlafaxine 100 mg group showed a significant improvement from baseline in overall pain score compared to the placebo group on the VAS-PI scale (-13.9 vs 5.9; P=0.002, respectively). There was no significant difference in either the 200 mg (-5.4; P=0.357) or the 400 mg (-10.1; P=0.069) groups. There was a significantly higher OR for response to the 100 mg group (2.15; 95% CI, 1.25 to 3.73; P=0.006) and 400 mg group (1.91; 95% CI, 1.11 to 3.32; P=0.020). The OR for response to the 200 mg group was not significant (1.60; 95% CI, 0.93 to 2.76; P=0.089) compared to the placebo group. There was a significantly higher OR for remission in the 400 mg group compared to the placebo group (2.20; 95% CI, 1.17 to 4.14; P=0.014). The OR of the 100 mg group (1.86; 95% CI, 0.99 to 3.52; P=0.053) and 200 mg group (1.73; 95% CI, 0.92 to 3.26; P=0.088) were not significant compared to the placebo group. There was a statistically significant increase in supine pulse rate in the desvenlafaxine 400 mg group compared to baseline (4.19; P<0.001). The increase was considered statistically significant when compared to the placebo group (0.15; P<0.05). The change in supine pulse rate from baseline in the desvenlafaxine 100 mg (-0.03) and 200 mg (1.06) groups were not considered significant compared to the placebo group (P value not significant). The mean increase in supine SBP was considered significant in all groups compared to baseline compared to the placebo group (P<0.05). The increase in DBP was considered significant in all treatment groups compared to baseline (P<0.001 for the 200 and 400 mg groups and P<0.01 for 100 mg group). There was a significant increase in DBP from baseline in both the desvenlafaxine 200 and 400 mg groups compared to the placebo group (P<0.05). The increase in DBP from baseline in the 100 mg group was not considered significant compared to the placebo group (P

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				value not significant). There was a significant decrease in body weight in all desvenlafaxine treatment groups compared to baseline (P<0.001) and to the placebo group (P<0.05). Adverse events that occurred at twice the rate of placebo in at least 5% of desvenlafaxine-treated subjects included: nausea, somnolence, insomnia, dry mouth, sweating, dizziness, nervousness, anorexia, constipation, abnormal ejaculation/orgasm, asthenia and tremor (P values not reported).
Septein-Velez et al.[75] (2007) Desvenlafaxine 200 or 400 mg/day vs placebo	DB, MC, PC, PG, RCT Outpatients 18 to 75 years of age with a primary diagnosis of MDD, depressive symptoms ≥30 days prior to screening, HAM-D-17 total score ≥20, and CGI-S score ≥4	N=369 8 weeks (plus a 2 week taper)	Primary: Change from baseline to final on-therapy evaluation on HAM-D-17 score Secondary: Change from baseline in CGI-I, CGI-S, MADRS, VAS-PI, HAM-D-17 rate of response (percentage of patients with a HAM-D-17 score decrease ≥50%), HAM-D-17 rate of remission (percentage of patients with a HAM-D-17 score decrease to ≤7%), SDS, WHO-5	Primary: The decrease from baseline in HAM-D-17 score was significantly greater in the 200 mg group (-12.6; P=0.002) and the 400 mg group (-12.1; P=0.008) compared to the placebo group (-9.3). Secondary: A lower CGI-I score was observed in the 200 mg group (P=0.004) and the 400 mg group (P=0.028) compared to the placebo group. There was a significant difference in change in MADRS score from baseline favoring desvenlafaxine in the 200 mg (P=0.001) and 400 mg (P=0.005) groups compared to the placebo group. There was a significant difference in change in CGI-S score from baseline favoring patients treated with desvenlafaxine compared to patient treated with placebo (P=0.001 and P=0.013 for the desvenlafaxine 200 and 400 mg groups, respectively). There was a greater response on the HAM-D-17 rate of response assessment for the 200 mg (60%; P<0.001) and 400 mg (56%; P=0.005) groups compared to the placebo group (38%). A greater degree of remission was observed for the 200 mg group (37%; P=0.017) compared to the placebo group (23%). The degree of remission was not significant for the 400 mg group (P value not reported). The change in VAS-PI overall pain score from baseline favored the desvenlafaxine 200 mg group (P=0.002) compared to the placebo group. The difference between the 400 mg group and the placebo group was not considered significant (P=0.053).

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				There was a significant improvement from baseline in SDS total score for the desvenlafaxine 200 mg (P=0.004) and 400 mg (P=0.004) groups compared to the placebo group. There was a significant improvement from baseline in WHO-5 score for the desvenlafaxine 200 mg (P=0.001) and 400 mg (P=0.005) groups compared to the placebo group.
Tourian et al.[76] (2013) Desvenlafaxine 25 mg/day from days 1 to 14, with subsequent upward titration, to a maximum of 100 mg/day, determined by clinical response	MC, OL Japanese patients with MDD who had completed an 8-week, DB, PC study in which patients received 25 or 50 mg/day desvenlafaxine or placebo	N=304 10 weeks	Primary: Safety, HAM-D17 Secondary: Not reported	Primary: Treatment-emergent adverse events were reported by 240 patients (78.9%) during the on-therapy period; the most common adverse events were nasopharyngitis (37.2%), somnolence (11.5%), headache (10.5%), and nausea (10.2%). For the ITT-LOCF population, the mean change from baseline in the HAM-D17 total score was -4.76 (95% CI, -5.47 to -4.05). Continued numerical improvements in the HAM-D17 total scores and other depression outcome measures were observed irrespective of treatment in the previous study. Secondary: Not reported
Soares et al.[77] (2011) Desvenlafaxine 100 to 200 mg/day	MC, OL Post-menopausal women 40 to 70 years of age with MDD who did not achieve clinical response to acute, DB treatment with desvenlafaxine or escitalopram	N=123 6 months	Primary: HAM-D-17 total score Secondary: CGI-I, HAMA, QIDS-SR, VAS-PI, MADRS, CSFQ, EQ-5D, health state today, MRS, SDS, treatment response (HAM-D-17 and MADRS based), safety	Primary: At final evaluation, mean reductions from acute-phase baseline HAM-D-17 total scores were -11.33 and -11.41 with desvenlafaxine/desvenlafaxine and escitalopram/desvenlafaxine. Mean reductions from week eight of acute phase at the final evaluation of the OL extension phase were -6.13 and -6.59, respectively. Consistent improvements in mean HAM-D-17 total scores were observed among patients in both treatment groups from baselines of both the DB acute phase and the OL extension phase. Secondary: Improvements were demonstrated for additional efficacy and health outcome measures for patients in both groups during the OL extension phase. Throughout the course of the overall study, desvenlafaxine/ desvenlafaxine patients achieved mean improvements from baseline in CSFQ total scores after the acute phase and OL extension phase of 1.58±6.84 and 1.84±4.01, respectively; escitalopram/desvenlafaxine patients experienced improvements of 0.71±6.08 and 2.60±6.28 from respective baselines.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				HAM-D-17 response or remission rates after six months were achieved in 56 to 58 and 41 to 48% of desvenlafaxine/desvenlafaxine and escitalopram/desvenlafaxine patients. MADRS response rates were 72 and 64%, respectively. The median time to remission was 68 (95% CI, 41 to 84) and 70 days (95% CI, 44 to 125) with desvenlafaxine/desvenlafaxine and escitalopram/ desvenlafaxine patients. Treatment-emergent adverse events were reported by 91% of patients, the most common being headache (17%), insomnia (17%), nausea (16%), dizziness (15%), infection (15%), abnormal dreams (12%), dry mouth (11%), pain (11%), and sweating (10%).
Ferguson et al.[78] (2010) Desvenlafaxine 100 or 200 mg/day	MC, OL Outpatients ≥65 years of age with MDD	N=52 (safety analysis) ≤6 months	Primary: Safety Secondary: HAM-D-17 total scores	Primary: The most frequently reported adverse events were mild or moderate nausea (40%), dizziness (25%), and headache (21%). Primary and secondary adverse events led to discontinuation of treatment for 18 (35%) patients. The most common event cited as reasons for discontinuation were hypertension (10%) and nausea (10%). Two patients experienced three serious adverse events. Secondary: After three months of treatment, mean total HAM-D-17 score decreased 9.20 points (LOCF) from a baseline score of 21.68±3.20. This improvement was maintained for the duration of the trial; the mean change from baseline at final evaluation at month six was -9.28 points, resulting in a mean HAM-D-17 total score of 12.40±7.19. These improvements were maintained without dose escalation. HAM-D-17 based response rates were 42% (LOCF) at month three. The clinical responses were maintained by 65% of patients at month six. HAM-D-17 based remission rates were 28% at month two, which were maintained by 30% of patients at month six.
Soares et al.[79] (2010) Desvenlafaxine 100 to 200 mg/day	AC, DB, MC, RCT Postmenopausal women 40 to 70 years of age with	N=607 Acute phase: 8 weeks	Primary: HAM-D_{17} total score, response and remission rates, anxiety scores,	Primary: <u>Acute phase</u> There was no significant difference in HAM-D_{17} total score with desvenlafaxine and escitalopram (-13.63 vs -14.30, respectively; P=0.243).

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vs escitalopram 10 to 20 mg/day	MDD	Continuation phase: 6 months	QOL, menopause-related symptoms, safety and tolerability Secondary: Not reported	There were no significant differences in secondary efficacy and health outcomes data related to depression between treatment groups. On assessments of menopause-related symptoms, there were no significant between-group differences, and improvements from baseline were comparable for both groups. Significantly higher rates were found for escitalopram compared to desvenlafaxine for HAM-D_{17} remission (48 vs 38%, respectively; P<0.01) and response (73 vs 64%, respectively; P<0.05). No significant differences between the escitalopram and desvenlafaxine groups were observed in rates of response on the MADRS (70 and 67%, respectively) and CGI-I (75 and 70%, respectively). <u>Continuation phase</u> The proportion of women who maintained or improved their HAM-D_{17} response to treatment was similar between the treatment groups (desvenlafaxine, 82%; escitalopram, 80%; P=0.702). There were no significant differences between treatment groups in the proportion of women who achieved HAM-D_{17} remission during the continuation phase or at endpoint (desvenlafaxine, 68%; escitalopram, 61%; P=0.234). There were no significant differences between the desvenlafaxine and escitalopram groups in rates of response on the MADRS (92 and 88%, respectively) and CGI-I (90 and 86%, respectively). No significant differences between groups were found at endpoint in the analyses of secondary efficacy data or core health outcome measures, including assessments of menopause-related symptoms. In both phases, desvenlafaxine and escitalopram were generally safe and well tolerated. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Acharya et al.[80] (2006) Duloxetine 40 to 120 mg daily vs placebo	MA (12 trials) Patients taking duloxetine for MDD	N=2,996 Duration varied	Primary: Incidence of suicide-related events with duloxetine (MHID, MHRD, HAM-D Item-3) Secondary: Not reported	Primary: There were no significant differences in the incidence of suicide-related events with duloxetine vs placebo. The MHID for suicide-related behaviors was -0.03% (95% CI, -0.48 to 0.42) and MHRD -0.002 (95% CI, -0.02 to 0.02). Changes in HAM-D Item-3 suicidality scores showed a greater improvement with duloxetine (P<0.001) and less worsening of suicidal ideation with duloxetine (P<0.001). Secondary: Not reported
Gaynor et al.[81] (2011) Duloxetine 60 mg QD vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with a current episode of MDD and at least moderate pain	N=528 8 weeks	Primary: Mean change in MADRS total score and BPI average pain rating Secondary: Remission, PGI-I, SDS global functional impairment score, safety	Primary: Treatment with duloxetine resulted in a significantly greater improvement in MADRS total score compared to treatment with placebo (-16.77 vs -12.73, respectively; 57.9 vs 44.3% improvement from baseline, respectively; P<0.001). Duloxetine was more effective than placebo beginning at week two and at all remaining visits (P≤0.001). There was a significantly greater reduction in average pain rating from baseline to week eight with duloxetine compared to placebo (-1.93 vs -1.31, respectively; 35.1 vs 22.9% reduction in pain, respectively; P≤0.001). Patients also had a greater improvement in their average pain rating at weeks one, two, four, and eight with duloxetine compared to placebo (all P≤0.005). Secondary: A significantly greater proportion of patients receiving duloxetine met the criteria for remission than patients receiving placebo (P≤0.01). Overall scores for 'worst pain' and 'least pain' in the last 24 hours and for 'pain right now' were also reduced with duloxetine vs placebo (all P≤0.001).

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				The least squares mean PGI-I score demonstrated significantly greater improvements with duloxetine compared to placebo (P≤0.021). Scores of 1 ('very much better') or 2 ('much better') were reported by a significantly greater percentage of patients in the duloxetine group (50.8%) compared to the placebo group (35.2%; P≤0.001). Patients receiving duloxetine demonstrated significantly greater improvements in the SDS global functional impairment score compared to patients receiving placebo (48.2 vs 37.7%, respectively; P=0.019). Improvements in the individual items addressing social life/leisure activities and family life/home responsibilities were greater with duloxetine compared to placebo (P≤0.05). The improvement in the item addressing school/work life was not significantly different between duloxetine and placebo (P=0.112). Treatment emergent adverse events with duloxetine were nausea, somnolence, constipation, decreased appetite, and hyperhidrosis. Rates of discontinuation due to adverse events were greater for duloxetine than placebo (8.0 vs 3.4%, respectively; P=0.024).
Gaynor et al.[82] (2011) Duloxetine 60 mg QD vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with a current episode of MDD and at least moderate pain	N=527 8 weeks	Primary: Mean change in MADRS total score and BPI average pain rating Secondary: Remission, PGI-I, SDS global functional impairment score	Primary: Treatment with duloxetine resulted in a significantly greater improvement in MADRS total score compared to treatment with placebo (-14.96 vs -10.77, respectively; 48.3 vs 34.8% improvement from baseline, respectively; P<0.001). There was a significantly greater reduction in average pain rating from baseline to week eight with duloxetine compared to placebo (-1.66 vs -1.17, respectively; 27.7 vs 18.9% reduction in pain, respectively; P<0.001). Patients also had greater improvement in their average pain rating at weeks two, four, and eight with duloxetine compared to placebo (all P<0.01). Secondary: A significantly higher percentage of patients receiving duloxetine (37.3%) met the criteria for remission compared to patients receiving placebo (23.0%; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Greater improvements were observed for the other pain severity ratings (worst pain; P<0.001, least pain; P=0.003, pain right now; P<0.001), as well as ratings of interference of pain with functioning (all P<0.05) with duloxetine vs placebo. The least squares mean PGI-I score demonstrated significantly greater improvements with duloxetine compared to placebo (P≤0.01). Scores of 1 ('very much better') or 2 ('much better') were reported by a significantly greater percentage of patients in the duloxetine group compared to the placebo group (53.3 vs 26.8%, respectively; P<0.001). Patients receiving duloxetine demonstrated significantly greater improvements in the SDS global functional impairment score compared to placebo (46.4 vs 31.8%, respectively; P<0.001).
Rosso et al.[83] (2012) Duloxetine 120 mg/day vs bupropion ER 300 mg/day	RCT, SB Patients ≥18 years of age with MDD who failed to respond to 2 consecutive antidepressant trials with SSRIs	N=49 6 weeks	Primary: Change in HAM-D-17 Secondary: CGI-S, GAF	Primary: There was no significant difference in HAM-D-17 total score among the treatment groups (P=0.793). Secondary: There was no significant difference in CGI-S (P=0.653) or GAF (P=0.565) scores among the treatment groups. Compared to baseline, there was a significant improvement in HAM-D-17 and CGI-S total scores with duloxetine and bupropion ER compared to baseline (all P<0.001). The 6-item-HAM-D mean score decreased significantly by week two with duloxetine (from 11.84 to 6.04; P<0.001) and bupropion ER (from 12.05 to 5.52; P<0.001). There was no difference in the success rates (HAM-D response, HAM-D remission) between the treatment groups. Additional information obtained by the CGI-S success rate confirmed this finding.
Nierenberg et al.[84] (2007) Duloxetine 60 mg	AC, DB, PC, RCT Patients ≥18 years of age with MDD	N=547 8 weeks	Primary: Percentage of patients achieving onset criteria at	Primary: No significant difference was observed in the probability of patients meeting onset criteria at week two between the duloxetine group and the escitalopram group (P=0.097).

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daily vs escitalopram 10 mg daily vs placebo			week two (defined as 20% decrease from baseline in HAM-D) Secondary: Not reported	Duloxetine and escitalopram both showed significant improvement compared to placebo on primary efficacy analysis at week one and week eight ($P \leq 0.05$). Secondary: Not reported
Pigott et al.[85] (2007) <u>Acute Phase</u> Duloxetine 60 mg/day vs escitalopram 10 mg/day vs placebo <u>Extension Phase</u> Duloxetine 60 to 120 mg/day vs escitalopram 10 to 20 mg/day	DB, MC, PC, RCT Patients >18 years of age with MDD	N=684 <u>Acute Phase</u> 8 weeks <u>Extension Phase</u> 24 weeks	Primary: $HAM\text{-}D_{17}$, CGI-S, PGI-I, HAMA, remission rates Secondary: Not reported	Primary: After eight months of treatment, there were no significant differences in efficacy between duloxetine and escitalopram as assessed by mean changes from baseline in the $HAM\text{-}D_{17}$ total score and the $HAM\text{-}D_{17}$ Maier, anxiety/somatization, and retardation/ somatization subscales. The only $HAM\text{-}D_{17}$ subscale with a significant drug difference was the $HAM\text{-}D_{17}$ sleep subscale, which demonstrated that escitalopram was associated with a significantly greater improvement in insomnia than duloxetine at the eight-month study endpoint. There were no significant differences in efficacy among the treatment groups as assessed by the CGI-S and the PGI-I. After eight months of treatment, there were no significant differences between the treatment groups with regards to anxiety symptoms as measured by the HAMA total score and the HAMA subscales (psychic and somatic). There was no significant difference in remission at eight weeks (duloxetine 40%, escitalopram 33%; P=0.25) or at eight months (duloxetine 70%, escitalopram 75%; P=0.44). Secondary: Not reported
Detke et al.[86] (2004)	DB, PC, RCT	N=367 (acute phase)	Primary: HAM-D-17 total	Primary: In the acute phase, patients treated with duloxetine had significantly

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Duloxetine 40 or 60 mg BID vs paroxetine 20 mg/day vs placebo After acute treatment, patients who had a ≥30% reduction in baseline HAM-D-17 total score were allowed to continue on the same (blinded) treatment for a 6 month continuation phase.	Outpatients ≥18 years of age with MDD	N=273 (continuation phase) 8 weeks of acute treatment plus a 6 month continuation phase	scores Secondary: HAM-D-17 subscales, MADRS, HAMA, VAS for pain, CGI-S, PGI-I, SSI, SDS, safety	greater improvement in HAM-D-17 total scores at week eight (P=0.001 and P<0.001) compared to patients treated with placebo. Paroxetine also demonstrated significant superiority over placebo at week eight (P<0.001). In the acute phase, estimated probabilities of response at week eight for patients receiving duloxetine 80 (70%) and 120 mg/day (77%) were significantly more efficacious to that of placebo (47%; P=0.005 and P<0.001). The estimated probability of response for paroxetine-treated patients was also significantly greater compared to placebo-treated patients (P<0.001). In the acute phase, estimated probabilities of remission for patients receiving duloxetine 80 and 120 mg/day, and paroxetine 20 mg/day were significantly more efficacious to patients receiving placebo at week eight. In the continuation phase, patients within each active treatment group demonstrated significant within-group improvement in HAM-D-17 total score. In the continuation phase, a log-rank test demonstrated that duloxetine 80 mg/day, duloxetine 120 mg/day, and paroxetine each had a significantly longer time to loss of response compared to placebo (P=0.002, P=0.018, and P=0.002, respectively). Secondary: In the acute phase, duloxetine 80 mg/day, duloxetine 120 mg/day, and paroxetine showed significantly greater improvement on the HAM-D-17 anxiety/somatization, core factor, maier, and retardation subscales compared to placebo. Paroxetine-treated patients showed a significant improvement on the sleep subscale compared to patients receiving placebo. In the acute phase, patients receiving duloxetine 80 mg/day, duloxetine 120 mg/day, or paroxetine 20 mg/day has significantly greater improvements in MADRS (P≤0.001 vs placebo for all, P≤0.05 for duloxetine 120 vs 80 mg/day), HAMA (P≤0.01 for duloxetine 80 mg/day vs placebo, P≤0.001 for duloxetine 120 mg/day and paroxetine vs

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				placebo), CGI-S (P≤0.001 for all comparisons), and PGI-I (P≤0.01 for duloxetine 80 mg/day vs placebo, P≤0.001 for duloxetine 120 mg/day and paroxetine vs placebo, P≤0.05 for duloxetine 80 mg/day vs paroxetine) scales compared to patients receiving placebo. In the acute phase, patients receiving duloxetine or paroxetine showed significantly greater improvement on both SSI 26- and 28-Item Averages compared to placebo-treated patients. Using mean change analysis, in the acute phase patients treated with duloxetine and paroxetine showed significantly greater improvement on the SDS work item, social life item, family life item, and total score compared to patients receiving placebo. In the continuation phase, patients within each active treatment group demonstrated significant within-group improvement in MADRS, HAMA, CGI-S, and PGI-I. Patients receiving placebo exhibited significant within-group improvement in HAMA and PGI-I. In the continuation phase, patients receiving duloxetine 120 mg/day showed marginally significant improvement from baseline on the SSI 28-Item Average (P=0.054), while improvement was significant for the Pain Item Average (P=0.034). There were no deaths during the acute treatment phase. One serious adverse event occurred in a patient receiving paroxetine, but was considered to be non-treatment related. The proportion of patients who discontinued the study due to adverse events did not differ significantly across treatment groups (4.2, 3.2, 3.5, and 3.2%; P=1.00). The only adverse event leading to discontinuation in more than one patient within any treatment group was headache (two patients receiving duloxetine 120 mg/day). Treatment-emergent adverse events experienced by ≥5% of patients receiving duloxetine 120 mg/day are constipation, dry mouth, increased sweating, somnolence, nausea, headache, and insomnia. Three patients died during the six-month continuation phase (one patient receiving duloxetine 120 mg/day and placebo died as a result of suicide,

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				while one patient receiving duloxetine 80 mg/day died as a result of pulmonary edema). All three deaths were considered to be non-treatment related. Serious adverse events were reported by one placebo-treated patient, one duloxetine 80 mg/day-treated patient, and four duloxetine 120 mg/day-treated patients. The proportions of patients discontinuing treatment due to an adverse event were similar across groups.
Goldstein et al.[87] (2004) Duloxetine 20 to 40 mg BID vs paroxetine 20 mg daily vs placebo	DB, PC, RCT Outpatients with depression	N=353 8 weeks	Primary: HAM-D Secondary: Adverse effects	Primary: Duloxetine 80 mg/day was more effective than placebo on mean HAM-D-17 total change by 3.62 points (95% CI, 1.38 to 5.86; P=0.002). Duloxetine 40 mg/day was also significantly more efficacious than placebo by 2.43 points (95% CI, 0.19 to 4.66; P=0.034), while paroxetine was not (1.51 points; 95% CI, -0.55 to 3.56; P=0.150). Duloxetine 80 mg/day was more efficacious than placebo for most other measures, including overall pain severity, and was more efficacious than paroxetine on the HAM-D-17 improvement (by 2.39 points; 95% CI, 0.14 to 4.65; P=0.037) and estimated probability of remission (57% for duloxetine 80 mg/day, 34% for paroxetine; P=0.022). Secondary: The only adverse event reported significantly more frequently for duloxetine 80 mg/day than for paroxetine was insomnia (19.8% for duloxetine 80 mg/day, 8.0% for paroxetine; P=0.031).
Perahia et al.[88] (2006) Duloxetine 40 mg BID vs duloxetine 60 mg BID vs	DB, MC, PC, RCT Patients ≥18 years of age with MDD	N=392 8 months	Primary: Mean change from baseline in HAM-D-17 Secondary: Discontinuation of study drug due to adverse drug events	Primary: Patients treated with duloxetine 80 and 120 mg/day had significantly greater improvement in HAM-D-17 total scores at week eight compared to placebo-treated patients (P=0.045 and P=0.014, respectively). Paroxetine was not significantly different from placebo (P=0.089) on mean change on the HAM-D-17. Secondary: The proportion of patients who discontinued the study due to adverse events did not differ significantly (P=0.836) across treatment groups; placebo (2.0%), duloxetine 80 mg/day (4.3%), duloxetine 120 mg/day (3.9%), and paroxetine 20 mg (4.1%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
paroxetine 20 mg daily vs placebo				
Goldstein et al.[89] (abstract) (2002) Duloxetine, titrated from 20 to 60 mg BID vs placebo vs fluoxetine 20 mg/day	DB, MC, PC, RCT Patients 18 to 75 years of age with MDD	N=173 8 weeks	Primary: HAM-D-17 total score Secondary: MADRS, CGI-S, CGI-I, PGI-I, safety	Primary: Duloxetine was more efficacious to placebo in change in HAM-D-17 total score (P=0.009). Estimated probabilities of response and remission were 64 and 56%, respectively, with duloxetine compared to 52 and 30% with fluoxetine, and 48 and 32% with placebo. Duloxetine was numerically more efficacious to fluoxetine on the primary outcome. Secondary: Duloxetine was numerically more efficacious to fluoxetine on most secondary outcomes. Duloxetine was well tolerated; 76% of patients achieved the maximum dose, and insomnia and asthenia were the only adverse events reported significantly more frequently compared to placebo (P<0.05).
Martinez et al.[90] (2012) Duloxetine 30 to 120 mg QD vs generic SSRIs (citalopram 20 to 40 mg/day, fluoxetine 20 to 80 mg/day, paroxetine 20 to 50 mg/day, or sertraline 50 to	AC, MC, RCT Adult outpatients with severe MDD	N=750 12 weeks	Primary: Remission at week 12 as measured by QIDS-SR Secondary: Response as measured by QIDS-SR, probability of response and remission as measured by HAM-D_{17}, BPI, SDS	Primary: Remission rates derived from the QIDS-SR at week 12 did not significantly differ between the duloxetine and SSRI treatment groups (36 vs 32%, respectively). The groups did not differ significantly with respect to changes in QIDS-SR scores across 12 weeks of therapy. Secondary: The QIDS-SR estimated probability of response did not differ significantly between duloxetine-treated and SSRI-treated patients (71 vs 64%; P=0.085). On the HAM-D_{17}, patients treated with duloxetine had significantly greater probabilities of response compared to patients treated with SSRIs (73 vs 61%; P=0.001) and remission (53 vs 44%; P=0.034). The NNT for one additional case of remission was 25 for the QIDS-SR, and was 12 for the HAM-D_{17}. The NNT for one additional case of response was 15 for the QIDS-SR, and was 9 for the HAM-D_{17}.

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200 mg/day at the investigator's discretion)				Patients treated with duloxetine demonstrated significantly greater mean changes on the HAM-D_{17} total score and HAM-D subscales (anxiety/ somatization, Bech, Maier, and retardation). Improvement in associated painful symptoms was significantly greater with duloxetine compared to SSRIs as measured by the mean change in the BPI 24-hour average pain score in both the pain-enriched cohort of patients (P=0.034) and in the entire study population (P=0.030). Patients receiving duloxetine demonstrated significantly greater improvements on the SDS global functional score (P=0.002), and on each of the individual items that measure work/school (P=0.013), family functioning (P=0.015), and social functioning (P=0.005) compared to SSRIs. Dry mouth and constipation occurred at a significantly greater rate in patients treated with duloxetine vs patients treated with SSRIs (P=0.023 and 0.003, respectively). There was no significant difference between duloxetine and the SSRI group in the occurrence of any of the other most commonly reported treatment emergent adverse events.
Mancini et al.[91] (2012) Duloxetine vs placebo	MA (6DB, PC, PG, RCT) Patients with MDD	N=2,496 Short-term (7 to 13 weeks) and the long-term (>24 weeks) endpoint	Primary: SDS total score Secondary: Functional remission (SDS total< 6) rates, VAS	Primary: The between-treatment difference of -2.52 between duloxetine and placebo in the SDS total score at the short-term endpoint was statistically significant in favor of duloxetine vs placebo (95% CI, -3.17, -1.87; P<0.001). Secondary: The endpoint functional remission rates were 39.5% with duloxetine and 28.7% with placebo. Time since first depression episode, antidepressant pretreatment (yes/no), baseline VAS pain (<30/>30 mm), and sex were significant prognostic factors. The effect of duloxetine was maintained at the long-term endpoint.
Van Baardewijk et al.[92] (2005)	MA Adults with moderate to severe	N=not specified 6 months	Primary: Remission (an improvement in the HAM-D scale to a	Primary: Patients receiving duloxetine and venlafaxine ER experienced similar success rates after six months of treatment, 53 and 57%, respectively (P value not reported).

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Duloxetine 40 to 120 mg daily for at least 8 weeks vs venlafaxine ER 75 to 225 mg daily for at least 8 weeks	MDD and a score ≥15 on the HAM-D or ≥18 on the MADRS scale		score <7, or a score ≤10 on the MADRS scale), symptom-free days Secondary: Not reported	Patients receiving duloxetine and venlafaxine ER experienced similar number of symptom-free days after six months of treatment, 52.72 and 57.03%, respectively (P value not reported). Duloxetine therapy was associated with a greater hospitalization rate compared to venlafaxine ER therapy, 47 and 43%, respectively (P value not reported). Secondary: Not reported
Vis et al.[93] (2005) Duloxetine 40 to 120 mg/day vs venlafaxine ER 75 to 225 mg/day vs placebo	MA (8 trials) Outpatients >18 years of age with MDD	N=1,754 (efficacy) N=1,791 (safety) 8 weeks	Primary: Remission and response (HAM-D, MADRS) Secondary: Dropout rates and rates of adverse events	Primary: Both treatment groups demonstrated a significant difference compared to placebo for both remission and response (P<0.001 for all). Secondary: More patients receiving placebo dropped out due to lack of efficacy compared to patients in the treatment arms (P<0.001 for both drugs). Dropout rates due to adverse reactions were also significant when active drugs were compared to placebo (P value not reported). More patients in the treatment groups than in the placebo groups dropped out due to adverse reactions (venlafaxine ER; P<0.001 and duloxetine; P=0.008).
Perahia et al.[94] (2008) Duloxetine 60 to 120 mg/day vs venlafaxine ER 75 to 225 mg/day	DB, MC, RCT (pooled analysis of 2 trials) Patients >18 years of age with MDD	N=667 12 weeks	Primary: GBR (remission at endpoint using HAM-D-17 ≤7) Secondary: Efficacy	Primary: There were no significant differences in GBR with duloxetine and venlafaxine ER at the end of six weeks of therapy (-1.418 vs -1.079; P=0.217) or 12 weeks (-0.349 vs -0.121; P=0.440). Secondary: Mean changes from baseline to endpoint in the HAM-D-17 total scores were not different between the duloxetine and venlafaxine ER treatment groups. Comparisons of mean change from baseline to endpoint on secondary efficacy measures (HAM-D-17 item 1, HAM-D-17 subscales [core, Maier,

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				anxiety/somatization, retardation and sleep], HAMA total score, CGI-S, and PGI-I) were not significantly different between the treatment groups. Response and remission rates were not significantly different between duloxetine and venlafaxine ER at six weeks (response rate for duloxetine, 51.6%; venlafaxine, 54.5%; remission rate for duloxetine, 31.4%; venlafaxine, 35.2%) or 12 weeks (response rate for duloxetine, 62.6%; venlafaxine, 69.1%; remission rate for duloxetine, 48.1%; venlafaxine, 50.3%). Estimates of remission rates at two, four, eight and 12 weeks were 11.1, 36.6, 53.0, and 71.0% for the duloxetine-treated group and 10.4, 32.1, 51.7, and 67.4% for the venlafaxine-treated group, respectively (P=0.309).
Rush et al.[95] CO-MED (2011) Escitalopram 10 to 20 mg/day and placebo vs bupropion SR 300 to 400 mg/day and escitalopram 10 to 20 mg/day vs venlafaxine XR 150 to 300 mg/day and mirtazapine 15 to 45 mg/day	MC, PC, RCT, SB Patients 18 to 75 years of age with MDD	N=665 7 months	Primary: Symptom remission (QIDS-SR), attrition, anxiety (IDS-C), functioning, QOL, adverse events Secondary: Not reported	Primary: At 12 weeks, the remission rates were 38.8% for escitalopram plus placebo, 38.9% for bupropion SR plus escitalopram, and 37.7% for venlafaxine ER plus mirtazapine. The response rates were 51.6 to 52.4%. The treatment groups did not differ in the percentage of change in QIDS-SR score or in effects on QOL. At seven months, the treatment groups were not different in terms of remission rate (range, 41.8 to 46.6%), response rate (range, 57.4 to 59.4%), or attrition rate. There was no difference in the percentage of change in QIDS-SR, QOL, or work and social adjustment. The venlafaxine ER plus mirtazapine group had greater side effect frequency and intensity at 12 weeks and greater side effect frequency, intensity, and burden at seven months as compared to escitalopram plus placebo. Secondary: Not reported
Kerber et al.[96] CO-MED (2012)	Subgroup analysis of CO-MED	N=665 (6% [n=40] reported	Primary: Symptom remission (QIDS-	Primary: In general, patients with heart disease had fewer problems with treatment side effects at week 12 compared to patients without heart disease.

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Escitalopram 10 to 20 mg/day plus placebo vs bupropion SR 300 to 400 mg/day plus escitalopram 10 to 20 mg/day vs venlafaxine ER 150 to 300 mg/day plus mirtazapine 15 to 45 mg/day	Patients 18 to 75 years of age with MDD, with and without heart disease	having and being treated for heart disease) 7 months	SR), attrition, anxiety (IDS-C), functioning, QOL, adverse events Secondary: Not reported	At week 12, there were no significant differences between those with and without heart disease in terms of remission, response, QOL, or functional measures. This pattern was also seen with regard to measures at trial end (week 28). There were no significant differential treatment effects among those with and without heart disease in side effect burden and symptom severity at weeks 12 and 28. Secondary: Not reported
Morris et al.[97] CO-MED (2012) Escitalopram 10 to 20 mg/day plus placebo vs bupropion SR 300 to 400 mg/day plus escitalopram 10 to 20 mg/day vs venlafaxine ER 150 to 300 mg/day	Subgroup analysis of CO-MED Patients 18 to 75 years of age with MDD, with and without general medical conditions	N=665 (49.5% reported having no treated general medical conditions, 23.8% reported having 1, 14.8% reported having 2, and 11.9% reported having ≥3) 7 months	Primary: Symptom remission (QIDS-SR), attrition, anxiety (IDS-C), functioning, QOL, adverse events Secondary: Not reported	Primary: No differences in outcomes between antidepressant monotherapy and either of the antidepressant combination therapies, regardless of the number of general medical conditions a patient had. Specifically, within each group having a given number of conditions, the three treatments did not differ significantly with respect to any of the measures of efficacy or tolerability assessed, either at week 12 or 28. Secondary: Not reported

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plus mirtazapine 15 to 45 mg/day				
Moore et al.[98] (2005) Escitalopram 20 mg daily vs citalopram 40 mg daily	DB, MC, RCT Outpatients with MDD having an MADRS score of ≥30 at baseline	N=280 8 weeks	Primary: Change from baseline in the MADRS total score, adverse events, response to treatment, remission rate Secondary; Not reported	Primary: Escitalopram group exhibited a greater improvement in the MADRS score compared to the citalopram arm (–22.4 vs –20.3; P<0.05). There were more treatment responders with escitalopram than with citalopram (76.1 vs 61.3%; P<0.01). Remission rate was higher among patients on escitalopram compared to the citalopram group (56.1 vs 43.6%; P<0.05). Tolerability was similar in both treatment groups. Secondary; Not reported
Colonna et al.[99] (2005) Escitalopram 10 mg daily vs citalopram 20 mg daily	DB, RCT Patients with moderate-to-severe MDD	N=357 24 weeks	Primary: Change from base-line in MADRS Secondary: Change from baseline in CGI-S	Primary: No significant difference was observed between groups in the MADRS at week 24. Secondary: Escitalopram patients had significantly better scores on the CGI-S at week 24 compared to citalopram patients.
Burke et al.[100] (2002) Escitalopram 10 mg daily vs escitalopram 20 mg daily	DB, MC, RCT Outpatients 18 to 65 years of age with MDD	N=491 8 weeks	Primary: Change from baseline in the MADRS total score at week eight Secondary: Change from baseline in the MADRS total score at weeks one,	Primary: Mean changes from baseline for the MADRS score were significantly greater compared to placebo in the two escitalopram groups (P<0.01) and in the citalopram group (P<0.05). There were no significant differences in the mean change of MADRS score from baseline to endpoint between the escitalopram 20 mg daily and citalopram 40 mg daily groups (P=0.09). Secondary: Patients randomized to the two escitalopram groups and the citalopram

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vs citalopram 40 mg daily vs placebo			two, four, and six, change from baseline in the HAM-D, CGI-S, CGI-I, HAMA, QOL, and CES-D	arm exhibited significantly greater improvement in the HAM-D score from baseline compared to placebo (P<0.01 and P<0.05, respectively). Response to treatment was observed in 50% of escitalopram 10 mg, 51.2% of escitalopram 20 mg, and 45.6% of citalopram 40 mg groups; the difference in response rate was significantly greater than that of placebo group (P<0.01) but not statistically different among the three active groups. There were no significant differences in the mean change of CGI-I, HAM-D, and CGI-S scores from baseline to endpoint between the escitalopram 20 mg daily and citalopram 40 mg daily groups (P=0.09). All three treatment groups exhibited significantly improved HAM-D depressed mood scores from baseline to endpoint (P<0.01). Patients randomized to the escitalopram 10 and 20 mg group exhibited significantly greater improvement in the HAMA score from baseline compared to placebo (P=0.04 and P<0.01, respectively). Mean changes from baseline for the QOL score were significantly greater compared to placebo in the escitalopram 10 mg group (P=0.04) and in the escitalopram 20 mg group (P<0.01). Mean changes from baseline for the CES-D score were significantly greater compared to placebo in the escitalopram 10 mg group (P=0.02) and in the escitalopram 20 mg group (P<0.01). There was no statistically significant difference in the discontinuation rates due to adverse events between the escitalopram 10 mg and placebo groups; however, escitalopram 20 mg and citalopram 40 mg groups had significantly greater discontinuation rates compared to placebo (P<0.05). The rate of adverse effects was not significantly different between the escitalopram 10 mg group and placebo (79 vs 70.5%; P=0.14). Escitalopram 20 mg and citalopram 40 mg groups were associated with

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				significantly greater adverse event rates compared to placebo (85.6 vs 86.4%; P<0.01).
Yevtushenko et al.[101] (2007) Escitalopram 10 mg/day vs citalopram 10 mg/day vs citalopram 20 mg/day	AC, DB, MC, RCT Patients 25 to 45 years of age with MDD	N=330 6 weeks	Primary: MADRS total score Secondary: MADRS total score in severely depressed patients, MADRS core depression subscale score, CGI-S and CGI-I scores, proportions of patients classified as responders and remitters	Primary: The mean changes in MADRS total score were significantly greater in patients receiving escitalopram than citalopram 10 or 20 mg (-28.70 vs -20.11 and -25.19; both, P 0.001). The difference between the two citalopram groups was also significant (P<0.001). Secondary: In the severely depressed subpopulation, the differences in the mean change in MADRS score between the escitalopram group and the citalopram 10 and 20 mg groups were -9.46 and-3.99, respectively (both, P<0.001). The difference between the citalopram 20 and 10 mg groups was -5.47 (P<0.001). The differences in mean change in MADRS core depression subscale scores between the escitalopram group and citalopram 10 and 20 mg groups were -6.00 and -2.48, respectively (both, P<0.001). The difference between the citalopram 20 and 10 mg groups was -3.52 (P<0.001) The mean changes in CGI-S score were -2.60, -1.61, and -2.05 in the escitalopram, citalopram 10 mg, and citalopram 20 mg groups, respectively (all, P<0.001 vs baseline). The differences in mean changes from baseline between the escitalopram and citalopram 10 and 20 mg groups were -0.99 and -0.55, respectively (both, P<0.001). The difference between the citalopram 20 and 10 mg groups was significant at end point (-0.44; P<0.001). Response rates were 95.4 vs 44.3 and 83.3% in the escitalopram vs citalopram 10 and 20 mg groups, respectively (both, P<0.001). Remission rates were 89.8 vs 25.5 and 50.9% in the escitalopram vs citalopram 10 and 20 mg groups, respectively (both, P<0.001).
Lam et al.[102] (2006) Escitalopram 10 to	MA Outpatients with MDD	N=1,321 (3 trials) 8 weeks	Primary: MADRS, response rate	Primary: No significant difference in response rate between the two treatment groups was seen at week eight.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
20 mg daily vs citalopram 20 to 40 mg daily			Secondary: CGI-I, CGI-S, HAM-D	The analysis of pooled data demonstrated that the difference between citalopram and placebo was approximately constant; however, the difference between escitalopram and placebo (P=0.0010) and escitalopram and citalopram (P=0.0012) became greater the more severely depressed the patient was at baseline. Secondary: Similar results were seen in the secondary outcomes.
Gorman et al.[103] (2002) Escitalopram 10 to 20 mg daily vs citalopram 20 to 40 mg daily	MA Outpatients with MDD	N=1,321 (3 trials) 8 weeks	Primary: MADRS, CGI-I Secondary; Not reported	Primary: Mean change in MADRS score from baseline at week eight was significantly improved in both treatment groups compared to baseline (P<0.05). Mean change in MADRS score from baseline at week eight was significantly improved in the escitalopram group compared to the citalopram group (P<0.05). Mean change in CGI-I score from baseline at week eight was significantly improved in both treatment groups compared to baseline (P<0.05). No significant difference in CGI-I scores between the two treatment groups was reported at week eight (P>0.05).
Llorca et al.[104] (2005) Escitalopram 10 to 20 mg daily vs citalopram 20 to 40 mg daily vs placebo	MA Patient 18 to 80 years of age with depression	N=506 (3 trials) 8 weeks	Primary: MADRS Secondary: HAM-D, CGI-I, CGI-S	Primary: Mean change from baseline in MADRS total scores was significantly higher in the escitalopram-treated group compared to the citalopram-treated group (P=0.003). Response rates to escitalopram were 56% compared to 41% with citalopram (P=0.007). Secondary: The mean change in HAM-D from baseline between escitalopram and citalopram was in favor of escitalopram at endpoint (P=0.007). On both the CGI-I and CGI-S scales, patients showed a significant improvement at treatment endpoint in favor of escitalopram when compared to citalopram treatment (P=0.01 and P=0.001 for CGI-I and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				CGI-S, respectively).
Ou et al.[105] (2011) Escitalopram 10 to 20 mg/day vs citalopram 20 to 40 mg/day	DB, MC, RCT Patients 18 to 65 years of age with MDD	N=240 6 weeks	Primary: Change in HAM-D_{17} total score Secondary: Response and remission rates	Primary: At all time points, there was no significant difference in HAM-D_{17} total score, score change, or rate change among the treatment groups (all P>0.05). At the end of the study, the mean rate change was 62.5% in the escitalopram group and 60.7% in the citalopram group (P=0.653). Secondary: Overall, response rates were 72.17% with escitalopram compared to 74.36% with citalopram (P=0.707). Remission rates were 60.87% with escitalopram compared to 56.41% with citalopram (P=0.982). For severe MDD patients, response rates were 72.50 vs 71.79% with escitalopram and citalopram, respectively (P=0.991). Remission rates were 57.50 and 46.15% with escitalopram and citalopram, respectively (P=0.350). There was no significant difference in adverse events with escitalopram and citalopram (28.7 vs 29.9%, respectively; P=0.8384). Nausea and other gastrointestinal reactions (including stomach discomfort, burning sensation) were the most frequently reported adverse events. No serious adverse events were observed.
Wade et al.[106] (2007) Escitalopram 20 mg/day vs duloxetine 60 mg/day	DB, RCT Patients 18 to 65 years of age with MDD	N=294 24 weeks	Primary: Mean change in MADRS total score from baseline to week 24 Secondary: MADRS total score, HAM-D_{17}, CGI-I, CGI-S, HAMA scores	Primary: The mean change from baseline in MADRS total scores was –23.4 for escitalopram-treated patients and –21.7 for duloxetine treated patients (P=0.055). Secondary: At week eight, the mean change from baseline in MADRS total scores was –19.5 for escitalopram-treated patients and –17.4 for duloxetine-treated patients (P<0.05). There was no significant difference in the mean change from baseline in HAM-D_{17} (7.13 vs 8.47; P=0.096), HAMA (7.73 vs 8.62; P=0.267), CGI-I (1.76 vs 1.99; P=0.077), CGI-S (2.11 vs 2.28; P=0.214) at 24 weeks between escitalopram-treated patients and duloxetine-treated patients.
Khan et al.[107]	DB, MC, PG, RCT	N=278	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2007) Escitalopram 10 to 20 mg daily vs duloxetine 60 mg daily	Patients with MDD	8 weeks	Change from base-line to week eight in MADRS scores using the LOCF Secondary: Not reported	At week eight, a significantly greater decrease in MADRS scores (LOCF) was observed in the escitalopram group compared to the duloxetine group (P<0.05). No significant differences in MADRS scores were observed between groups in the observed case analysis (P=0.79). Secondary: Not reported
Boulenger et al.[108] (2006) Escitalopram 20 mg daily vs paroxetine 40 mg daily	DB, MC, RCT Patients with MDD	N=459 24 weeks	Primary: Change in MADRS score, withdrawal Secondary: HAMA, CGI-S, remitters	Primary: The difference in MADRS scores at 24 weeks compared to baseline was -25.2 for the escitalopram treated patients compared to -23.1 for the paroxetine-treated patients (P=0.0105). Significantly more patients withdrew from the study in the paroxetine group (32%) compared to the escitalopram group (19%; P<0.05). Secondary: The difference in HAMA scores at 24 weeks compared to baseline was –15.1 for the escitalopram-treated patients compared to –13.2 for the paroxetine-treated patients (P=0.01). The difference in CGI-S scores at 24 weeks compared to baseline was –2.8 for the escitalopram-treated patients compared to –2.6 for the paroxetine-treated patients (P=0.05). After 24 weeks of treatment the proportion of remitters was 75% in the escitalopram group compared to 66.8% in the paroxetine group (P<0.05).
Montgomery et al.[109] (2004) Escitalopram 10 to 20 mg daily vs	DB, RCT Patients with MDD	N=293 8 weeks	Primary: Change from baseline in MADRS scores Secondary: Not reported	Primary: No significant difference between groups was observed at week eight in MADRS scores. Escitalopram-treated patients achieved remission significantly faster compared to venlafaxine patients in a post-hoc analysis. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
venlafaxine ER 75 to 150 mg daily				
Fava et al.[110] (2002) Fluoxetine 20 mg daily vs sertraline 50 mg daily vs paroxetine 20 mg daily	DB, MC, RCT Patients ≥18 years of age with depression	N=284 10 to 16 weeks	Primary: HAM-D_{17} scores Secondary: Improvement in insomnia/sleep disturbances	Primary: As indicated by baseline-to-endpoint improvement on the HAM-D_{17}, there were no statistically significant differences between fluoxetine, sertraline, and paroxetine on all outcome measures (P=0.365). Secondary: Insomnia improvement when using the sleep disturbance factor was similar in all patients with no significant difference between groups (P=0.868).
Thase et al.[111] (2002) Imipramine (mean dosage, 221 mg/day) vs sertraline (mean dosage, 163 mg/day)	DB, SC Patients with chronic major depression who failed to respond to 12 weeks of treatment with either imipramine or sertraline	N=168 12 weeks	Primary: HAM-D, CGI Secondary; Not reported	Primary: The two groups were equal in response rates for completers, 63 and 55% for the sertraline and imipramine groups, respectively (P=0.16). However, in the ITT analysis there was a statistically better outcome for the sertraline group (P=0.03). Those patients going from sertraline to imipramine experienced significant increases in eight adverse events and significant reductions in three adverse events while those patients going from imipramine to sertraline experienced a significant reduction in seven adverse events and no increase in any adverse event. Secondary; Not reported
Le Noury et al.[112] (2015) Imipramine (200 to 300 mg/day)	Reanalysis of DB, MC, PC, RCT Adolescents 12 to 18 years of age who met DSM-IV	N=275 8 weeks	Primary: HAM-D Secondary: CGI, autonomous functioning	Primary: There was no statistical significance (considered at P<0.05) or clinical significance shown for any of the prespecified primary or secondary efficacy variables in either the observed case or last observation carried forward datasets. HAM-D scores decreased by 10.7 (95% CI, 9.1 to 12.3), 9.0 (95% CI, 7.4 to 10.5), and 9.1 (95% CI, 7.5 to 10.7) points (least

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs paroxetine (20 to 40 mg/day) vs placebo	criteria for a current episode of major depression of at least eight weeks' duration		checklist, adverse events	squares mean) for the paroxetine, imipramine, and placebo groups, respectively. Secondary: There were clinically significant increases in harms, including suicidal ideation and behavior and other serious adverse events in the paroxetine group and cardiovascular problems in the imipramine group.
Asnis et al.[113] (2013) Levomilnacipran 40 mg QD or levomilnacipran 80 mg QD or levomilnacipran 120 mg QD vs placebo	DB, MC, PC, RCT Patents 18 to 65 years of age, met the diagnostic criteria of MDD per the DSM-IV-TR, current ongoing depressive episode ≥8 weeks in duration, MADRS score ≥30 at baseline, MADRS-SR ≥26 at baseline	N=708 N=506 completed study 8 weeks	Primary: Mean reduction of MADRS score from baseline at week eight (reported as LSMD from placebo) Secondary: Mean reduction of SDS score from baseline at week eight, mean reduction on $HDRS_{17}$ from baseline at week eight, mean change from baseline of CGI-S total score at week eight and mean reduction from baseline of CGI-I total score at week eight (all reported as LSMD from placebo)	Primary: The LSMD from placebo of MADRS scores for levomilnacipran 40, 80 and 120 mg at week eight were -3.23; P=0.0186, -3.99; P=0.0038 and -4.86; P=0.0005, respectively. Secondary: The LSMD from placebo on the SDS total score for levomilnacipran 40, 80 and 120 mg was -1.4; P>0.05, -2.51; P<0.05, -2.57; P<0.05, respectively. The LSMD from placebo on the $HDRS_{17}$ for levomilnacipran 40, 80 and 120 mg was -1.2; P>0.05; -2.09; P<0.05 and -2.34; P<0.05, respectively. The LSMD from placebo on the CGI-S for levomilnacipran 40, 80 and 120 mg was -.04; P>0.05, -0.43; P<0.01 and -0.35; P<0.05, respectively. The LSMD from placebo on the CGI-I score for levomilnacipran 40, 80 and 120 mg was -0.1; P>0.05, -0.34; P<0.05 and -0.32; P<0.05, respectively.
Bakish et al.[114] (2013)	DB, MC, PC, RCT Patients 18 to 75	N=557 N=441	Primary: Mean reduction of MADRS score	Primary: The LSMD from placebo week eight for levomilnacipran 40 and 80 mg was -3.3; P=0.003 and -3.1; P=0.004, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Levomilnacipran 40 mg QD or levomilnacipran 80 mg QD vs placebo	years of age, met diagnostic criteria per the DSM-IV-TR for recurrent MDD, current ongoing depressive episode 6 weeks to 12 months in duration, 5 or fewer major depressive episodes within the previous 5 years, MADRS score ≥26 at baseline, CGI-S score ≥4 at baseline	completed study 8 weeks	from baseline at week eight (reported as LSMD from placebo) Secondary: Mean reduction of SDS score from baseline at week eight, mean reduction on $HDRS_{17}$ from baseline at week eight and mean reduction from baseline of CGI-S total score at week eight (all reported as LSMD from placebo)	Secondary: The LSMD from placebo at week eight for levomilnacipran 40 and 80 mg was -1.8; P=0.046 and - 2.7; P=0.003, respectively. The LSMD from placebo on $HDRS_{17}$ scores for levomilnacipran 40 and 80 mg were -2.2; P=0.007 and -1.6; P=0.043. The LSMD from placebo on CGI-S scores for levomilnacipran 40 and 80 mg was -0.3 for both arms with P=0.020 and P=0.015, respectively.
Sambunaris et al.[115] (2013) Levomilnacipran 40 to 120 mg vs placebo	DB, FD, MC, PC, RCT Patients 18 to 80 years of age, met the diagnostic criteria for MDD per the DSM-IV-TR, ongoing major depressive episode of at least 4 weeks in duration, MADRS score ≥30 at baseline and MADRS-SR ≥26 at baseline	N=429 N=335 completed study 8 weeks	Primary: Mean reduction of MADRS score from baseline at week eight (reported as LSMD from placebo Secondary: Mean reduction of SDS score from baseline at week eight, mean reduction on $HDRS_{17}$ from baseline at week eight, mean change	Primary: The LSMD from placebo on the MADRS score at week eight was -3.095; P=0.0051 for levomilnacipran 40 to 120 mg. Secondary: The LSMD from placebo on the SDS at week eight was -2.632; P=0.0010 for levomilnacipran 40 to 120 mg. The LSMD from placebo on the $HDRS_{17}$ score for levomilnacipran 40 to 120 mg was -2.146; P=0.0038. Levomilnacipran 40 to 120 mg did not show statistically significant results for the LSMD from placebo on the CGI-I total score at week eight (-0.207; P=0.0881). Levomilnacipran 40 to 120 mg showed a LSMD from placebo on the CGI-S at week eight of -0.352; P=0.0083. The LSMD from placebo on the MEI-SF for levomilnacipran 40 to 120 mg at week eight was 5.048; P=0.0382.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			from baseline of CGI-I total score at week eight, mean reduction from baseline of CGI-S total score at week eight and mean change from baseline on MEI-SF total score at week eight (all reported as LSMD from placebo)	
Montgomery et al.[116] (2013) Levomilnacipran 75 or 100 mg QD Levomilnacipran dose was increased to 100 mg/day over 12 days. vs placebo	DB, FD, MC, PC, RCT Outpatients 18 to 70 years of age who met DSM-IV criteria for MDD (duration > 1 month) with a HDRS17 score > 22 and SDS score > 10	N=553 10 weeks	Primary: MADRS score change from baseline to week 10 Secondary: HDRS17, SDS, CGI-I, MADRS response (>50% decrease from baseline) and remission (score <10), safety	Primary: Levomilnacipran was significantly "superior" to placebo on MADRS total score change from baseline to week 10 (LSMD, -4.2; 95% CI, -5.7 to -2.6; P<.0001). Secondary: Statistical significance in favor of levomilnacipran was demonstrated on change from baseline to week 10 in HDRS17 total score (LSMD, -3.4; 95% CI, -4.7 to -2.2; P<0.0001) and SDS total score (LSMD, -3.4; 95% CI, -4.6 to -2.2; P<0.0001) and subscales. Significantly more levomilnacipran patients vs placebo patients achieved MADRS response (59.1 vs 42.2%; P<0.0001) and remission (46.4 vs 26.0%; P<0.0001). Levomilnacipran was generally safe and well tolerated; more levomilnacipran patients (9.4%) vs placebo patients (6.5%) discontinued due to adverse events, but more placebo patients vs levomilnacipran patients discontinued overall (24.9 vs 20.2%).
Montgomery et al.[117] (2015) Levomilnacipran ER 40 to 120 mg/day	MA (5 studies) Patients 18 to 80 years of age with MDD	N=2598 8 or 10 weeks	Primary: MADRS total score, treatment response (≥50% improvement in MADRS), remission (MADRS score	Primary: Significantly greater improvements from baseline in MADRS total score were seen with levomilnacipran ER compared with placebo in four of five studies. The LSMDs between levomilnacipran ER and placebo were statistically significant in two fixed-dose studies (range, –3.1 to –4.9; P<0.05) and two flexible-dose studies (range, –3.1 to –4.2; P<0.05). In one flexible-dose study, the LSMD from placebo did not reach statistical significance (–1.5; P=0.25).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo			≤10) Secondary: Not reported	The percentage of patients meeting the MADRS criterion for treatment response was higher with levomilnacipran ER than with placebo. In the overall population, the difference between levomilnacipran ER and placebo response rates was 10.2% (P<0.001). The difference between levomilnacipran ER and placebo in remission rates was 6.2% (P<0.05) in the overall population. Secondary: Not reported
Versiani et al.[118] (2005) Mirtazapine 15 to 60 mg daily vs fluoxetine 20 to 40 mg daily	DB, RCT Patients 18 to 65 years of age with MDD	N=297 8 weeks	Primary: Change from baseline in HAM-D_{17} score Secondary: MADRS, CGI	Primary: No statistically significant differences were noted between the two groups in change from baseline HAM-D_{17} score at any time point. Secondary: Mirtazapine treatment was associated with greater change in MADRS score at day 14 (–10.9 vs –8.5; P=0.006) and the proportion of patients with ≥50% decrease in MADRS score (21.4 vs 10.9%; P=0.031). On the CGI, the proportion of "much/very much improved" patients tended to be greater with mirtazapine (significant at day seven; 9.7 vs 3.4%, P=0.032). No significant between-group differences were observed for the majority of QOL measures. Mirtazapine produced significantly better improvements on "sleeping assessment 1" (14.9±5.2 vs 13.7±5.4; P=0.028) and "sleeping assessment 2" (P=0.013) than fluoxetine. Both agents were generally well tolerated but mirtazapine-treated patients experienced a mean weight gain of 0.8±2.7 kg compared to a mean decrease in weight of 0.4±2.1 kg for fluoxetine-treated patients (P<0.001).
Wheatley et al.[119] (1998) Mirtazapine 15 to	DB, MC, RCT Patients with MDD 18 to 75 years of	N=123 6 weeks	Primary: HAM-D Secondary;	Primary: The mean HAM-D_{17} scores were not different at week six for the two groups; although at week three (the estimated treatment difference was -3.4 in favor of mirtazapine; 95% CI, –6.1 to –0.76; P=0.006) and week

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
60 mg/day vs fluoxetine 20 to 40 mg/day	age		Not reported	four (the estimated treatment difference was -3.8 in favor of mirtazapine: 95% CI, –6.61 to –1.02; P=0.009), statistical significance was reported for mirtazapine. No other assessment endpoints were statistically different between the two groups at week six.
Blier et al.[120] (2009) Mirtazapine 30 mg at bedtime (may be increased to 45 mg after 4 weeks) vs paroxetine 20 mg in the morning (may be increased to 30 mg after 4 weeks) vs mirtazapine 30 mg/day plus paroxetine 20 mg/day for 6 weeks After 6 weeks, non-responders on monotherapy had the second trial drug added to their current regimen.	DB, RCT Patients with MDD	N=61 8 weeks	Primary: MADRS, HAM-D_{17}, CGI Secondary; Not reported	Primary: There was a greater improvement on the MADRS at day 28 with combination therapy (P=0.045) when compared to monotherapy (mirtazapine; P=0.046, paroxetine; P=0.02). There was a greater improvement on the MADRS at days 35 (P=0.006) and 42 (P=0.002) with combination therapy compared to monotherapy (mirtazapine; P=0.003 and 0.001, respectively; paroxetine; P=0.011 and 0.003, respectively). Statistical significance was achieved on the HAM-D_{17} in the combination group at day 35 (P=0.02) when compared to mirtazapine (P=0.005), and at day 42 (P=0.007) when compared to both drugs alone (mirtazapine; P=0.002, paroxetine; P=0.04). Statistical significance was achieved on the CGI in the combination group at day 35 vs mirtazapine (P=0.004) and for both drugs at day 42 (mirtazapine; P=0.002, paroxetine; P=0.04). Four patients remitted by day 42 in the mirtazapine group (19%) and 5 in the paroxetine group (26%) compared to 9 patients remitted in the combination group (43%; P>0.05). At day 42, 10 patients in each of the monotherapy arms received the other drug in combination. The mean scores improved rapidly in both groups with seven and five patients achieving remission in the subsequent two weeks in the mirtazapine and paroxetine groups, respectively. Five patients on the combination had their regimens increased to 45 mg/day of mirtazapine and paroxetine 30 mg/day. Two of these patients achieved remission by day 56.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Non-responders on combination therapy had the dosage of both drugs increased by 50%.				Secondary; Not reported
Behke et al.[121] (2003) Mirtazapine orally disintegrating tablets 30 to 45 mg/day vs sertraline 50 to 150 mg/day	DB, RCT Patients with MDD	N=345 8 weeks	Primary: HAM-D Secondary: CSFQ	Primary: Mirtazapine was significantly (P<0.05) more effective than sertraline at all assessments during the first two weeks of the study. After this time, HAM-D total scores were similar in both groups. Secondary: The CSFQ revealed a greater improvement in sexual functioning with mirtazapine than with sertraline at all assessments in both females and males. The differences were not statistically significant.
Guelfi et al.[122] (2001) Mirtazapine 15 to 60 mg/day vs venlafaxine 75 to 375 mg/day	DB, MC, RCT Hospitalized patients with severe depressive episode with melancholic features	N=157 8 weeks	Primary: HAM-D, MADRS Secondary: Adverse effects	Primary: A significant difference favoring mirtazapine was found on the HAM-D Sleep Disturbance factor at all assessment points (P≤0.03). Secondary: A significantly higher percentage of patients treated with venlafaxine (15.3%) than mirtazapine (5.1%) dropped out because of adverse events (P=0.037).
Feighner et al.[123] (1998) Nefazodone 200 mg BID vs placebo	DB, PC, PG Patients that were hospitalized due to depression	N=120 6 weeks	Primary: HAM-D_{17}, CGI-I, MADRS Secondary: Not reported	Primary: Nefazodone treatment resulted in a significant reduction (P<0.01) of the HAM-D_{17} total score compared to placebo from the end of the first treatment week through the end of the study (–12.2 nefazodone vs –7.7 placebo). At the end of the trial, significantly more nefazodone-treated patients (50%) than placebo-treated patients (29%) had responded, as indicated by their CGI-I score (P=0.021) or by a ≥50% reduction in their HAM-D_{17}

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				scores (P=0.017). Significantly more patients treated with nefazodone (36%) than placebo-treated patients (14%) had a HAM-D_{17} score ≤10 at the end of treatment (P=0.004). Significant treatment differences (P<0.01) in favor of nefazodone were also seen in the MADRS; the HAM-D retardation, anxiety, and sleep disturbance factors; and HAM-D item 1 (depressed mood). Patients with dysthymia in addition to major depression also showed significant improvement (P<0.05) when treated with nefazodone, with significant differences in response rates seen as early as week two and through the end of the trial. Secondary: Not reported
Dunner et al.[124] (2005) Paroxetine CR 12.5 to 62.5 mg vs placebo	DB, PC, RCT (Pooled analysis) Adults with MDD	N=303 (4 trials) 8 to 12 weeks	Primary: Changes in depressive symptoms according to HAM-D_{17} and CGI-I, patients achieving remission Secondary; Not reported	Primary: Statistically significant improvements in depressive symptoms in favor of paroxetine CR compared to placebo were observed in patients with both severe MDD (HAM-D treatment difference, –4.37; 95% CI, –6.31 to –2.42; P<0.001) and nonsevere MDD (HAM-D_{17} treatment difference, -1.89; 95% CI, –2.91 to –0.87; P<0.001). The odds of CGI-Improvement response were also significantly higher for patients receiving paroxetine CR than those receiving placebo, regardless of baseline depressive symptomatology (severe MDD: OR, 2.42; 95% CI, 1.50 to 3.91; P<0.001, nonsevere MDD: OR, 1.63; 95% CI, 1.21 to 2.19; P<0.002).
Birkenhager et al.[125] (2004) Phenelzine 10 mg BID vs tranylcypromine 10 mg BID	DB, RCT Patients 18 to 65 years of age with depression	N=77 5 weeks	Primary: HAM-D Secondary: Side effects	Primary: Seventeen patients (44%) responded to tranylcypromine and 18 patients (47%) responded to phenelzine (≥50% reduction in HAM-D; P=0.82). The mean reduction in HAM-D score was 10.4 for the tranylcypromine group vs 8.3 for the phenelzine group (P=0.23). No significant differences in response rates were demonstrated between the treatment groups (P=0.97). Secondary: A substantial number of patients experienced severe side effects, mainly

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				dizziness, agitation, and insomnia. The incidence was the same in both samples (21%).
Rossini et al.[126] (2005) Sertraline 150 mg daily vs fluvoxamine 200 mg daily	DB, RCT Patients >59 years of age with MDD	N=88 7 weeks	Primary: Response rate (HAM-D) Secondary; Not reported	Primary: Response rates were 55.6% for sertraline and 71.8% for fluvoxamine. No significant difference in final response rates were observed between treatment groups (P=0.12). Secondary; Not reported
Sheehan et al.[127] (2009) Trazodone ER 150 to 375 mg/day vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with MDD, current episode of MDD for a minimum of 1 month, dysphoria for most days over the previous 4 weeks, and a MADRS total score ≥26 at screening and baseline	N=412 8 weeks	Primary: Change from baseline in HAM-D-17 total score Secondary: HAM-D-17 responders, HAM-D-17 remitters, change in HAM-D-17 depressed mood item from baseline, change in MADRS total score from baseline, CGI-I responders, PGI-I responders, change in CGI-S from baseline, CGI-I at last study visit, PGI-I at last study visit, discontinuations due to lack of efficacy, and	Primary: The change in the HAM-D-17 total score from baseline decreased by an average of 11.4±8.2 and 9.3±7.9 in the trazodone and placebo groups, which statistically favored treatment with trazodone (P=0.012). Results demonstrated a significantly greater improvement in the mean HAM-D-17 total score in the trazodone group compared to the placebo group by the first week of treatment (day seven of titration: 5.6±5.2 vs 3.9±4.8, respectively; P=0.005). The significantly greater differences were maintained throughout the study. Secondary: The number of HAM-D-17 responders (decrease ≥50% from baseline HAM-D-17 total score) in the trazodone group was significantly greater compared to the placebo group (54.0 vs 41.2%; P=0.003). No difference in the proportion of HAM-D-17 remitters (HAM-D-17 total score ≤7) was observed between treatment groups (35.6 vs 31.9%; P=0.22). The change in the HAM-D-17 depressed mood item from baseline decreased by average of 1.6±1.3 and 1.3±1.2 in the trazodone and placebo groups, which statistically favored treatment with trazodone (P=0.030). The change in MADRS total score from baseline also statistically favored

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			overall quality of sleep	treatment with trazodone (-16.6±11.3 vs -14.1±11.9; P=0.036). No difference in the proportion of CGI-I responders ("much improved" or "very much improved" at last study visit) was observed between treatment groups (53.3 vs 48.6%; P=0.22). No difference in the proportion of PGI-I responders ("much improved" or "very much improved" at last study visit) was observed between treatment groups (51.1 vs 43.7%; P=0.15). The change in the CGI-S from baseline decreased by 1.7±1.4 and 1.4±1.4 in the trazodone and placebo groups, which statistically favored treatment with trazodone (P=0.036). The CGI-I scores at the last study visit were comparable in both treatment groups (P=0.22). The PGI-I scores at the last study visit were comparable in both treatment groups (P=0.084). Four percent of patients in the trazodone group discontinued treatment due to lack of efficacy compared to 4.4% of patients in the placebo group (P>0.99). At the end of the study, patients treated with trazodone had statistically significant improvements compared to placebo in all quality of sleep parameters.
Lenox-Smith et al.[128] (2008) Venlafaxine ER 75 to 300 mg/day vs citalopram 20 to	DB, MC, RCT Patients 18 to 65 years of age with MDD who had not experienced a treatment response to 8 weeks of monotherapy with an adequate	N=406 12 weeks	Primary: HAM-D_{21} total score Secondary: MADRS, CGI-S, CGI-I	Primary: There was no significant difference between venlafaxine ER and citalopram on the HAM-D_{21} total score (-17.0 vs -16.5, respectively; P=0.4778). Secondary: There were no significant differences between venlafaxine ER and citalopram on the MADRS total scores (P=0.5002) or CGI-S (P=0.3014), or in the analyses of response (P=0.953).

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60 mg/day	regimen of an SSRI			Significant differences between treatment groups were observed for one subscale analysis: more venlafaxine ER patients had a CGI-I score of 1 at week 12 (P=0.024).
Bielski et al.[129] (2004) Venlafaxine ER 225 mg/day vs escitalopram 20 mg/day	DB, RCT Patients with MDD	N=195 8 weeks	Primary: MADRS Secondary: Adverse effects	Primary: There were no significant differences in efficacy, remission rates, or response rates between venlafaxine ER and escitalopram. Mean changes from baseline to endpoint in MADRS total score for escitalopram and venlafaxine ER were –15.9 and –13.6, respectively. Remission (MADRS score of ≤10) rates at endpoint were 41.2% for escitalopram and 36.7% for venlafaxine ER. Response (≥50% reduction from baseline MADRS score) rates for the escitalopram and venlafaxine ER groups were 58.8 and 48.0%, respectively. Secondary: More patients in venlafaxine ER group had treatment-emergent adverse effects compared to escitalopram (85.0 vs 68.4%) but this was not statistically significant and may have been due to rapid titration of the venlafaxine dose. Venlafaxine ER had a higher incidence of discontinuation due to adverse events (16.0 vs 4.1%; P<0.01).
Nemeroff et al.[130] (2007) Venlafaxine 75 to 225 mg/day vs fluoxetine 20 to 60 mg/day vs placebo	DB, MC, PC, RCT Outpatients ≥18 years of age with MDD	N=308 6 weeks	Primary: HAM-D Secondary: Not reported	Primary: On the HAM-D, overall differences among treatment groups at week six did not reach significance (P=0.051), though the difference between the venlafaxine and placebo groups was significant (P=0.016). The differences between fluoxetine and placebo (P=0.358) and between venlafaxine and fluoxetine (P=0.130) were not significant. The difference on the HAM-D depressed mood item was significant among treatment groups at week six (P<0.001); both active treatments were significantly more effective than placebo (venlafaxine; P<0.001, fluoxetine; P=0.024). The difference between the active treatments was not statistically significant (P=0.117). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Rudolph et al.[131] (1999) Venlafaxine ER 75 to 225 mg/day vs fluoxetine 20 to 60 mg/day vs placebo	DB, MC, PC, PG, RCT Outpatients ≥18 years of age with MDD	N=301 8 weeks	Primary: HAM-D, MADRS, CGI Secondary: Not reported	Primary: The percentages of patients who achieved full remission of their depression (HAM-D total score ≤7) at the end of treatment were 37, 22, and 18% for the venlafaxine ER, fluoxetine and placebo groups, respectively. The differences in remission rates between venlafaxine ER and the other groups were significant (P<0.05). Venlafaxine ER produced a significant lower mean total score on the MADRS analysis than did fluoxetine (P=0.048). The P value for the statistical test of center by center interaction was not significant, indicating that treatment outcomes did not differ significantly between individual investigational sites. Secondary: Not reported
Benkert et al.[132] (1996) Venlafaxine 150 to 375 mg/day vs imipramine 200 mg/day	DB, PG, RCT Hospitalized patients with major depression and melancholia	N=167 6 weeks	Primary: HAM-D, MADRS Secondary: Not reported	Primary: No differences in the response rates on the HAM-D or MADRS were observed between treatments. Among patients who demonstrated a response on the HAM-D, there was a significantly faster onset of response (P=0.036) and sustained response (P=0.018) in the venlafaxine group. The median time to response on the HAM-D among responders was 14 days with venlafaxine and 21 days with imipramine. However, no differences between treatments were observed among responders on the MADRS. Secondary: Not reported
Kok et al.[133] (2007) Venlafaxine ER 75 to 375 mg/day vs	DB, RCT Inpatients ≥60 years of age with MDD	N=81 12 weeks	Primary: Remission (MADRS ≤10) Secondary: Remission on HAM-D and GDS,	Primary: There was no significant difference in remission between the treatment groups as measured by a reduction in MADRS (venlafaxine, 27.5% vs nortriptyline, 36.6%; P=0.381). Secondary: There was no significant difference in remission rates between the

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nortriptyline 25 to 200 mg/day			response rates	treatment groups as measured by HAM-D and GDS (P=NS). There was no significant difference in response rates between the treatment groups as measured by MADRS, HAM-D, GDS, and CGI-I (P=NS).
Richard et al.[134] (2012) Venlafaxine ER, up to a maximum of 225 mg/day vs paroxetine, up to a maximum of 40 mg/day vs placebo	DB, PC, RCT Patients ≥30 years of age with idiopathic PD, without dementia, and depressive disorder or operationally defined subsyndromal depression	N=115 12 weeks	Primary: HAM-D-17 total score Secondary: MADRS, BDI-II, GDS, UPDRS, safety	Primary: Treatment effects relative to placebo, expressed as mean 12 week reduction in HAM-D-17 total score, were 6.2 points (97.5% CI, 2.2 to 10.3; P=0.0007) with paroxetine and 4.2 points (97.5% CI, 0.1 to 8.4; P=0.02) with venlafaxine ER. There was no difference noted between paroxetine and venlafaxine ER (P=0.28). Secondary: Significant beneficial effects of paroxetine and venlafaxine ER relative to placebo were apparent for the secondary outcomes (MADRS, BDI-II, and GDS; P≤0.01 for all comparisons). UPDRS total and motor scores improved in all three treatment groups, but there were no significant group differences in mean response. There was no evidence of treatment-associated worsening of motor function. One hundred patients reported at least one adverse event during the trial: 86, 85, and 90% with paroxetine, venlafaxine ER, and placebo. Insomnia was reported significantly less frequently with paroxetine compared to venlafaxine ER and placebo. There were three serious adverse events.
Mazeh et al.[135] (2007) Venlafaxine 75 to 300 mg/day vs paroxetine 10 to 60 mg/day	RCT, SB Inpatients ≥65 years of age with MDD who did not respond to two adequate pharmacological treatments for depression during the current depressive episode	N=30 6 weeks	Primary: CGI, HAM-D, GDS Secondary: Not reported	Primary: Nine patients treated with venlafaxine (60%) and five patients treated with paroxetine (33%) remitted after eight weeks of treatment. Three patients from each group responded without achieving remission after eight weeks of treatment (20%). Four patients treated with venlafaxine (26.7%) and eight patients treated with paroxetine (53.3%) failed to respond. Mean score changes from baseline to endpoint for paroxetine were: HAM-D=-12.5, CGI=-2.3, and GDS=-3.2. Mean score changes from baseline to

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				endpoint for venlafaxine were: HAM-D=-19.1, CGI=-2.3, and GDS=-6.0 in the venlafaxine group. Venlafaxine was more effective than paroxetine on CGI and HAM-D measures (P<0.0003). Secondary: Not reported
DeSilva et al.[136] (2012) Venlafaxine vs an SSRI	MA Published, randomized, DB, head-to-head trials, which compared venlafaxine and an SSRI in the treatment of MDD in adults	N=26 trials Duration varied	Primary: Remission, response, discontinuation Secondary: Not reported	Primary: MA using a random effect model showed that venlafaxine was more efficacious compared to SSRIs in achieving remission (OR, =1.13; 95% CI, 1.0 to 1.28; P=0.05) and response (OR, 1.17; 95% CI, 1.03 to 1.34; P=0.02). Subgroup analysis found that venlafaxine had a significantly better response rate than fluoxetine (OR, 1.28; 95% CI, 1.05 to 1.55; P=0.01). There were no significant differences in response or remission between venlafaxine and other individual SSRIs. There was no significant difference in all cause discontinuation between venlafaxine and SSRIs (OR, 1.10; 95% CI, 0.97 to 1.25; P=0.15). Venlafaxine had significantly higher discontinuation due to adverse events compared to SSRIs (OR, 1.41; 95% CI, 1.10 to 1.79; P=0.006). Secondary: Not reported
Reed et al.[137] (2012) Vilazodone 40 mg QD vs placebo	2 DP, PC, RCT Patients with MDD	N=410 (RCT-1), 481 (RCT-2) 8 weeks	Primary: Change from baseline to end of treatment MADRS total score; mixed-effects repeated-measures analyses were conducted in the PC trials; effectiveness	Primary: Vilazodone-treated patients in both short-term studies showed greater improvement from baseline to end of treatment in mean MADRS scores than placebo-treated patients (LSM treatment difference, -3.2; P=0.00 RCT-1 and -2.5; P=0.009 RCT-2). CGI-I mean scores at end of treatment reflected greater improvement with vilazodone compared to placebo in both studies (LSM treatment difference, -0.4; P=0.001 RCT-1 and -0.3; P=0.004 RCT-2). MADRS response rates were significantly greater among patients receiving vilazodone vs those receiving placebo (RCT-1, 40.4 vs 28.1%, respectively; P=0.007 and RCT-2, 43.7 vs 30.3%,

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			analyses in the long-term study included mean MADRS score change over time Secondary; Not reported	respectively; P=0.002). The greater efficacy of vilazodone vs placebo was consistent for the majority of demographic and MDD characteristic subgroups. In the long-term study, the mean MADRS score improved from 29.9 (baseline) to 11.4 (week eight), 8.2 (week 24), and 7.1 (week 52). Secondary; Not reported
Khan et al.[138] (2011) Vilazodone 40 mg QD vs placebo	DB, MC, PC, RCT Patients 18 to 70 years of age with MDD (single episode or recurrent)	N=481 8 weeks	Primary: Change in MADRS total score Secondary: MADRS and HDRS-17 response, HDRS-21, HARS, CGI-S, CGI-I scores, CSFQ	Primary: Patients receiving vilazodone showed significantly greater improvements in mean MADRS scores compared to placebo (LSM treatment difference, -2.5; P=0.009). Secondary: Treatment with vilazodone resulted in significant improvements for the HDRS-17 (P=0.026), HDRS-21 (P=0.029), HARS (P=0.037) and CGI-S (P=0.004) scores. CGI-I scores at week eight showed significantly greater global improvement with vilazodone compared to placebo (P=0.004). The MADRS response rate was significantly greater among patients receiving vilazodone compared to placebo (43.7 vs 30.3%, respectively; P=0.002), as was the HDRS-17 response rate (44.2 vs 32.9%; P=0.013). Remission rates for vilazodone were not significantly different than placebo based on MADRS (27.3 vs 20.3%, respectively; P=0.066) or HDRS-17 (24.2 vs 17.7%, respectively; P=0.088). More patients receiving vilazodone (82.1%) experienced a treatment-related adverse event compared to placebo (64.4%). The most frequently reported adverse events with vilazodone compared to placebo were diarrhea (30.6 vs 10.7%), nausea (26.0 vs 5.6%) and headache (12.8 vs 10.3%). Most adverse events were considered mild-to-moderate in nature. Treatment-related effects on sexual function as measured by CSFQ were small and similar among the treatment groups. Effects on weight were similar to placebo.
Rickels et al.[139] (2009)	DB, MC, PC, RCT	N=410	Primary: Change in	Primary: The mean change on the MADRS total score was significantly greater

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Vilazodone 40 mg QD vs placebo	Patients 18 to 65 years of age with MDD (single episode or recurrent)	8 weeks	MADRS total score, HAM-D_{17} total score, and HAM-A total score, CGI-S and CGI-I scores Secondary: Response (≥50% decrease in total score on MADRS, and HAM-D_{17} total scores, or a score of 1 or 2 on the CGI-I)	with vilazodone compared to placebo (-12.9 vs -9.6, respectively; P=0.001). The difference was evident by week one (P<0.001) and on each subsequent visit (P<0.05). The mean change on the HAM-D_{17} total score was significantly greater with vilazodone compared to placebo (-10.4 vs -8.6, respectively; P=0.022). The difference was evident by week one and on each subsequent visit (P<0.05). The mean score change on the CGI-S was significantly greater with vilazodone compared to placebo (-1.4 vs -1.0, respectively; P=0.001). The mean score change on the CGI-I was significantly improved with vilazodone compared to placebo (2.6 vs 3.0, respectively; P=0.001). The mean change on the HAM-A total score was significantly greater with vilazodone compared to placebo (-6.6 vs -5.1, respectively; P=0.045). Secondary: Response rates were significantly better with vilazodone than with placebo on the MADRS (P=0.007), HAM-D_{17} (P=0.011), and CGI-I (P=0.001). Treatment-emergent adverse events with vilazodone included diarrhea, nausea and somnolence. Most of the adverse events were mild-to-moderate in severity.
Croft et al.[140] (2014) Vilazodone 40 mg/day vs placebo	DB, MC, PC, RCT Patients 18 to 70 years of age with ongoing major depressive episode lasting eight or more weeks and up to 12 months, MADRS total score ≥26	N=505 8 weeks	Primary: MADRS Secondary: CGI-S, sustained response (MADRS total score ≤12 for at least the last two consecutive double-blind visits)	Primary: Statistically significant reductions that were consistent with greater symptom improvement were seen for vilazodone- versus placebo-treated patients (LSMD, –5.117; P<0.00001, effect size=0.54). Secondary: Decrease from baseline to week eight in CGI-S score was statistically greater for vilazodone versus placebo (LSMD, –0.622; P<0.00001, effect size =0.50). The difference in the rate of MADRS sustained response was also statistically significant in favor of vilazodone (27%) versus placebo (17%; P=0.0047).
Mathews et al.[141] (2015)	DB, MC, PC, RCT	N=1133	Primary: MADRS	Primary: Vilazodone treatment (20 and 40 mg/day) compared with placebo was

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Vilazodone 20 mg/day or vilazodone 40 mg/day vs citalopram 40 mg/day vs placebo	Patients 18 to 70 years of age with ongoing major depressive episode lasting eight or more weeks and up to 12 months, MADRS total score ≥26	10 weeks	Secondary: CGI-S, sustained response (MADRS total score ≤12 for at least the last two consecutive double-blind visits), HAMA, adverse events	associated with significantly greater reduction in MADRS total scores from baseline to week 10. Statistical significance in favor of both vilazodone groups appeared at week two and was sustained throughout the double-blind period. MADRS mean change from baseline to week 10 was also significantly greater for citalopram versus placebo, demonstrating sensitivity of the study to detect treatment effects in the primary efficacy measure. Secondary: Both vilazodone groups relative to placebo showed significantly greater improvement from baseline in CGI-S scores. Sustained MADRS response rates were numerically higher for all active treatment groups compared with placebo, although the differences did not reach statistical significance. HAMA change from baseline improved over time but did not achieve statistical significance relative to placebo. The most commonly reported adverse events leading to discontinuation was nausea (placebo, n=1; vilazodone 20 mg/day, n=6; vilazodone 40 mg/day, n=3, citalopram, n=4). Adverse events that occurred in at least 5% of patients in either vilazodone group and at twice the rate of placebo were diarrhea, nausea, insomnia, and vomiting (40 mg/day group only).
Henigsberg et al.[142] (2012) Vortioxetine 1 mg QD or vortioxetine 5 mg QD or vortioxetine 10 mg QD	DB, MC, PC, PG, RCT Patients 18 to 75 years of age, had a current MDE per DSM-IV-TR criteria, ambulatory and a baseline MADRS total score ≥26	N=556 (N=505 completed study) 8 weeks	Primary: Change from baseline in HAMD-24 after eight weeks of treatment Secondary: Decrease from baseline on SDS, CGI-I score and decrease from baseline on MADRS	Primary: At eight weeks, all treatment groups had a significantly greater decrease from baseline in HAMD-24 compared to placebo. Vortioxetine 1 mg had a decrease from baseline on the HAMD-24 of -14.82 (P<0.001). Vortioxetine 5 mg had a decrease from baseline of -15.42 (P<0.001), and vortioxetine 10 mg had a decrease from baseline on the HAMD-24 of -16.23 (P<0.001). Secondary: None of the vortioxetine treatment groups had statistically significant decrease from baseline on the SDS as compared to placebo for (P values not reported). Vortioxetine 1, 5 and 10 mg all met the secondary endpoint of CGI-I compared to placebo; 2.37, 2.37 and 2.29 respectively (P<0.001 for all comparators). Vortioxetine 1, 5, and 10 mg all met statistical significance for the endpoint of decrease from baseline on the MADRS

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vs placebo				total score; -14.89, -15.09 and -15.65, respectively (P<0.001 for all).
Mahableshwarkar et al.[143] (2015) Vortioxetine 10 mg QD or vortioxetine 15 mg QD vs placebo	DB, MC, PC, RCT Patients 18 to 75 years of age with MDD and a baseline MADRS total score >26 and CGI-S score ≥4	N=1111 8 weeks	Primary: Change from baseline in MADRS total score Secondary: MADRS response (≥50% decrease in the MADRS total score from baseline), MADRS remission (MADRS total score ≤10), CGI-S remission (CGI-S score ≤2), and CGI-I response (CGI-I score ≤2)	Primary: Differences from placebo in mean change from baseline MADRS scores were not statistically significant for the vortioxetine 10 mg or 15 mg groups. Secondary: For all five key secondary efficacy end points, the results were similar between the two vortioxetine groups, and differences from placebo did not reach statistical significance at the 0.025 level.
Jacobsen et al.[144] (2015) Vortioxetine 10 mg QD vs vortioxetine 20 mg QD vs placebo	DB, MC, PC, RCT Patients 18 to 75 years of age with MDD and a baseline MADRS total score >26 and CGI-S score ≥4	N=462 8 weeks	Primary: MADRS total score Secondary: Change from baseline in MADRS total score, MADRS responders, mean CGI-I score, change from baseline in MADRS total	Primary: The mean difference between vortioxetine 20 mg and placebo for MADRS total score was –3.64 (SE ± 1.161; P=0.002). The difference between vortioxetine 10 mg and placebo in MADRS change from baseline did not reach significance at week eight (P=0.058). Vortioxetine 20 mg separated from placebo at week four and remained separated at weeks six and eight. The vortioxetine 10 mg dose also separated from placebo at weeks four and six but not at week eight. Secondary: MADRS response at eight weeks (≥50% decrease from baseline in MADRS total score) was achieved in 33.8, 39.2, and 28.4% of subjects in the vortioxetine 10 mg, 20 mg, and placebo groups, respectively (P=0.301 [10 mg vs placebo]; P=0.044 [20 mg vs placebo]). Since the difference did

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			score in subjects with baseline HARS score ≥20, MADRS remission, and change from baseline in SDS total score	not reach the predefined level of statistical significance (0.025), the hierarchical testing strategy was stopped, and all subsequent P values (<0.05) were considered nominal and not statistically significant.
Jain et al.[145] (2013) Vortioxetine 5 mg QD vs placebo	DB, PC Patients 18 to 75 years of age with MDD and a baseline MADRS total score >30	N=600 8 weeks	Primary: Change from baseline in HAMD-24 total score at week six compared to placebo Secondary: Response and remission rates, CGI-I, HAMA, MADRS-S total score, adverse events	Primary: There were no significant differences in efficacy measures between subjects in the 5 mg vortioxetine and placebo groups at week six. Secondary: HAMD-24 total score in subjects with baseline HAMA >19 in the 5 mg vortioxetine group was improved at weeks three to six compared to the placebo group (P<0.05). The most common adverse events for the vortioxetine and placebo groups were nausea (19.1 and 9.4%), headache (17.1 and 15.1%) and diarrhoea (11.4 and 7.0%), respectively.
Katona et. al.[146] (2012) Vortioxetine 5 mg QD or duloxetine 60 mg QD vs placebo QD	AC, DB, MC, PC, PG, RCT Patients ≥65 years of age, with a primary diagnosis of MDD per DSM-IV-TR criteria and a MADRS score ≥26	N=453 (N=392 completed the study) 8 weeks	Primary: Change from baseline in HAMD-24 total score at weeks one, two, four, six, and eight. Secondary: Change in baseline from CGI-I, MADRS total score, HAMA and CGI-S at week	Primary: The vortioxetine treatment group did not meet the primary endpoint until week six of the study, and it was not reported when the duloxetine treatment group began to separate from placebo for the primary endpoint. The vortioxetine treatment group began to separate on the HAMD-24 scale from placebo at week six (P=0.024). At week eight, vortioxetine 5 mg had a mean change from baseline in HAMD-24 score of -13.7 (P<0.01), and duloxetine 60 mg had a mean change from baseline on the HAMD-24 of -15.8 (P<0.0001). Secondary: Vortioxetine 5 mg and duloxetine 60 mg both met all secondary endpoints at week eight. A change in CGI-I of -0.56 (P<0.001) was reported for the vortioxetine group, along with a decrease in MADRS total change of -4.29

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			eight. Cognitive changes from baseline assessed via the RAVLT and DSST at week eight	(P<0.001), a decrease in HAMA scores of -2.35 (P<0.01) and a decrease of CGI-S of -0.60 (P<0.001). Duloxetine showed similar results for these secondary endpoints with a P<0.001 for all of these measures. The cognitive measures also showed positive results for both treatment groups. Vortioxetine 5 mg showed a difference from placebo on the DSST change of 2.79 (P>0.05), and vortioxetine showed a difference from placebo in RAVLT for acquisition change of 1.14 (P<0.05) and delayed recall change of 0.47 (P<0.05). The duloxetine group did not show statistical significance for DSST change with a value of 0.77 (no P value reported). The duloxetine group did show statistical significance on the RAVLT for acquisition of change of 1.41 (P<0.01) and delayed recall change of 0.64 (P<0.01)
Mahableshwarkar et al.[147] (2013) Vortioxetine 2.5 mg QD or vortioxetine 5 mg QD vs duloxetine 60 mg QD vs placebo QD	DB, PC Adult patients with MDD	N=611 8 weeks	Primary: Change from baseline in the HAM-D24 Secondary: Responder rate, CGI-I), and remission rate; adverse events, ASEX	Primary: Both doses of vortioxetine were associated with declines in HAM-D24 total scores compared to placebo but were not statistically significant. At eight weeks, changes from baseline were [mean]: -10.50 (0.76) placebo, -12.04 (0.74) 2.5 mg vortioxetine, and -11.08 (0.74) 5 mg vortioxetine. Secondary: CGI-I and remission rate were not significantly different from placebo. Duloxetine treatment was associated with declines in HAM-D24 total score [-13.47(0.75); P=0.005] as well as significant improvements in secondary outcome measures vs placebo (P<0.05). The most common adverse events for vortioxetine were nausea, dry mouth, and headache. Rates of sexual dysfunction (ASEX) were 51.0, 37.5, 46.9, and 33.3% in the vortioxetine 2.5 mg, vortioxetine 5 mg, duloxetine, and placebo groups, respectively.
Boulenger et al.[148] (2014) Vortioxetine 15	DB, MC, PC, RCT Patients 18 to 75 years of age with	N=607 8 weeks	Primary: Change from baseline MADRS total score	Primary: Both doses of vortioxetine improved mean change from baseline in MADRS total score at week eight, with a mean treatment difference to placebo of −5.5 (vortioxetine 15 mg, standard error=1.1, P<0.0001) and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg QD or vortioxetine 20 mg QD vs duloxetine 60 mg QD vs placebo QD	MDD, MADRS score ≥26, CGI-S ≥4		Secondary: MADRS responders, CGI-I, remission (MADRS ≤10), SDS	−7.1 points (vortioxetine 20 mg, standard error=1.1, P<0.0001). The active reference duloxetine was also significantly superior to placebo (nominal P<0.0001). Secondary: Both doses of vortioxetine were statistically significantly superior to placebo in all the predefined key secondary efficacy analyses, including response and remission based on the MADRS.
Mahableshwarkar et al.[149] (2015) Vortioxetine 15 mg QD or vortioxetine 20 mg QD vs duloxetine 60 mg QD vs placebo QD	DB, MC, PC, PG, RCT Patients 18 to 75 years of age with MDD	N=614 8 weeks	Primary: Change from baseline MADRS total score Secondary: HAMA, CGI-I, CGI-S, adverse events, ASEX	Primary: Treatment with vortioxetine 20 mg reduced the MADRS total score at week eight more than placebo (P=0.023). Vortioxetine 15 mg was not significantly different from placebo at week eight (P=0.224). Duloxetine 60 mg separated from placebo (P<0.001) on the primary endpoint, confirming assay sensitivity. Secondary: The key secondary efficacy endpoints did not separate from placebo (P>0.050) with either vortioxetine dose. Discontinuation due to adverse events occurred in 2.5% of patients in the placebo group, 9.5% in the vortioxetine 15-mg group, 9.1% in the vortioxetine 20-mg group, and 6.6% in the duloxetine 60-mg group. Treatment-emergent sexual dysfunction, suicidal ideation or behavior, and discontinuation symptoms were not significantly different between vortioxetine and placebo.
Robinson et al.[150] (2011)	MC, OL	N=616	Primary: Safety, sexual	Primary: A total of 93.8% of patients had ≥1 treatment-emergent adverse events.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Vilazodone 40 mg QD	Patients 18 to 70 years of age with MDD	52 weeks	function (CSFQ), effectiveness (MADRS, CGI-S and CGI-I scales) Secondary: Not reported	The most frequent treatment-emergent adverse events were diarrhea (35.7%), nausea (31.6%), and headache (20.0%). The incidence of severe adverse events was 14.9%. The incidence of severe gastrointestinal adverse events was 3.5% and the incidence of severe headache was 1.2%. Mean weight increase was 1.7 kg at week 52. At six months, mean weight change for patients with normal baseline weight was 1.3 kg; for overweight and obese patients, mean weight increases were 1.6 and 1.0 kg, respectively. The mean CSFQ scores at baseline were 46.9 for men and 38.7 for women; both scores indicative of sexual dysfunction. The CSFQ mean scores improved and exceeded threshold values for sexual dysfunction at week four for men and week eight for women. Adverse events pertaining to impaired sexual desire or function were decreased libido (4.2%) and anorgasmia including abnormal orgasm (2.3%). Those pertaining to males only were erectile dysfunction (4.2%) and delayed ejaculation (3.1%). There were a total of eight patients who had adverse events of either suicidal ideation or behavior. The mean MADRS scores improved from 29.9 at baseline to 11.4 at week eight (change, -18.5), 8.2 at week 24 (change, -21.7), and 7.1 at one year (change, -22.8). The mean CGI-S improved from 4.3 at baseline to 2.5 at week eight (change, -1.9) and 1.7 at one year (change, -2.6). The CGI-I mean score decreased from 3.5 at week one to 1.9 at week eight and 1.4 at one year. Secondary: Not reported
Baldwin et al.[151] (2012) Vortioxetine 2.5 mg QD	OL Patients with MDD	N=535 52 weeks	Primary: Safety and tolerability, MADRS Secondary:	Primary: Adverse events reported by >10% of patients were nausea, headache, and nasopharyngitis. Six patients had eight adverse events related to sexual dysfunction. There were no clinically significant safety findings with respect to mean changes of vital signs, weight, ECG parameters, or clinical laboratory values.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
or vortioxetine 5 mg QD or vortioxetine 10 mg QD			Not reported	Patients entered the ES with a mean MADRS total score of 13.5+8.7. The mean MADRS total score decreased (improved) by approximately 8 points to 5.5+6.0 at week 52. By the end of the study, the proportion of responders had increased from 63 to 94%, as had the proportion in remission (MADRS <10), increasing from 42 to 83%. Patients in remission (n=226) at the start of this study had a relapse rate (MADRS >22) of 9.7%. Secondary: Not reported
Cipriani et al.[152] (2009) New-generation antidepressants (bupropion, citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, milnacipran, mirtazapine, paroxetine, reboxetine, sertraline, venlafaxine)	MA (117 trials) Patients with MMD receiving acute treatment	N=25,928 6 to 12 weeks	Primary: Response (defined as the proportion of patients who had a reduction ≥50% from the baseline score on the HDRS or MADRS, or who scored much improved or very much improved on the CGI at eight weeks) and dropout rates Secondary: Not reported	Primary: *Direct Comparisons* Efficacy favored escitalopram over citalopram; citalopram over reboxetine and paroxetine; mirtazapine over fluoxetine and venlafaxine; sertraline over fluoxetine; and venlafaxine over fluoxetine and fluvoxamine. For dropouts, fluoxetine was better tolerated than reboxetine and citalopram than sertraline. *Multiple-treatments MA* Escitalopram, mirtazapine, sertraline, and venlafaxine were significantly more efficacious than duloxetine, fluoxetine, fluvoxamine, paroxetine, and reboxetine. Reboxetine was significantly less efficacious than all the other 11 antidepressants. Duloxetine and paroxetine were less well tolerated than escitalopram and sertraline; fluvoxamine was less well tolerated than citalopram, escitalopram, and sertraline; venlafaxine was less well tolerated than escitalopram; reboxetine was less well tolerated than many other antidepressants, such as bupropion, citalopram, escitalopram, fluoxetine, and sertraline; and escitalopram and sertraline were better tolerated than duloxetine, fluvoxamine, paroxetine, and reboxetine. Mirtazapine, escitalopram, venlafaxine, and sertraline were more efficacious than fluoxetine, and fluoxetine was more efficacious than reboxetine. Fluoxetine was better tolerated than reboxetine.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Mirtazapine, escitalopram, venlafaxine, and sertraline were among the most efficacious treatments, and escitalopram, sertraline, bupropion, and citalopram were better tolerated than the other remaining antidepressants. The cumulative probabilities of being among the four most efficacious treatments were: mirtazapine (24.4%), escitalopram (23.7%), venlafaxine (22.3%), sertraline (20.3%), citalopram (3.4%), milnacipran (2.7%), bupropion (2.0%), duloxetine (0.9%), fluvoxamine (0.7%), paroxetine (0.1%), fluoxetine (0.0%), and reboxetine (0.0%). The cumulative probabilities of being among the four best treatments in terms of acceptability were escitalopram (27.6%), sertraline (21.3%), bupropion (19.3%), citalopram (18.7%), milnacipran (7.1%), mirtazapine (4.4%), fluoxetine (3.4%), venlafaxine (0.9%), duloxetine (0.7%), fluvoxamine (0.4%), paroxetine (0.2%), and reboxetine (0.1%). Secondary: Not reported
Moncrieff et al.[153] (2004) Antidepressants vs placebo	MA Patients with MDD	N=751 (9 trials) Variable duration	Primary: Efficacy Secondary; Not reported	Primary: TCAs were statistically better than active placebo in the pooled analysis (0.39, 95% CI, 0.24 to 0.54). Secondary; Not reported
Walsh et al.[154] (2002) Antidepressants vs placebo	MA Adult outpatients with MDD	N=not specified (75 trials) Variable duration	Primary: HAM-D, CGI Secondary: Not reported	Primary: The mean proportion of patients in the placebo group who responded was 29.7% (range, 12.5 to 51.8). Response was determined by a reduction of at least 50% in their score on the HAM-D and/or CGI rating of markedly or moderately improved. Both the proportion of patients responding to placebo and the proportion responding to medication were significantly positively correlated with the year of publication (for placebo P<0.001; for medication P=0.02).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The association between year of publication and response rate was more statistically robust for placebo than medication. Secondary; Not reported
Geddes et al.[155] (2003) Antidepressants vs placebo	MA Studies evaluating relapse prevention of depression	N=4,410 (31 trials) 6 to 36 months	Primary: Proportion of patients relapsing; withdrawal from the trial Secondary: Not reported	Primary: Continuing treatment with antidepressants reduced the odds of relapse by 70% (95% CI, 62 to 78; P<0.00001) compared to treatment discontinuation. The average rate of relapse on placebo was 41% compared to 18% on active treatment. The treatment effect seemed to persist for up to 36 months, although most trials were of 12 months duration, and so the evidence on longer-term treatment requires confirmation. Significantly more participants allocated antidepressants withdrew from the trials than did those allocated to placebo (18 vs 15%, respectively; OR, 1.30; 95% CI, 1.07 to 1.59). Secondary: Not reported
Saveanu et al.[156] (2015) iSPOT-D Escitalopram vs sertraline vs venlafaxine ER Dose adjustments managed by each participant's usual	MC, PRO, RCT Patients 18 to 65 years of age with diagnosis of nonpsychotic MDD and HDRS-17 score ≥16	N=1008 8 weeks	Primary: HDRS-17 (response rate was defined as a ≥50% decrease in severity from baseline; remission by an HDRS-17 score ≤7) Secondary: Self-reported response and remission on the QIDS-SR16, for which response rate was a ≥50%	Primary: Of the 71.6% of patients who completed the full eight weeks and at least one outcome measure at week eight, over 60% of participants met criteria for response, of which 45.4% were in remission. Response and remission rates did not significantly differ between the treatment arms. Secondary: By the QIDS-SR16, 53.3% of participants had responded, of which 37.6% were in remission at week eight. Most domains of function showed improvement on the order of one standard deviation, a clinically meaningful shift over the acute treatment phase. None of the score changes differed significantly between the three treatment arms. Adverse events (any medical symptom or condition occurring or worsening after the baseline visit) were reported by 44.8% of participants, 88.3% (399/452) of whom experienced events likely to be related to the antidepressants. Overall, 3.6% of participants discontinued due to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
treating clinician according to their usual clinical practice.			decrease in severity from baseline to week 8, and remission a score ≤5, functional capacity, adverse events	intolerance.
Chuang et al.[157] (2014) Paroxetine (20 mg/day) vs venlafaxine (75 to 225 mg/day) vs milnacipran (100 mg/day)	OBS, OL Patients 18 to 65 years of age with diagnosis of MDD and HDRS-17 score ≥16	N=249 24 weeks	Primary: HDRS-17: response (score decreased more than 50%), remission (score ≤7 or ≤5, as stated) Secondary: Not reported	Primary: There were no significant differences between the three groups in response (P=0.72). There were no significant differences in remission rates between the three groups when the criterion for remission was an HDRS-17 score ≤5. However, Milnacipran was more efficacious than paroxetine in relieving the symptoms of MDD when the remission criterion was an HDRS-17 score ≤7, and, using LOCF analysis, paroxetine was more efficacious than venlafaxine when the remission criterion was an HDRS-17 score ≤5. Secondary: Not reported
Thase et al.[158] (1995) Phenelzine (PHZ) vs isocarboxazid (ISO) vs tranylcypromine (TRP)	MA Patients with MDD	Review of Medline and Psychological abstracts from 1959 to 1992	Primary: Efficacy Secondary; Not reported	Primary: For outpatients using ITT samples, all three agents appear to be equally effective (PHZ=57.9%±4.0%; ISO=60.1%±7.1%; TRP=52.6%±12.4%). When compared to placebo in outpatients, ISO (41.3%±18.0%) had a larger relative advantage compared to either PHZ (29.5% ±11.1%) or TRP (22.1%±25.4%) in the doses studied. For inpatients, PHZ was somewhat more effective (22.3%±30.7%) than placebo, whereas the ISO-placebo difference was smaller (15.3%±12.6%). Secondary; Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				
Cipriani et al.[159] (2005) Fluoxetine, sertraline, nortriptyline, amitriptyline, venlafaxine, imipramine, nefazodone, citalopram, desipramine, paroxetine, pramipexole, fluvoxamine, trazodone, bupropion, clomipramine, duloxetine, mirtazapine, doxepin	MA (132 trials) Patients with depression	N=9,311 Duration varied	Primary: Number of patients who responded to treatment (HAM-D, MADRS) Secondary: Tolerability	Primary: On a dichotomous outcome fluoxetine was less effective than sertraline (PetoOR, 1.40; 95% CI, 1.11 to 1.76), mirtazapine (PetoOR, 1.64; 95% CI, 1.01 to 2.65) and venlafaxine (PetoOR, 1.40; 95% CI, 1.15 to 1.70; P values not reported). On a continuous outcome, fluoxetine was less effective than venlafaxine (SMD random effect, 0.11; 95% CI, 0.00 to 0.23; P value not reported). Secondary: Fluoxetine was better tolerated than TCAs considered as a group (PetoOR, 0.78; 95% CI, 0.68 to 0.89), and was better tolerated in comparison with individual antidepressants, in particular than amitriptyline (PetoOR, 0.64; 95% CI, 0.47 to 0.85) and imipramine (PetoOR, 0.79; 95% CI, 0.63 to 0.99), and among newer antidepressants than pramipexole (PetoOR, 0.20; 95% CI, 0.08 to 0.47; P values not reported).
Stahl et al.[160] (1997) Mirtazapine up to 35 mg daily vs amitriptyline up to 280 mg daily vs	MA Patients with MDD	N=580 (4 trials) 6 weeks	Primary: HAM-D, HDRS, responder rate (percentages of patients with ≥50% decrease in baseline 17-item HDRS score), remitter rate (patients with a total 17-item HDRS score ≤7),	Primary: Compared to placebo, both mirtazapine and amitriptyline therapy significantly improved patient HDRS, MADRS, and CGI scores from baseline (P<0.05). Significantly greater percentages of patients responded to mirtazapine or amitriptyline therapy, assessed with the HDRS criteria, compared to placebo (P<0.05). Significantly greater percentages of patients randomized to mirtazapine or amitriptyline therapy exhibited remission compared to placebo (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo up to 7 capsules daily			MADRS, CGI Secondary: Change from baseline in the "depressed mood" item on the HDRS scale, anxiety/ somatization factor, sleep disturbance factor, melancholia factor, tolerability	There were no statistically significant differences between mirtazapine and amitriptyline in any of the primary endpoints. Secondary: Significantly greater improvement from baseline in the "depressed mood" item was seen in the mirtazapine and amitriptyline groups compared to placebo (P<0.05). Significantly greater improvement from baseline in the anxiety/soma-tization, sleep disturbance, and melancholia factors was seen in the mirtazapine and amitriptyline groups compared to placebo (P<0.05). There were no statistically significant differences between mirtazapine and amitriptyline in the "depressed mood", anxiety, somatization, sleep disturbance, or melancholia factors on the HDRS scale. Patients on amitriptyline therapy experienced a significantly higher incidence of restlessness (14.0 vs 2.1%), vertigo (2.1 vs 0), blurred vision (6.2 vs 0.5%), dyspepsia (10.4 vs 0.5%), dry mouth (80.8 vs 34.0%), constipation (31.1 vs 18.0%), palpitations (8.8 vs 3.6%), and tachycardia (4.7 vs 0.5%) compared to patients receiving mirtazapine therapy (P<0.05). Patients on mirtazapine therapy experienced a significantly higher incidence of weight gain compared to the amitriptyline group (14.4 vs 6.7%; P<0.05). Drowsiness and sedation were more common in the active groups compared to the placebo group (P<0.05). Hypotension was more common in the amitriptyline group compared to the placebo (3.6 vs 0.5%; P<0.05). Increased appetite was more common in the mirtazapine group compared to the placebo group (3.6 vs 0; P<0.05).
Bull et al.[161] (2002)	RETRO	N=137,401	Primary: Patient-physician	Primary: While 72% of physicians reported instructing their patients on taking

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Continuation of an SSRI vs discontinuation of an SSRI vs switching of an SSRI	Adult patients diagnosed with a depressive disorder, taking an SSRI for at least 6 months were interviewed over the phone; prescribing physicians were asked to complete a survey	6 months	communication about therapy duration and adverse effects, therapy discontinuation or switching of medication within three months of SSRI use, BDI-FS, depression symptoms Secondary; Not reported	SSRIs for a minimum of 6 months, only 34% of patients acknowledged receiving this information from their physician and 56% reported receiving no instructions at all. Patients instructed to continue therapy for less than 6 months were 3 times more likely to discontinue therapy prematurely compared to those told to continue therapy for a longer duration (OR, 3.12; 95% CI, 1.21 to 8.07; P<0.001). Patients who were informed about adverse effects common with their medication were less likely to discontinue therapy than patients who did not have this discussion with their physician (OR, 0.49; 95% CI, 0.25 to 0.95). Patients who discussed adverse effects with their physicians were more likely to switch medications (RR, 5.60; 95% CI, 2.31 to 13.60). Patients experiencing adverse effects were 3 times more likely to switch their medication (OR, 3.09; 95% CI, 1.30 to 7.31). Less than three follow-up visits, and lack of therapeutic response to medication at three months were also associated with a higher incidence of therapy discontinuation (P=0.002, P<0.001, respectively). Patients who continued to have severe symptoms, based on the BDI-FS scale, were six times more likely to switch their medication (OR, 6.15; 95% CI, 2.11 to 17.89). Secondary; Not reported
Anderson et al.[162] (2000) TCAs vs SSRIs	MA Patients with MDD	N=10,706 (102 trials) Variable duration	Primary: HAM-D, MADRS Secondary: Adverse events	Primary: Efficacy was based on 102 studies (5,533 SSRI patients and 5,173 TCA patients). Efficacy was determined by comparing the mean reduction in depression scores based upon the HAM-D or the MADRS. There was no statistical difference in efficacy between the two groups (effect size, –0.03; 95% CI, –0.09 to 0.03). TCAs did appear more effective for inpatients (–0.23; 95% CI, –0.4 to -0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: SSRIs were better tolerated with discontinuations due to adverse effects significantly greater in the TCA group (12.4 vs 17.3%; P<0.0001).
MacGillivray et al.[163] (2003) TCAs vs SSRIs	MA Patients with MDD	N=2,951 (11 trials) Variable duration	Primary: HAM-D; MADRS Secondary: Tolerability	Primary: Efficacy between SSRI and tricyclics did not differ significantly (standardized weighted mean difference, fixed effects 0.07; 95% CI, –0.02 to 0.15; P<0.11). Secondary: Significantly more patients receiving a tricyclic withdrew from treatment (RR, 0.78; 95% CI, 0.68 to 0.90; P<0.0007) and withdrew specifically because of side effects (RR, 0.73; 0.60 to 0.88; P<0.001).
Steffens et al.[164] (1997) TCAs vs SSRIs	MA Patients with MDD	N=not specified (34 trials) Variable duration	Primary: HAM-D Secondary: Frequency of side effects	Primary: Overall, the response rate to treatment for patients who completed a trial was 63.2% for SSRIs and 68.2% for TCAs (P=0.038). For the ITT groups, these rates dropped to 48.0 and 48.6% (P=NS), respectively. Significantly more TCA-treated than SSRI-treated patients dropped out due to either lack of efficacy or adverse reactions (30.0 vs 24.7%; P=0.01). Secondary: Patients taking SSRIs experienced more gastrointestinal problems and sexual dysfunction, whereas treatment with TCAs produced significantly more complaints of sedation, dizziness, and anticholinergic symptoms.
Diabetic Neuropathy				
Yan et al.[165] (2010) Duloxetine 60 to 120 mg daily vs placebo	DB, PC, RCT Adult Chinese patients with diabetic peripheral neuropathic pain and BPI 24-hour average pain severity rating ≥4	N=215 12 weeks	Primary: Change from baseline to endpoint in BPI average pain score Secondary: BPI-S and BPI-I, PGI-I, CGI-S, EQ-5D, Athens	Primary: Mean change from baseline to endpoint in BPI pain score was not significantly different between treatments (-2.31±0.18 vs -2.69±0.19; P=0.124). Duloxetine-treated patients showed significantly greater pain reduction compared to placebo-treated patients at weeks one, two, and four (P=0.004, P=0.009, and P=0.006), but not at week eight (P=0.125) and 12 (P=0.107). Secondary: Duloxetine-treated patients experienced significant improvement in PGI-I (2.32±0.11 vs 2.64±0.10; P=0.028), CGI-S (-1.24±0.11 vs -0.99±0.11;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Insomnia Scale	P=0.036), AUC for pain relief, BPI-S pain right now (-2.72±0.26 vs -1.99±0.25; P=0.012), and BPI-I walking ability (-2.45±0.24 vs -1.82±0.23; P=0.016). Patients receiving duloxetine had numerically higher 30 and 50% response rates on BPI average pain compared to placebo-treated patients. A higher proportion of patients receiving duloxetine (62.5%) met the criteria for sustained response compared to patients receiving placebo (50.5%). All other secondary efficacy measures, including health outcomes measures, were numerically but not significantly improved in patients receiving duloxetine compared to patients receiving placebo.
Armstrong et al.[166] (2007) Duloxetine 20 or 60 mg QD, or 60 mg BID vs placebo	3 DB, MC, PC, RCT Patients with diabetic peripheral neuropathic pain	N=1,139 12 weeks	Primary: Patient-reported functional outcomes (SF-36, BPI, EQ-5D) Secondary: Not reported	Primary: Diabetic peripheral neuropathic pain patients treated with duloxetine 60 mg QD or BID had greater improvement, compared to placebo, in all SF-36 domains of physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. Within treatment group changes among the domain scores ranged from 0.9 to 23.5 points. Duloxetine 60 mg BID showed some advantage over duloxetine 60 mg QD on general health (P=0.02) and mental health (P=0.04) status. Consistent results were seen in the ITT population with the exception that the above indicated advantages of duloxetine 60 mg BID over 60 mg QD in the domains of general and mental health were not significant. Duloxetine 60 mg QD and 60 mg BID were significantly more efficacious to placebo at reducing scores in all BPI-I items thereby indicating improvements in all seven items, with similar results demonstrated for the ITT population. In the analysis of the EQ-5D, patients on duloxetine 60 mg QD (P=0.004) and 60 mg BID (P<0.001) were both significantly better compared to placebo for the trial completers. Results for the ITT analysis were consistent, thus demonstrating the superiority of duloxetine 60 mg QD and BID compared to placebo with regard to changes in all included function and QOL measures.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Kajdasz et al.[167] (2007) Duloxetine 20 or 60 mg QD, or 60 mg BID vs placebo	Post-hoc analysis of 3 DB, MC, PC, RCT Patients with diabetic peripheral neuropathic pain	N=1,139 12 weeks	Primary: Response rate (defined as ≥30 and ≥50% reductions from baseline in weekly mean of the 24-hour average pain severity scores) Secondary: NNH (based on rates of dis-continuation due to adverse events)	Primary: NNTs based on 50% reduction for patients receiving duloxetine 60 mg QD and 60 mg BID were 5.2 (95% CI, 3.8 to 8.3) and 4.9 (95% CI, 3.6 to 7.6), respectively, based on LOCF. Similarly, NNTs of 5.3 (95% CI, 3.8 to 8.3) for 60 mg QD and 5.7 (95% CI, 4.1 to 9.7) for 60 mg BID observed based on baseline observation carried forward. Secondary: The NNHs based on discontinuation due to adverse events were 17.5 (95% CI, 10.2 to 58.8) with duloxetine 60 mg QD and 8.8 (95% CI, 6.3 to 14.7) with duloxetine 60 mg BID.
Lunn et al.[168] (2009) Duloxetine vs placebo or control Only outcomes for painful peripheral neuropathy are reported.	SR (6 RCTs) Patients with painful peripheral neuropathy or chronic pain conditions	N=2,200 ≥8 weeks	Primary: Short term (≤12 weeks) improvement in pain Secondary: Long term (>12 weeks) improvement in pain, improvement in short and long term pain ≥30%, improvement in any validated QOL score ≥30%	Primary: Three trials in painful diabetic neuropathy reported data on the primary outcome measure of 50% improvement of pain compared to baseline at <12 weeks. Patients were treated with duloxetine 20, 60, or 120 mg/day. Combining data from all doses from the three trials together, the RR of 50% improvement with any dose was 1.63 (95% CI, 1.35 to 1.97) greater than placebo. The RR of improvement was significantly greater compared to placebo for the 60 and 120 mg/day doses, but not 20 mg/day, for which it was 1.43 (95% CI, 0.98 to 2.09). The RR of improvement with 120 mg/day (1.66; 95% CI, 1.35 to 2.04) was not significantly greater compared to 60 mg/day (1.65; 95% CI, 1.34 to 2.03). The mean improvement in pain at <12 weeks on an 11-point Likert scale was significantly greater compared to placebo with 60 (-1.04; 95% CI, -1.37 to -0.71) and 120 mg/day (-1.16; 95% CI, -1.49 to -0.83) of duloxetine. Secondary: None of the included trials of painful diabetic neuropathy included outcomes >12 weeks.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Two trials included data on >30% improvement of pain at ≤12 weeks. The results were similar to those for ≥50% improvement. Relative rates of improvement were significantly greater compared to placebo with duloxetine for the 60 mg/day (1.53; 95% CI, 1.27 to 1.83), 120 mg/day (1.55; 95% CI, 1.30 to 1.86), and for both doses combined (1.54; 95% CI, 1.30 to 1.82). Trials that included QOL information used the SF-36. In painful diabetic neuropathy, the effect of duloxetine 20 mg was not significant on any of the selected SF-36 subscores at up to 12 weeks (relevant physical, mental, and bodily pain subsections). The WMD of improvement on the physical summary component was significantly greater with 60 mg/day (2.51; 95% CI, 1.00 to 4.01) and 120 mg/day (2.80; 95% CI, 1.04 to 4.55). The WMD on the mental summary component was significantly greater only with 120 mg/day (2.23; 95% CI, 0.69 to 3.77). The WMD on the bodily pain subscale showed significantly more improvement compared to placebo with 60 mg/day (5.58; 95% CI, 1.74 to 9.42) and with 120 mg/day (8.19; 95% CI, 4.33 to 12.05). Three trials reported the PGI-C and pain at rest, and two reported the bodily pain index. The WMD for each outcome was significant and similar in magnitude for 60 and 120 mg/day. However, a clinically meaningful differences in the PGI-C is suggested as one point and hence the change associated with 60 mg/day (-0.59; 95% CI, -0.78 to -0.41) may not be clinically significant. The RR for the bodily pain index is significantly reduced by -0.97 (95% CI, -1.38 to -0.57) but again this borders on a change considered clinically significant.
Kaur et al.[169] (2011) Duloxetine 20 to 60 mg QD for 6 weeks vs amitriptyline 10 to 50 mg QD at	AC, DB, RCT, XO Patients 18 to 75 years of age with type 2 diabetes who had painful diabetic neuropathy for ≥1 month	N=58 14 weeks	Primary: Reduction in the median pain score from baseline Secondary: Assessment of pain by McGill Pain Questionnaire, overall improvement	Primary: There was a significant improvement in pain at six weeks with both treatments compared to their baseline values (P<0.001 for both). For duloxetine, 59% of patients showed good improvement, 22% showed moderate improvement, and 9% showed mild improvement. For amitriptyline, 55% of patients showed good improvement, 24% showed moderate improvement, and 16% showed mild improvement. Overall pain relief of >30% was observed in 64% of patients receiving duloxetine and 62% of patients receiving amitriptyline. A >50%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
bedtime for 6 weeks			score, 24-point HAM-D, change in sleep pattern, and patient self-evaluation of change in PGI-C scale	improvement was seen in 50% of patients receiving duloxetine and 55% of patients receiving placebo. Secondary: There was no significant difference in efficacy among the treatment groups as assessed by the McGill Pain Questionnaire and Likert scale. Significant improvement in sleep and overall well being was observed with both drugs (P<0.001 for both). Overall, 48% of patients preferred duloxetine compared to 36% of patients who preferred amitriptyline (P=0.18). Based on pain relief and tolerability, 5, 14 and 30% of patients preferred duloxetine 20, 40, and 60 mg, respectively. A total of 5, 22, and 9% of patients preferred amitriptyline 10, 25, and 50 mg. The number of mild treatment-emergent adverse effects was higher with duloxetine compared to amitriptyline (P<0.02). The number of moderate to severe treatment emergent adverse event was higher with amitriptyline (P<0.01). Dry mouth was significantly more common with amitriptyline that duloxetine (55 vs 24%, respectively; P<0.01).
Boyle et al.[170] (abstract) (2012) Duloxetine 60 mg/day vs amitriptyline 50 mg/day vs pregabalin 300 mg/day	AC, DB, PG, RCT Patients ≥18 years of age with diabetes (type 1 or type 2) for ≥1 year and neuropathic pain of diabetic origin (≥1 of the following: dysesthesia, burning pain, cold or heat allodynia, shooting or lancinating pains and hyperalgesia affecting both lower extremities at any	N=83 4 weeks	Primary: BPI Secondary: SF-36, sleep, mood and daytime sleepiness	Primary: All three treatments significantly reduced pain compared to placebo. No one treatment was “superior” to the others with regard to pain. Secondary: For sleep, pregabalin improved sleep continuity (P<0.001), whereas duloxetine increased wake and reduced TST (P<0.01 and P<0.001). Despite negative effects on sleep, duloxetine enhanced central nervous system arousal and performance on sensory motor tasks. There were no significant safety findings; however, there were a significantly higher number of adverse events in the pregabalin treatment group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	level below the mid-thighs) and LANSS score >12			
Tanenberg et al.[171] (2011) Duloxetine 60 mg/day vs pregabalin 300 mg/day vs duloxetine 60 mg/day and gabapentin ≥900 mg/day (existing therapy)	MC, NI, OL, RCT Adult patients with type 1 or 2 with HbA_{1c} ≤12%, and diabetic peripheral neuropathic pain who had been treated with gabapentin (900 mg/day) and had an inadequate response	N=407 12 weeks	Primary: Reduction from baseline in the weekly mean of the daily 24-hour pain diary ratings at week 12 Secondary: Worst pain and night pain ratings, Clinician Global Impression of Severity, BPI-S and BPI-I, BDI-II, PGI-I, SDS, response rate	Primary: The estimated mean change in the daily pain severity score at 12 weeks was -2.6 for duloxetine and -2.1 for pregabalin, representing an observed 0.49 advantage of duloxetine; therefore, NI was established. Significant superiority vs pregabalin in the mean daily pain diary ratings was observed at weeks, two, three, and five through 11 with duloxetine and with duloxetine plus gabapentin at weeks two and eight, but between-treatment differences at the 12 week end point met NI criteria, not statistical superiority. The NI comparison between duloxetine and combination therapy on the differences between end point mean changes in daily pain diary ratings in the ITT patient population was also met. Secondary: Reduction from baseline in BPI average pain and BPI worst pain severity ratings was significantly greater with duloxetine vs pregabalin, but differences between treatments were not significant for the other BPI pain measures, CGI-S, depressive symptoms, or the SDS global measure. Also, no significant between-treatment differences were found among the various response outcomes.
Quilici et al.[172] (2009) Duloxetine vs pregabalin and gabapentin Placebo was used a common	MA (11 RCTs; duloxetine, 3 trials; pregabalin, 6 trials; gabapentin, 2 trials) Patients with diabetic peripheral neuropathic pain	N=not specified ≥5 to 13 weeks	Primary: Reduction in 24-hour pain severity, response rate (≥50% pain reduction), overall health improvement (PGI-I and PGI-C) Secondary: Not reported	Primary: Direct comparisons All three agents were more efficacious to placebo for all efficacy parameters. For 24-hour pain severity effect values were -1.13 (95% CI, -1.36 to -0.89), -0.90 (95% CI, -1.23 to -0.57), and -1.44 (95% CI, -2.21 to -0.66) with duloxetine, pregabalin, and gabapentin. Corresponding effect values for response rates were 0.86 (95% CI, 0.63 to 1.09; NNT, 5; 95% CI, 3 to 7) and 0.84 (95% CI, 0.52 to 1.16; NNT, 5; 95% CI, 4 to 8) with duloxetine and pregabalin, and for PGI-I/C were -0.76 (95% CI, -1.00 to -0.51) and -1.29 (95% CI, -1.72 to -0.86) with duloxetine and pregabalin. Indirect comparisons

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
comparator.				For the primary efficacy outcome of 24-hour reduction in pain severity, a difference of -0.248 (95% CI, -0.677 to 0.162) was observed in favor of duloxetine over pregabalin. Duloxetine was not inferior to pregabalin on this outcome. For response rates, the difference between duloxetine and pregabalin was close to zero and not significant. For PGI-I/C outcomes, pregabalin showed an improvement of 0.542 points over duloxetine, a difference that reached significant (95% CI, 0.016 to 1.060). Secondary: Not reported
Wernicke et al.[173] (2007) Duloxetine 60 mg BID vs routine care (gabapentin, amitriptyline, and venlafaxine)	ES, OL, RCT Adult patients who presented with pain due to bilateral peripheral neuropathy caused by type 1 or 2 diabetes	N=293 52 weeks	Primary: Not reported Secondary: Health outcomes	Primary: Not reported Secondary: There were significant treatment-group differences observed in favor of duloxetine in the SF-36 physical component summary score, and subscale scores of physical functioning, bodily pain, mental health, and vitality. A significant treatment-by-investigator interaction was seen for general health perceptions (P=0.073), mental health (P=0.092), and social functions (P=0.003) subscales. There were no significant treatment-group differences observed on the EQ-5D questionnaire. During the trial, four deaths occurred. Deaths were considered to be unrelated to the study drug or protocol procedures. During the trial, 22 (11.2%) duloxetine vs 16 (16.7%) routine care-treated patients experienced at least one serious adverse event. The most frequently reported serious adverse events for both treatments together were cerebrovascular accident and diabetes, and these events were not considered to be drug-related. Fourteen (4.8%) patients discontinued due to any adverse event; which included 11 and three duloxetine- and routine care-treated patients (P=0.560). A total of 157 (53.6%) patients reported at least one treatment-emergent adverse event, and there were no treatment-group differences in the overall incidence of these events. There was a significant increase in mean uric acid levels in routine care-

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				treated patients compared to duloxetine-treated patients with regard to chemistry/urinalysis. Both treatments experienced a slight increase in HbA_{1c}, with duloxetine-treated patients experiencing a larger increase in the mean change from baseline to endpoint (P<0.001). No significant treatment-group differences were observed in low density lipoprotein cholesterol, high density lipoprotein cholesterol, and triglyceride levels. There were no significant treatment-group differences observed in the mean change in the Michigan Neuropathy Screening Instrument score from baseline to endpoint. There were no significant treatment-group differences observed in either subset of patients in the ulnar F-wave, ulnar distal sensory latency, and peroneal compound muscle action potential from baseline to endpoint for all patients. There was a significant increase observed in the peroneal F-wave measure for routine care-treated patients (P=0.05). There were no significant treatment-group differences observed for any of the ophthalmologic exam measures. There was a significant treatment-group difference observed in the mean change in microalbumin/creatinine ratio from baseline to endpoint (P=0.031), with duloxetine-treated patients experiencing a bigger mean decrease compared to routine care-treated patients. There was no significant treatment-group difference observed in the mean change from baseline to endpoint vital signs and weight. One duloxetine-treated patient and one routine care-treated patient met the definition for sustained elevation in SBP, and there were no significant differences between treatments. There were no ECG parameters that were significantly different between treatments. Significantly more routine-care patients had potentially clinically significant Fridericia-corrected QT interval increases (P=0.034).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Raskin et al.[174] (2006) Duloxetine 60 mg BID vs routine care (gabapentin, amitriptyline, and venlafaxine)	ES, OL, RCT Adult patients who presented with pain due to bilateral peripheral neuropathy caused by type 1 or 2 diabetes	N=237 52 weeks	Primary: Not reported Secondary: SF-36, EQ-5D	Primary: Not reported Secondary: No significant treatment-group differences were observed in the SF-36 subscales or in the EQ-5D questionnaire.
Fibromyalgia				
Arnold et al.[175] (2012) Duloxetine 30 mg/day	DB, PC, RCT Patients meeting the criteria for primary fibromyalgia as defined by the American College of Rheumatology	N=308 12 weeks	Primary: Average pain severity item from the BPI-Modified Short Form, Secondary: PGI-I, FIQ total score and those measuring pain, depression, anxiety, health outcomes, and safety	Primary: Duloxetine-treated patients did not have a statistically significant BPI-Modified Short Form average pain severity reduction vs placebo-treated patients (-2.04 vs -1.70; P=0.202). Secondary: There was a significant difference between duloxetine-treated and placebo-treated patients (P<0.05) for the PGI-I endpoint score (2.97 vs 3.35) and the changes in FIQ total score (-14.62 vs -9.75) and the SF-36 mental component score. Discontinuations due to adverse events did not differ significantly between treatment groups; nausea and dry mouth were the only adverse events with a significantly higher incidence with duloxetine vs placebo.
Arnold et al.[176] (2009) Duloxetine 60 to 120 mg/day vs placebo	DB, MC, PC, RCT (pooled analysis of 4 trials) Outpatients ≥18 years of age with fibromyalgia and a score ≥4 on the average pain severity item of the	N=1,332 12 to 15 weeks	Primary: Pain severity (BPI) Secondary: BPI pain interference items, FIQ, CGI-S, PGI-I, HAM-D, SF-36, SDS, MFI	Primary: In both depressed and nondepressed patients, significantly more duloxetine-treated patients achieved ≥30% reduction in BPI average pain score from baseline compared to placebo-treated patients (P<0.001). The treatment-by-MDD status interaction was not significant (P=0.34). In both depressed and nondepressed patients, significantly more duloxetine-treated patients achieved ≥50% reduction in BPI average pain score from baseline compared to placebo-treated patients (P<0.001). The treatment-by-MDD status interaction was not significant (P=0.39).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	BPI			Secondary: For both depressed and nondepressed patients, mean changes from baseline to endpoint on the FIQ, SDS, and CGI-S were significantly greater for duloxetine-treated patients compared to placebo-treated patients (P<0.05). All treatment-by-MDD status interactions were not significant for these assessments (P value not significant). In patients with MDD, significant differences in baseline to endpoint mean changes between duloxetine-treated and placebo-treated patients were observed for the following SF-36 domains: mental component score, mental health score, bodily pain, physical role functioning, social functioning score, and vitality score. In patients without MDD, significant differences in baseline to endpoint mean changes between duloxetine-treated and placebo-treated patients were observed for the following SF-36 domains: mental component score, mental health score, general health score, bodily pain, physical functioning, emotional role functioning score, and vitality score. With the exception of the mental health subscale, for all SF-36 domains and composite scales, the treatment-by-MDD status interactions were not significant. In patients with MDD, significant differences in baseline to endpoint mean changes between duloxetine-treated and placebo-treated mental fatigue and reduced motivation; whereas in patients without MDD, the only significant difference between the duloxetine-treated and placebo-treated groups was observed for the mental fatigue score. For all MFI domains, the treatment-by-MDD status interactions were not significant. In the MDD subgroup, the mean improvement on the clinician-rated HAM-D-17 total score from baseline to endpoint was significantly greater for duloxetine-treated patients compared to placebo-treated patients. In patients without MDD, the mean improvement on the HAM-D-17 total score from baseline to endpoint was not significantly different between the treatment groups. The treatment by- MDD status interaction was not significant (P=0.14). For both depressed and nondepressed patients, significantly more duloxetine-treated patients rated themselves as ‘‘much improved’’ or

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				‘‘very much improved’’ compared to placebo-treated patients (P<0.001). The treatment-by-MDD status interaction was not significant (P=0.45).
Russell et al.[177] (2008) Duloxetine 20 mg/day vs duloxetine 60 mg/day vs duloxetine 120 mg/day vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with fibromyalgia	N=502 6 months	Primary: Pain severity (BPI), PGI-I Secondary: FIQ, CGI-S, tender-point pain assessments, MFI, HAM-D-17, SDS, SF-36, EQ-5D	Primary: After three months of therapy, patients treated with duloxetine 60 and 120 mg/day experienced significantly greater improvements in average pain severity score compared to patients treated with placebo (-1.99, -2.31, -1.39, respectively; P≤0.05 and P≤0.001 vs placebo, respectively). There was no significant difference in pain severity with duloxetine 20 mg/day. At the six-month endpoint, patients treated with duloxetine experienced greater improvements in average pain severity score compared to patients treated with placebo (duloxetine 20/60 mg/day, -2.22 [P≤0.05]; duloxetine 60 mg/day, -1.98 [P≤0.05]; duloxetine 120 mg/day, -2.26 [P≤0.01]). After three months of therapy, the mean endpoint PGI-I score was significantly lower in patients treated with duloxetine 20 and 120 mg/day compared to patients treated with placebo (2.79, 2.93, 3.37, respectively; P≤0.01 and P≤0.05 vs placebo, respectively). There was no significant difference in PGI-I scores with duloxetine 60 mg/day compared to placebo. After six months of therapy, the mean endpoint PGI-I score was significantly lower in the duloxetine 20/60 mg/day (2.79; P≤0.01) and duloxetine 120 mg/day groups (2.93; P≤0.05), but not the duloxetine 60 mg/day group (3.08; P value not significant) compared to the placebo group (3.37). Secondary: After three months of therapy, duloxetine-treated patients demonstrated greater improvements in the CGI-S score (60 and 120 mg; P≤0.01 and P≤0.001, respectively), SF-36 mental component score (120 mg; P≤0.05), and some of the MFI domains (20, 60, 120 mg; P≤0.05, P≤0.01, and P≤0.001) compared to placebo-treated patients. There were no differences between duloxetine and placebo on other secondary efficacy and health outcome measures. After six months of therapy, duloxetine-treated patients demonstrated greater improvements in the CGI-S score (20/60 mg/day; P≤0.05, 60 mg/day; P≤0.01, 120 mg/day; P≤0.001) and MFI mental fatigue domain (20/60 mg/day; P≤0.05, 60 mg/day; P≤0.05, 120 mg/day; P≤0.01). The

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				other efficacy and health outcome measures that achieved significance in the duloxetine treatment groups compared to the placebo group included the MFI physical fatigue domain and EQ-5D (duloxetine 20/60 mg/day) and the MFI physical fatigue, reduced motivation, and reduced activity domains, as well as SF-36 mental component score (duloxetine 120 mg/day). Response rates (defined as a ≥50% improvement from baseline to the three-month endpoint in the average pain severity score) were significantly greater for duloxetine 120 mg/day (40.1%; P=0.003), but not for duloxetine 60 mg/day (34.0%; P=0.067) or for duloxetine 20 mg/day (32.5%; P=0.200) compared to placebo (23.7%). Response rates from baseline to the six-month endpoint were significantly greater for duloxetine 20/60 mg/day (36.4%; P=0.025), duloxetine 60 mg/day (32.6%; P=0.045), and duloxetine 120 mg/day (35.9%; P=0.009) compared to placebo (21.6%). In patients diagnosed with MDD at study entry, least squares mean changes in HAM-D-17 total score at six months were -4.8 for placebo, -5.2 for duloxetine 20/ 60 mg/day, -6.9 for duloxetine 60 mg/day, and -7.2 for 120 mg/day. Treatment group differences were not statistically significant when compared to placebo.
Mease et al.[178] (2010) Duloxetine 60 to 120 mg/day	ES Patients ≥18 years of age with fibromyalgia	N=278 6 months	Primary: Safety, efficacy Secondary: Not reported	Primary: Overall study drug compliance during the six-month ES was 81% in Study 1 and 79% in Study 2. The most common adverse events leading to discontinuation were fatigue and insomnia in Study 1, and diarrhea and nausea in Study 2. The most common treatment-emergent adverse events in Study 1 were nausea, dry mouth, and insomnia. The most common treatment-emergent adverse events in Study 2 were dry mouth, nausea, headache, hyperhidrosis, and muscle spasm. The majority of the treatment groups showed small mean change improvements in the BPI average pain severity score over the final six-month period. The placebo/duloxetine groups in both studies showed significant improvement in the PGI-I, as well as improvement in nearly all

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				other efficacy and health outcome measures, including significant improvement in several SF-36 measures. The maintenance of efficacy analysis in Study 2 did not demonstrate statistical significance (90% CI, -0.39 to 0.77; P=0.580). The mean change in the BPI average pain severity score increased by 0.19 point during the extension phase. Secondary: Not reported
Hauser et al.[179] (2013) Duloxetine or milnacipran vs placebo	MA, SR (10 RCTs) Adult patients >18 years of age with clinical diagnosis of fibromyalgia syndrome by any published, recognized and standardized criteria	N=6,038 Study duration had to be >4 weeks	Primary: Reduction in pain (50%), fatigue, sleep problems, disease-related QOL as measured by total score of FIQ, safety Secondary: 30% reduction in pain, depression, anxiety, disability, sexual function, PGI-C or CGI, cognitive disturbances, tenderness	Primary: Duloxetine and milnacipran had a small effect over placebo in reducing pain (SMD, -0.23; 95% CI, -0.29 to -0.18; 6.1% relative improvement; P<0.001). One-hundred and ninety-two participants per 1,000 on placebo reported an at least 50% pain reduction compared to 286 per 1,000 on duloxetine or milnacipran (RR, 1.49; 95% CI, 1.35 to 1.64; NNT, 11; 95% CI, 9 to 15; P<0.0001). Duloxetine and milnacipran did not reduce fatigue substantially (SMD, -0.14; 95% CI, -0.19 to -0.08; 2.5% relative improvement; NNT, 17; 95% CI, 12 to 29; P<0.001), and did not improve QOL substantially (SMD, -0.20; 95% CI, -0.25 to -0.14; 4.6% relative improvement; NNT, 12; 95% CI, 9 to 17; P<0.001) compared to placebo. There were no statistically significant differences between either duloxetine or milnacipran and placebo in reducing sleep problems (SMD, -0.07; 95% CI, -0.16 to 0.03; 2.5% relative improvement; P=0.15). Secondary: Duloxetine and milnacipran had a significant effect over placebo in 30% pain reduction (RR, 1.36; 95% CI, 1.26 to 1.46; P<0.0001). Duloxetine and milnacipran did not reduce depression substantially (SMD, -0.15; 95% CI, -0.21 to -0.10; P<0.001), and did not improve disability substantially (SMD, -0.22; 95% CI, -0.28 to -0.16; P<0.001) compared to placebo. There were no statistically significant differences between either duloxetine or milnacipran and placebo in reducing anxiety (P=0.54).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Out of two studies that reported on sexual function, one study lacked data for reporting and the other study found no difference in reducing sexual problems between milnacipran and placebo. Duloxetine and milnacipran did not improve PGI-C substantially (SMD, -0.27; 95% CI, -0.33 to -0.21; P<0.001), did not have a substantial effect on cognitive disturbances (SMD, -0.15; 95% CI, -0.21 to -0.10; P<0.001), and did not substantially raise the tender point pain threshold (SMD, -0.23; 95% CI, -0.35 to -0.12; P<0.001), compared to placebo. Dropout rates due to adverse events were significantly higher in duloxetine or milnacipran groups at 20.6% compared to 10.9% in the placebo groups (RR, 1.83; 95% CI, 1.53 to 2.18; NNH, 11; 95% CI, 9 to 13; P<0.001). There was no statistically significant difference in serious adverse events between either duloxetine or milnacipran and placebo (RR, 0.78; 95% CI, 0.55 to 1.12; P=0.15). The most frequently reported symptoms leading to stopping medication were nausea, dry mouth, constipation, headache, somnolence/dizziness and insomnia.
Hauser et al.[180] (abstract) (2010) Duloxetine, milnacipran or pregabalin vs placebo	MA (17 RCTs) Patients with fibromyalgia syndrome	N=7,739 Not noted (efficacy noted up to 6 months)	Primary: Symptom reduction (pain, fatigue, sleep disturbance, depressed mood, reduced HRQoL) and adverse events Secondary: Not reported	Primary: Duloxetine, milnacipran and pregabalin were superior to placebo for the outcomes noted except for the following: duloxetine for fatigue, milnacipran for sleep disturbance, and pregabalin for depressed mood were not more efficacious to placebo. There were no significant differences between duloxetine, milnacipran, or pregabalin for 30% pain relief per adjusted indirect comparisons. Differences in average symptom reduction were noted as follows: duloxetine and pregabalin were more efficacious to milnacipran in reduction of pain and sleep disturbances; duloxetine was more efficacious to milnacipran and pregabalin in reducing depressed mood; and milnacipran and pregabalin were more efficacious to duloxetine in reducing fatigue. Secondary: Not reported.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Generalized Anxiety Disorder (GAD)				
Rynn et al.[181] (2008) Duloxetine 60 or 120 mg/day vs placebo	DB, PC, RCT Adult patients with GAD	N=327 10 weeks	Primary: HAMA total score Secondary: Response rate (HAMA total score reduction ≥50% from baseline), CGI-I, SDS, safety	Primary: Duloxetine resulted in significantly greater improvement in HAMA total scores compared to placebo (P=0.023); mean decrease for duloxetine was 8.12 (36% improvement from baseline) compared to a mean decrease of 5.89 (25% improvement from baseline). Significant differences between the two treatments were observed at week two of treatment and remained significant at each subsequent visit (P≤0.001). Secondary: Response and sustained improvement rates were significantly greater for duloxetine-treated patients compared to placebo-treated patients (P<0.05). With duloxetine, the response rate was 40% and sustained improvement was 43.7% compared to 32.0 and 33.1% with placebo. There was no difference in the proportion of patients meeting the criteria for remission (28 vs 23%; P=0.27). Duloxetine resulted in a significantly greater functional improvement based on CGI-I scores compared to placebo (2.68 vs 2.97; P=0.04). Duloxetine-treated patients were significantly more improved compared to placebo-treated patients on SDS global functioning (P<0.01), and work, social, and family/home improvement scores (P<0.05). The rate of discontinuation due to an adverse event was significantly higher with duloxetine compared to placebo (P=0.002). The most commonly reported adverse events with duloxetine treatment were nausea, dizziness, and somnolence.
Koponen et al.[182] (2007) Duloxetine 60 or 120 mg/day vs placebo	DB, MC, PC, PG, RCT Patients ≥18 years of age with GAD of at least moderate severity	N=513 9 weeks	Primary: HAMA total score Secondary: SDS; HAMA psychic and somatic anxiety factor scores; HAMA response,	Primary: Both doses of duloxetine demonstrated significantly greater improvements in HAMA total scores compared to placebo (P≤0.001 for both). Both doses of duloxetine resulted in mean decreases in HAMA total score that were more than four points greater than the decreases achieved with placebo; the mean change represents a 49% decrease from baseline with duloxetine. Significant differences between duloxetine and placebo were observed as early as two weeks after treatment initiation, and remained significant at each subsequent visit.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			remission, and sustained improvement rates, safety	Secondary: Both doses of duloxetine demonstrated significantly greater functional improvements in SDS global and specific domain scores compared to placebo (P≤0.001). Both doses of duloxetine achieved a mean decrease of more than three points greater than the decreases achieved with placebo; the mean change represents a 47% improvement from baseline with duloxetine. Both doses of duloxetine demonstrated significantly greater improvements in HAMA psychic and somatic anxiety factor scores compared to placebo (P≤0.001 for all comparisons). Both doses of duloxetine resulted in significantly greater HAMA response (58, 56, and 31% with duloxetine 60 mg/day, duloxetine 120 mg/day, and placebo; P≤0.001 for both), remission (31, 38, and 19%; P≤0.01 for duloxetine 60 mg/day vs placebo and P≤0.001 for duloxetine 120 mg/day vs placebo), and sustained improvement rates (64, 67, and 43%; P≤0.001 for both) compared to placebo. There were no significant differences between the two doses of duloxetine on any of the efficacy outcome measures. Approximately 20% of patients receiving duloxetine had their dose decreased during the first two weeks of acute treatment. The rate of study discontinuation due to an adverse event was 11.3, 15.3, and 2.3% with duloxetine 60 mg/day, duloxetine 120 mg/day, and placebo (P≤0.001). Overall, nausea was the most frequent adverse event, which resulted in study discontinuation for 6.0 and 2.4% of duloxetine 60- and 120 mg/day-treated patients.
Alaka et al.[183] (2014) Duloxetine 30 to 120 mg/day vs	DB, MC, PC, RCT Patients ≥65 years of age with GAD with at least moderately severe symptoms	N=291 10 weeks	Primary: HAMA total score Secondary: SDS, adverse events	Primary: Patients treated with duloxetine versus placebo had significantly greater baseline-to-endpoint improvement on the HAMA total score (−15.9 vs −11.7; P<0.001). Significance between treatment group differences began as early as week four and continued to study end at week 10. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				Duloxetine demonstrated a greater effect than placebo on mean changes from baseline in SDS global scores (−8.6 vs −5.4; P<0.001). Treatment-emergent adverse events occurred in ≥5% of duloxetine-treated patients and twice the rate than with placebo including constipation (9 vs 4%; P=0.06), dry mouth (7 vs 1%; P=0.02), and somnolence (6 vs 2%; P=0.14).
Davidson et al.[184] (2008) Duloxetine vs placebo All patients received OL duloxetine for 26 weeks. Treatment responders (≥50% reduction in HAMA total score to ≤11 and "much"/"very much improved" ratings for the last 2 visits of the OL phase.	DB, PC, RCT Patients ≥18 years of age with moderate to severe GAD	N=533 (N=887 OL phase) 26 weeks	Primary: Time to relapse (increase in CGI-S rating ≥2 points from randomization to a score ≥4 while meeting criteria for GAD or by discontinuation due to lack of efficacy) Secondary: HAMA total score, HAMA psychic factor score, HAMA somatic factor scores, HADS-A, CGI-I, PGI-I, SDS, EQ-5D VAS, safety	Primary: Significantly more placebo-treated patients (41.8%) met relapse criteria compared to duloxetine-treated patients (13.7%; P≤0.001). Among patients who did relapse, duloxetine-treated patients had a longer time to relapse compared to patients who were switched to placebo (P≤0.001). Secondary: Patients who continued duloxetine maintained the improvements that were demonstrated during the OL phase. Patients who were switched to placebo significantly worsened on each of the secondary outcomes, including HAMA total score, HAMA psychic factor score, HAMA somatic factor scores, and HADS-A (P≤0.001 for all comparisons). The remission rate for duloxetine-treated patients at endpoint was 68.1 and 39.3% for placebo-treated patients (P≤0.001). Patients receiving placebo were rated as overall less improved by the CGI-I and PGI-I mean endpoint scores compared to patients receiving duloxetine (P≤0.001 for both). Patients treated with placebo also had worsening of their role functioning in all SDS domains of work/school, social life, and family/home management compared to patients who continued with duloxetine (P≤0.001). By endpoint, mean SDS global functioning impairment score with placebo had significantly increased into the range indicating mild to moderate impairment (P≤0.001). The switch to placebo was also associated with decreased life satisfaction and poorer perceived health, as measured by changes in EQ-5D VAS scores (P≤0.001 for all comparisons) compared to patients who continued

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				duloxetine. During the OL phase, 15 treatment-emergent adverse events occurred at a frequency of ≥5%: nausea (28.3%), headache (18.7%), dry mouth (14.3%), diarrhea (14.2%), dizziness (13.4%), constipation (12.5%), fatigue (11.5%), hyperhidrosis (10.0%), insomnia (9.8%), somnolence (8.2%), decreased appetite (6.1%), upper respiratory tract infection (5.5%), decreased libido (5.4%), vomiting (5.4%), and nasopharyngitis (5.0%). Most adverse events were mild to moderate in severity. During the DB, continuation phase patients experienced discontinuation-emergent adverse events as the study medication was being withdrawn. Compared to patients receiving duloxetine, dizziness was the only adverse event to occur significantly more often with patients receiving placebo (9.9 vs 3.7%; P≤0.05). No significant increases in pulse rate, DBP, or SBP were observed in duloxetine-treated patients compared to placebo-treated patients. Most events were mild to moderate in severity. Discontinuation from study due to adverse events occurred in four and two patients receiving duloxetine and placebo.
Hartford et al.[185] (2007) Duloxetine 60 to 120 mg/day vs venlafaxine ER 75 to 225 mg/day vs placebo	DB, MC, PC, RCT Outpatients ≥18 years of age with GAD	N=487 10 weeks	Primary: HAMA total score Secondary: HAMA psychic anxiety factor score, somatic anxiety factor score, mood item, and tension item; HADS anxiety and depression subscales scores; CGI-I, PGI-I; SDS	Primary: Patients receiving duloxetine or venlafaxine ER experienced greater improvements in anxiety symptom severity (as measured by HAMA) compared to patients receiving placebo (duloxetine; P=0.007 and venlafaxine ER; P<0.001). The mean decrease in the HAMA total scores was 11.8 for duloxetine and 12.4 for venlafaxine ER compared to 9.2 for placebo. Secondary: Patients treated with duloxetine and venlafaxine ER demonstrated greater improvements in HAMA psychic anxiety factor score, HAMA anxious mood, HAMA tension, and HADS anxiety and depression subscales compared to patients treated with placebo (P<0.01 for all comparisons). Patients treated with both duloxetine and venlafaxine ER had greater improvement ratings at endpoint on the CGI-I and PGI-I compared to patients treated with placebo (P<0.01 for all comparisons).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Treatment response was seen in 47% of patients receiving duloxetine, 54% of patients receiving venlafaxine ER, and 37% of patients receiving placebo (P<0.001 for venlafaxine ER vs placebo). Using the CGI-I endpoint score, the percentage of responders was greater for duloxetine (55.7%; P=0.007) and venlafaxine ER (60.4%; P<0.001) compared to placebo (41.8%). More venlafaxine ER-treated patients met remission criteria (30%) than placebo-treated patients (19%; P<0.05). The difference was not significant for duloxetine compared to placebo (23%; P value not significant). Sustained improvement rates were greater with duloxetine (55%) and venlafaxine ER (54%) compared to placebo (39%; P<0.01). Duloxetine and venlafaxine ER-treated patients experienced greater improvements in their functioning (SDS global improvement score) from baseline to endpoint compared to placebo (duloxetine, -8.03; venlafaxine ER, -7.97; placebo,-5.42; P<0.01).
Nicolini et al.[186] (2009) Duloxetine 20 mg/day vs duloxetine 60 to 120 mg/day vs venlafaxine ER 75 to 225 mg/day vs	DB, MC, PC, RCT Outpatients ≥18 years of age with GAD	N=581 10 weeks	Primary: HAMA total score Secondary: HAMA psychic and somatic factor scores, SDS, HAMA, CGI-I, PGI-I	Primary: For the HAMA total score, all three treatment groups demonstrated significant improvements from baseline compared to treatment with placebo (duloxetine 20 mg/day, -14.7 [P≤0.01]; duloxetine 60 to 120 mg/day, -15.3 [P≤0.001]; venlafaxine ER, -15.5 [P≤0.001]; placebo -11.6). Secondary: For the HAMA psychic factor scores, all three treatment groups demonstrated significant improvements from baseline compared to treatment with placebo (duloxetine 20 mg/day, -8.1 [P≤0.01]; duloxetine 60 to 120 mg/day, -8.7 [P≤0.001]; venlafaxine ER, -8.6 [P≤0.001]; placebo -6.0). For the HAMA somatic factor score, all three treatments led to improvements from baseline compared to placebo (duloxetine 20 mg/day, -6.6 [P=0.07]; duloxetine 60 to 120 mg/day, -6.6 [P≤0.05]; venlafaxine ER, -7.0 [P≤0.01]; placebo -5.5).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				Response rates were 60% for duloxetine 20 mg/day (P<0.01), 65% for duloxetine 60 to 120 mg/day (P<0.001), 61% for venlafaxine ER (P<0.001), and 42% for placebo. Remission rates were 42% for duloxetine 20 mg/day, 44% for duloxetine 60 to 120 mg/day, 44% for venlafaxine ER, and 20% for placebo (P<0.001 for each comparisons vs placebo). Overall improvement ratings at endpoint were greater for duloxetine-treated patients (20 or 60 to120 mg/day) and venlafaxine ER-treated patients compared to placebo-treated patients by the CGI-I scores (P<0.001 for all comparisons). All three treatments demonstrated significant improvement on the mean HADS anxiety subscale scores compared to placebo (duloxetine 20 mg/day, -7.0 points; duloxetine 60 to 120 mg/day, -7.7 points; venlafaxine ER, -6.9 points; placebo, -4.9 points; P<0.001 for all comparisons). All three treatments demonstrated significant improvement on the mean HADS depression subscale score compared to placebo (duloxetine 20 mg/day, -3.3 points; duloxetine 60 to 120 mg/day, -3.5 points; venlafaxine ER, -3.6 points; placebo, -1.9 points; P<0.001 for all comparisons). For the SDS global functioning improvement score, all three treatment groups demonstrated significant improvements from baseline compared to treatment with placebo (duloxetine 20 mg/day group, -8.5 [P<0.05]; duloxetine 60 to 120 mg/day, -8.9 [P<0.01]; venlafaxine ER, -9.1 [P<0.001]; placebo, -6.2).
Davidson et al.[187] (2005) Escitalopram 10 to 20 mg daily	MC, OL Patients who completed an 8-week, DB, PC, lead-in and were diagnosed with GAD were eligible to enter extension	N=526 24 weeks	Primary: CGI-I, HAMA core ≤7 Secondary: Safety	Primary: Ninety two percent of the patients were considered responders. Secondary: Adverse events led to study withdrawal in 9.9% of patents. The most frequent adverse events leading to study withdrawal were ejaculations disorder (1.6%), insomnia (1.3%), and nausea (1%). Serious adverse events were reported by 2.1% of patients, including one

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	trial			completed suicide.
Goodman et al.[188] (2005) Escitalopram 10 to 20 mg daily vs placebo	DB, MC, PC Patients 18 to 80 years of age with DSM-IV defined GAD	N=850 8 weeks	Primary: HAMA Secondary: CGI-S, CGI-I	Primary: Escitalopram significantly improved mean HAMA total scores (the primary efficacy measure) relative to placebo with the mean change from baseline to week eight in HAMA total score –10.1±0.3 for escitalopram and –7.6±0.3 for placebo (P<0.001). Secondary: Escitalopram led to statistically significant improvements compared to placebo in both HAMA subscales: psychic anxiety (–5.8+0.2 vs –3.9±0.2; P<0.001; and somatic anxiety (–4.3±0.2 vs –3.7±0.2; P=0.02). At endpoint, 47.5% of escitalopram-treated patients and 28.6% of placebo-treated patients were responders (P<0.001), and 26.4% of escitalopram-treated patients and 14.1% of placebo-treated patients were remitters (P<0.001). CGI-I response rates at endpoint were 52% for escitalopram and 37% for placebo (P<0.001).
Bielski et al.[189] (2005) Escitalopram 10 to 20 mg/day vs paroxetine 20 to 50 mg/day	DB, RCT Patients with GAD	N=121 24 weeks	Primary: Mean change from baseline in the HAMA scores at week 24, treatment-emergent adverse effects Secondary; Not reported	Primary: After 24 weeks of treatment, patients receiving escitalopram had significantly greater improvement in the HAMA scores compared to the paroxetine group (–15.3 vs –13.3; P=0.13). Significantly fewer patients withdrew from escitalopram than paroxetine treatment due to adverse events (6.6 vs 22.6%; P=0.02). Significantly more patients on paroxetine than on escitalopram experienced treatment-related adverse events (88.7 vs 77.0%). The following adverse events were noted to occur more frequently in the paroxetine group compared to the escitalopram-treated patients: insomnia (25.8 vs 14.8%), constipation (14.5% vs 1.6%), ejaculation disorder (30.0 vs 14.8%), anorgasmia (26.2 vs 5.9%), and decreased libido (22.6 vs 4.9%). In contrast, diarrhea and upper respiratory tract infection were reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				more frequently with escitalopram than paroxetine (21.3 vs 8.1%, and 14.8 vs 4.8%, respectively). Secondary; Not reported
Bose et al.[190] (2008) Escitalopram 10 to 20 mg/day vs venlafaxine ER 75 to 225 mg/day vs placebo	DB, PC, RCT Outpatients 18 to 65 years of age with GAD	N=404 8 weeks	Primary: Change from baseline to week eight in the HAMA total score Secondary: HAMA psychic anxiety subscale, CGI-I, CGI-S, VAS, HADS QOL, SDS	Primary: The mean change in HAMA total score (LOCF) for escitalopram and venlafaxine ER vs placebo was -1.52 (P=0.09) and -2.27 (P=0.01), respectively at week eight. The mean change in HAMA total score for escitalopram and venlafaxine ER vs placebo was -1.92 (P=0.033) and -3.02 (P=0.001), respectively at week eight. Secondary: Neither escitalopram nor venlafaxine produced greater HAMA response or remission than placebo (response: 52.8 and 52.0% for escitalopram and venlafaxine, respectively vs 42.2% for placebo; remission: 31.2% for both escitalopram and venlafaxine vs 23.7% for placebo; P>0.05 vs placebo, LOCF). Both escitalopram and venlafaxine had significantly higher CGI-I response rates than the placebo (escitalopram 60.0%, venlafaxine 65.6%, placebo 45.9%, P<0.05, LOCF). Both groups had higher CGI-S and HADS response rates compared to placebo. There was no significant difference in VAS, QOL or SDS for escitalopram compared to placebo (LOCF). There was no significant difference in VAS or QOL for venlafaxine compared to placebo (LOCF).
Ball et al.[191] (2005) Paroxetine 10 to 40 mg daily vs sertraline 25 to 100 mg daily	DB, FD, PG Patients with GAD	N=55 8 weeks	Primary: HAMA scores as well as responder and remission rates based on the CGI scale Secondary: Improvement in IU-GAM	Primary: Both sertraline and paroxetine groups displayed significant reductions in HAMA scores from baseline to end of treatment (P<0.001). The mean percent reduction in HAMA scores was 57.3% for the paroxetine group and 55.9% for the sertraline group. The percent of treatment responders was 68% in the paroxetine group and 61% in the sertraline group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Both sertraline and paroxetine groups displayed significant reductions in IU-GAMS scores from baseline to end of treatment (P<0.001). With treatment response defined as a reduction of greater than 50% in IU-GAMS scores from baseline to posttreatment, 40% of the paroxetine group responded compared to 25% of the sertraline group.
Dahl et al.[192] (2005) Sertraline 50 to 150 mg daily vs placebo	MC, RCT Outpatients with GAD	N=373 12 weeks	Primary: Change from baseline to endpoint in HAMA total score of the ITT population Secondary: CGI-S, CGI-I, MADRS, Q-LES-Q	Primary: Sertraline treatment was associated with significant improvement (P<0.001) in the HAMA psychic anxiety factor. Significant separation from placebo in primary endpoint was significant by week 4 for sertraline (52%) compared to placebo (34%; P=0.001). Clinically meaningful improvement (≥30% reduction in psychic symptom severity) was achieved by week four in the majority of patients (P=0001). Secondary: Global improvement was modestly but consistently better correlated with improvement in psychic anxiety. The degree of correlation was similar, regardless of study treatment. QOL was significantly improved in the sertraline group compared to placebo with improvement seen in 51% of patients on sertraline compared to 35% on placebo (P<0.01).
Schmitt et al.[193] (2005) Venlafaxine, paroxetine, imipramine, trazodone, diazepam, sertraline	MA RCTs evaluating antidepressants in GAD	N=2,238 8 to 28 weeks	Primary: Absence of treatment response (defined as absence of sufficient symptoms to meet diagnostic criteria for GAD) Secondary: Acceptability of	Primary: Antidepressants (imipramine, venlafaxine, and paroxetine) were found to be more effective when compared to placebo in treating GAD. The calculated NNT for antidepressants as a group in GAD was 5.15. Considering all trials, the pooled RR for nontreatment response was 0.70 (95% CI, 0.62 to 0.79), favoring antidepressant treatment. The calculated NNT was 5.5 (95% CI, 4.1 to 8.4). For imipramine the calculated RR was 0.67 (95% CI, 0.50 to 0.91) and the NNT was 4.0 (95% CI, 2.4 to 13.7).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			the treatment as measured by the number of people dropping out during the trial	For venlafaxine the calculated RR for nontreatment response was 0.68 (95% CI, 0.46 to 0.99), and the calculated NNT was 5.00 (95% CI, 3.58 to 8.62). For paroxetine the calculated RR was 0.72 (95% CI, 0.56 to 0.92), and the calculated NNT was 6.72 (95% CI, 3.90 to 24.70). For paroxetine vs imipramine the calculated RR was 1.73 (95% CI, 0.31 to 9.57). Secondary: No significant differences were found between antidepressants and placebo with regard to drop out rate. The RR for dropout for any antidepressant was 0.95 (95% CI, 0.84 to 1.09). Similarly, when individual antidepressants were considered, no differences were found between individual treatments and the placebo group: imipramine: RR, 0.71 (95% CI, 0.41 to 1.24); venlafaxine: RR, 0.86 (95% CI, 0.72 to 1.02); sertraline: RR, 0.45 (95% CI, 0.03 to 5.84); paroxetine: RR, 1.15 (95% CI, 0.74 to 1.78); and paroxetine vs imipramine: RR, 1.62 (95% CI, 0.58 to 4.48).
Insomnia				
Roth et al.[194] (2007) Doxepin 1 mg vs doxepin 3 mg vs doxepin 6 mg	DB, PC, RCT, XO Patients 18 to 64 years of age with chronic primary insomnia	N=67 2 nights	Primary: WTDS Secondary: WASO, sleep efficiency, TST, LPS, number of awakenings after sleep onset, WTAS, and sleep architecture	Primary: WTDS was significantly reduced with doxepin 3 mg (P<0.0001) and doxepin 6 mg (P<0.0001) compared to placebo. There was no significant difference in WTDS with doxepin 1 mg compared to placebo (P=0.0918). Secondary: WASO was significantly decreased with doxepin (all doses) compared to placebo (1 mg; P=0.0090, 3 mg; P<0.0001, and 6 mg; P<0.0001). There were no significant differences in NAASO with doxepin (all doses) compared to placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				There was no significant difference in LPS with doxepin (all doses) compared to placebo. TST and overall sleep efficiency were significantly increased with doxepin (all doses) compared to placebo (all P≤ 0.0005). WTAS was significantly reduced with doxepin 6 mg compared to placebo (P=0.0088). There was no significantly difference with doxepin 1 mg (P=0.1421) or doxepin 3 mg (P=0.0697) compared to placebo. WASO was not significantly decreased with doxepin 1 mg (56.4; P=0.8915), doxepin 3 mg (49.4; P=0.8789), or doxepin 6 mg (45.1; P=0.1168) compared to placebo (54.4). Number of awakenings after sleep onsest was significantly decreased with doxepin 3 mg (2.8; P=0.0207) compared to placebo (3.2). LSO was significantly decreased with doxepin 6 mg (43.0; P=0.0244), but not significantly decreased with doxepin 1 mg (46.5; P=0.1944) or doxepin 3 mg (45.3; P=0.0905) compared to placebo (49.6). TST was significantly increased with doxepin 6 mg (380.7; P=0.0190), but not with doxepin 1 mg (364.8; P=0.9992) or doxepin 3 mg (380.0; P=0.0562) compared to placebo (364.2). Sleep quality was significantly improved with doxepin 6 mg (0.8; P=0.0071) compared to placebo (0.4). There were no significant differences among doxepin doses for percentage or min of Stage 1 sleep. There was a significant increase in percentage of Stage 2 sleep (3 mg, 57.8%; P=0.0003, 6 mg, 58.7%; P<0.0001; placebo, 54.7%). There was a significant increase in min of Stage 2 sleep (1 mg, 228.5 min; P=0.0008, 3 mg, 240.4 min; P<0.0001, 6 mg, 245.8 min; P<0.0001; placebo, 212.9 min). There was a significant decrease in percentage of REM sleep (3 mg, 18.3%, P=0.0046; 6 mg, 17.8%, P=0.0002; placebo, 20.0%). The number of min spent in REM sleep was not significantly different among the doxepin doses. There were no

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				significant differences among doxepin doses for either percentage or min of Stage 3/4 sleep. There were no significant differences among the treatment groups on any of the measures assessing either psychomotor function (DSST) or next-day alertness (VAS). Adverse events were comparable to placebo, with no reported anticholinergic effects, no memory impairment, and no significant hangover/next-day residual effects.
Scharf et al.[195] (2008) Doxepin 1 mg vs doxepin 3 mg vs doxepin 6 mg vs placebo	DB, PC, RCT, XO Elderly patients with primary insomnia	N=76 2 nights	Primary: WTDS Secondary: WASO, TST, sleep efficiency, latency to sleep onset	Primary: Compared to placebo, treatment with doxepin (all doses) led to significant improvements WTDS (P<0.0001). Secondary: Compared to placebo, treatment with doxepin (all doses) led to significant improvements in WASO (P<0.0001). Compared to placebo, treatment with doxepin (all doses) led to significant improvements in TST (P<0.0001). Compared to placebo, treatment with doxepin (all doses) led to significant improvements in overall sleep efficiency (P<0.0001). Sleep efficiency was significantly improved during all thirds of the night with doxepin 3 and 6 mg compared to placebo (P<0.05). Treatment with doxepin 6 mg led to significant improvements in latency to sleep onset compared to placebo (P=0.0181). The incidence of adverse events with doxepin was comparable to placebo.
Krystal et al.[196] (2010) Doxepin 1 mg vs	DB, PC, RCT Patients ≥65 years of age with primary insomnia	N=240 12 weeks	Primary: WASO on night one Secondary: WASO at other	Primary: WASO was significantly improved on night one for doxepin 3 mg (P<0.0001) and doxepin 1 mg (P=0.0053) compared to placebo. Secondary: WASO was significantly improved on night 29 (P=0.0005) night 85

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
doxepin 3 mg vs placebo			time points, LPS, number of awakenings after sleep onset, TST, sleep efficiency, and WTAS, CGI-S, CGI-I	(P<0.0001) for doxepin 3 mg, and on night 85 (P=0.0330) for doxepin 1 mg compared to placebo. Mean change from night one to 85 were: placebo, 0.4 (P=0.96); doxepin 1 mg, 3.0 (P=0.57); doxepin 3 mg, 0.9 (P=0.62). TST and overall sleep efficiency were significantly improved on night one (P<0.0001), night 29 (P=0.0161), and night 85 (P=0.0007) for doxepin 3 mg, and on night one (P=0.0119) and night 85 (P=0.0257) for doxepin 1 mg compared to placebo. There was a significant improvement in sTST at weeks one (P=0.0043), four (P=0.0035), and 12 (P=0.0001) for doxepin 3 mg, and at weeks four (P=0.0343) and 12 (P=0.0027) for doxepin 1 mg compared to placebo. Sleep efficiency in the last quarter of the night was significantly increased on night one1 (P<0.0001), night 29 (P=0.0004), and night 85 (P=0.0014) for doxepin 3 mg compared to placebo. For doxepin 1 mg, sleep efficiency in the last quarter of the night was significantly increased on night one (P=0.0011) compared to placebo. Sleep efficiency in hour eight was significantly increased on night one (P<0.0001) and night 29 (P=0.0029) for doxepin 3 mg compared to placebo. For doxepin 1 mg, sleep efficiency in hour eight was significantly increased on night one compared to placebo (P=0.0211). WTAS was significantly decreased on N85 (P=0.0284) for doxepin 3 mg compared to placebo. LPS was not significantly reduced at any time point when compared to placebo. Sleep quality was significantly increased at weeks one (P=0.0039), four (P=0.0049), and 12 (P=0.0100) for doxepin 3 mg, and at weeks four (P=0.0464) and 12 (P=0.0107) for doxepin 1 mg compared to placebo. There was significant improvement after two weeks (P=0.0047), after four weeks (P=0.0356), and after 12 weeks (P=0.0005) on the CGI-S scale

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				score for doxepin 3 mg, and after 12 weeks (P=0.0101) for doxepin 1 mg compared to placebo. There was significant improvement after two weeks (P=0.0060), after four weeks (P=0.0334), and after 12 weeks (P=0.0008) on the CGI-I scale score for doxepin 3 mg, and after 12 weeks (P=0.0082) for doxepin 1 mg compared to placebo. Daytime function ratings were significantly improved on night one for doxepin 3 mg (P=0.0282) and 1 mg (P=0.0192) and on night 85 for doxepin 3 mg (P=0.0028) and 1 mg (P=0.0102) compared to placebo. Sleep stages were preserved compared to placebo, with no apparent evidence of suppression of REM duration. There were no significant differences between placebo and either dose of doxepin on any of the measures assessing objective psychomotor function (DSST) or subjective next-day alertness (VAS) or drowsiness at any time point during the trial. Rates of treatment-emergent adverse events were lower in patients treated with doxepin 1 mg (40%) and doxepin 3 mg (38%) compared to placebo (52%). The most common adverse events were headache and somnolence.
Krystal et al.[197] (2011) Doxepin 3 mg vs doxepin 6 mg vs placebo	DB, PC, RCT Patients 18 to 64 years of age with primary insomnia	N=229 35 days	Primary: WASO on night one Secondary: WASO at other time points, LPS, number of awakenings after sleep onset, TST, sleep efficiency, and	Primary: WASO was significantly improved on night one for doxepin 3 mg (P<0.0001) and doxepin 6 mg (P<0.0001) compared to placebo. Secondary: WASO was significantly improved on night 15 (P=0.0053) and night 29 (P=0.0299) for doxepin 3 mg, and on night 15 (P=0.0023) and night 29 (P=0.0012) for doxepin 6 mg compared to placebo. There were no significant differences between doxepin groups on WASO. TST and sleep efficiency were significantly improved on night one (P<0.0001) and night 29 (P=0.0262) for doxepin 3 mg, and on night one (P<0.0001), night 15 (P=0.0157), and night 29 (P=0.0003) for doxepin 6 mg compared to placebo. There were no significant differences in number of awakenings after sleep

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				onset for any dose at any time point. Sleep efficiency in the last quarter of the night was significantly improved on night one (P=0.0008) and night 15 (P=0.0220) for doxepin 3 mg, and on night one (P<0.0001), night 15 (P=0.0239), and night 29 (P=0.0029) for doxepin 6 mg compared to placebo. Sleep efficiency in hour eight was significantly improved on night one (P<0.0001) and night 29 (P=0.0315) for doxepin 3 mg, and on night one (P<0.0001), night 15 (P=0.0162), and night 29 (P=0.0020) for doxepin 6 mg compared placebo. WTAS was significantly improved on night one (P=0.0001) for doxepin 3 mg, and also on night one (P=0.0016) for doxepin 6 mg compared to placebo. LPS was significantly improved on night one (P=0.0047) for doxepin 3 mg, and on night one (P=0.0007) for doxepin 6 mg compared to placebo. There were significant improvements in patient-reported WASO for both doses of doxepin on night one compared to placebo (3 mg; P=0.0003, 6 mg; P=0.0004). There were significant improvements in patient-reported TST for both doses of doxepin at night one compared to placebo (3 mg; P=0.0088, 6 mg; P=0.0135). Sleep quality was significantly improved for both doses of doxepin at night one compared to placebo (3 mg; P=0.0068, 6 mg; P<0.0001). Subjective LSO was significantly improved on night one with doxepin 6 mg compared to placebo (P=0.0492). There was no evidence of tolerance to the sleep maintenance effects. There is evidence to suggest the development of tolerance to the sleep onset effects. There were increases in the duration of stage two sleep for both doses of doxepin, which were significant at most time points. There were no significant differences between the two doxepin groups vs placebo in minutes of stage one sleep, stage 3/4 sleep, or REM sleep.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Across two nights, rebound insomnia was experienced by 1% of the placebo group, 1% of the doxepin 3 mg group, and 4% of the doxepin 6 mg group.
Roth et al.[198] (2010) Doxepin 6 mg vs placebo	DB, PC, MC, RCT Healthy adults 25 to 55 years of age with normal sleep habits	N=565 Single dose	Primary: LPS Secondary: WASO, TST, WTDS, WTAS, sleep efficiency, and number of awakenings after sleep onset, sleep architecture measurements, DSST, symbol copying test, and VAS	Primary: LPS was significantly lower for doxepin compared to placebo (21 vs 34 minutes, respectively; P<0.0001). Secondary: WASO was significantly lower for doxepin compared to placebo (38 vs 78 minutes, respectively; P<0.0001). WTDS was significantly lower for doxepin compared to placebo (P value not reported). There were no significant differences among the treatment groups in number of awakenings after sleep onset (P value not reported). TST was significantly higher for doxepin compared to placebo (425.2 vs 374.1 minutes, respectively; P<0.0001). Overall sleep efficiency was significantly higher for doxepin compared to placebo (P value not reported). WTAS, sleep efficiency in the final quarter of the night, and sleep efficiency at hours seven and eight were significantly improved for doxepin compared to placebo (all P<0.0001). Doxepin had significantly higher sleep efficiency at each hour compared to placebo (P<0.0001). Subject- reported LSO was significantly lower for doxepin compared to placebo. WASO and sNAASO were significantly lower for doxepin compared to placebo. TST was significantly higher for doxepin compared to placebo. Sleep quality was significantly improved for doxepin compared to placebo. There were no significant differences between doxepin and placebo in the mean change in DSST score from predose to postdose. There were no

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				significant differences in sleepiness with doxepin compared to placebo (symbol copying test; P=0.0228, VAS; P=0.0241). The incidence of adverse events with doxepin was comparable to placebo.
Musculoskeletal Pain				
Skljarevski et al.[199] (2010) Duloxetine 60 mg QD vs placebo	DB, PC, RCT Patients ≥18 years of age with chronic low back pain	N=401 12 weeks	Primary: Reduction of pain severity (BPI 24-hour average pain rating) Secondary: PGI-I, RMDQ-24, CGI-S, BPI-S, BPI-I, response rates, health outcomes (EQ-5D and SF-36)	Primary: There was a significantly greater reduction in the BPI 24-hour average pain in patients treated with duloxetine compared to patients treated with placebo (P≤0.001). Secondary: Duloxetine-treated patients reported significantly greater improvements in PGI-I scores compared to placebo-treated patients (2.88 vs 3.19, respectively; P=0.011). There was no significant difference in RMDQ-24 scores with duloxetine compared to placebo (-2.69 vs -2.22, respectively; P=0.255). There was no significant difference in CGI-S among the treatment groups. There was a significant reduction in all four domains of BPI-S (average pain, worst pain, least pain, and pain right now) pain scores reported with duloxetine compared to placebo. All seven domains of the BPI-I (general activity, mood, walking ability, normal work, relations with others, sleep, enjoyment of life) were significantly better with duloxetine compared to placebo. A greater percentage of patients receiving duloxetine reported ≥50% pain reduction compared to patients receiving placebo (P=0.006). There was no significant difference in the 30% pain response rates among the treatment groups. There were significant differences in changes on four of six mood states on the POMS-Brief Form, along with the total mood disturbance score, between the two treatment groups: tension-anxiety (P≤0.001), anger-hostility (P≤0.001), vigor-activity (P=0.003), confusion-bewilderment (P=0.006), and total mood disturbance (P≤0.001). Changes in depression-

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				dejection and fatigue-inertia states were not significant. The change in EQ-5D was significantly different between duloxetine and placebo with the United Kingdome index (P≤0.001) and United States index (P=0.002). In the SF-36 domains, the differences between duloxetine and placebo treatments were significant with regard to mental component summary (P=0.010), bodily pain (P=0.016), mental health transformed (P≤0.001), social functioning (P=0.030), and vitality transformed (P=0.022). There was no significant difference among the treatment groups in other domains. The WPAI questionnaire demonstrated a significant difference between the treatment groups with regard to activity impairment (P=0.007). There was no significant difference among the treatment groups in other domains. Significantly more patients in the duloxetine group (15.2%) than patients in the placebo group (5.4%) discontinued because of adverse events (P=0.002). Nausea and dry mouth were the most common treatment-emergent adverse events with rates significantly higher in duloxetine-treated patients.
Skljarevski et al.[200] (2010) Duloxetine 60 to 120 mg QD vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with chronic low back pain	N=236 13 weeks	Primary: Reduction of pain severity (BPI 24-hour average pain rating) Secondary: PGI-I, RMDQ-24, BPI-S, BPI-I, CGI-S, Athens Insomnia Scale response rates, health outcomes (EQ-5D and SF-36), WPAI	Primary: There was a significantly greater reduction in the BPI 24-hour average pain in patients treated with duloxetine compared to patients treated with placebo at all time points (-1.42 vs -0.78, respectively; P=0.016 at week four; -2.06 vs -1.17, respectively; P=0.001 at week seven; and -2.32 vs -1.50, respectively; P=0.004 at week 13). Secondary: Duloxetine-treated patients reported significantly greater improvements in PGI-I scores compared to placebo-treated patients at all time points (3.12 vs 3.51, respectively; P=0.007 at week four; 2.82 vs 3.32, respectively; P=0.001 at week seven; 2.59 vs 3.16, respectively; P=0.001 at week 13). There was a significant difference in RMDQ-24 scores at endpoint with duloxetine compared to placebo (-3.60 vs -1.93, respectively; P=0.009).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The mean changes in pain scores, including BPI-S (worst pain, least pain, and pain right now) items; BPI-I average pain; and weekly mean of the 24-hour average pain, night pain, and worst pain scores from patient diaries were significantly improved with duloxetine compared to placebo. There was no significant difference in the CGI-S and Athens Insomnia Scale scores among the treatment groups. There was no significant difference in response rates with duloxetine compared to placebo (30% response: 53.2 vs 40.0%, respectively; P=0.060 and 50% response: 38.5 vs 27.0%, respectively; P=0.087). The depression and anxiety scores were not significantly changed from baseline to endpoint. The improvement in BPI average pain was because of the direct analgesic effect (80.4%; P=0.012) of duloxetine treatment and not dependent on the improvement in mood (BDI-II total score, 19.2%) or anxiety (HADS-A, 0.3%) symptoms. The United Kingdome and United States indexes of EQ-5D did not change significantly in patients treated with duloxetine compared to patients treated with placebo. Among the eight subscales of SF-36 only bodily pain (P=0.038), general health (P=0.041), and vitality (P=0.040) were significantly improved with duloxetine compared to placebo. In the WPAI, work activity impairment was the only item that significantly (P=0.002) improved with duloxetine compared to placebo. Significantly more patients in the duloxetine group (13.9%) compared to the placebo group (5.8%) discontinued because of adverse events (P=0.047). The most common treatment-emergent adverse events in the duloxetine group included nausea, dry mouth, fatigue, diarrhea, hyperhidrosis, dizziness, and constipation.
Skljarevski et al.[201] (2010) Duloxetine 60 to 120 mg QD	ES Patients ≥18 years of age with chronic low back pain	N=181 41 weeks	Primary: Reduction of pain severity (BPI 24-hour average pain rating)	Primary: For patients who received duloxetine during the initial 13-week trial, pain reduction continued during the extension phase. The mean change in BPI average pain in the extension phase was -0.97 (P<0.001).

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			Secondary: Response rates, PGI-I, RMDQ-24, BPI-S, BPI-I, CGI-S, Athens Insomnia Scale response rates, health outcomes (EQ-5D and SF-36)	Secondary: The 30%, 50%, and sustained response rates were ~10% higher for patients who received duloxetine during the initial 13-week trial compared to those who received placebo. A total of 94.8% of PC phase duloxetine responders still met response criteria at the end of the 41-week extension phase. The BPI average pain, worst pain, least pain, pain right now, and average interference all showed significant within-group improvement for both treatment groups. Both treatment groups showed significant improvement on the RMDQ-24 measures, CGI-S measures, and most of the health outcome assessments. No significant change was observed in the BDI total score and HADS depression score. Duloxetine was well tolerated with no new safety findings reported.
Skljarevski et al.[202] (2009) Duloxetine 20, 60, or 120 mg/day vs placebo	DB, MC, PC, RCT Adult patients with non-radicular chronic low back pain	N=404 13 weeks	Primary: Weekly mean 24 hour average pain (duloxetine 60 mg/day vs placebo) Secondary: RMDQ-24, PGI-I, BPI, safety	Primary: Improvement in average weekly pain was significantly greater for duloxetine 60 and 120 mg/day doses beginning at week three, but the significance was lost at weeks 12 and 13, respectively. The mean change from baseline to endpoint in average weekly pain did not differ significantly from placebo for 60 mg/day (P=0.104) or any other duloxetine doses. Analysis of average weekly pain response rates (30% reduction from baseline to end-point) showed a significantly greater percentage of responders with duloxetine 120 mg/day (57.8%) compared to placebo (43.4%; P=0.033), but neither 20 (41.1%) or 60 mg/day (53.6%) differed significantly from placebo (P values not reported). There were no significant differences between any doses in 50% response rates. Secondary: Patients overall improvement (PGI-I) was greater for patients receiving duloxetine 60 mg/day, and improvement in physical functioning (RMDQ-24) was greater for patients receiving duloxetine 60 and/or 120 mg/day

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				compared to patients receiving placebo. Patients receiving duloxetine 60 mg/day also demonstrated significant improvement over patients receiving placebo on several measures of pain severity, interference of pain with activities, and sleep. Eight (1.98%) patients experienced at least one serious adverse event (three placebo-treated patients and one duloxetine 20- and 60 mg/day-treated patients, and three duloxetine 120 mg/day-treated patients). Duloxetine 120 mg/day was associated with a significantly higher proportion of treatment-emergent adverse events compare to placebo (P=0.038).
Chappell et al.[203] (2009) Duloxetine 60 to 120 mg QD vs placebo	DB, MC, PC, RCT Patients ≥40 years of age with osteoarthritis of the knee and pain for ≥14 days/month	N=231 13 weeks	Primary: Mean changes in the weekly mean 24-hour average pain score Secondary: Patients' perceived improvement as measured by PGI-I and on the change in patients' functioning as measured by the WOMAC physical functioning subscale, weekly mean of the 24-hour worst pain score, CGI-S, WOMAC pain and stiffness subscales, BPI-S and BPI-I, response to treatments, health outcomes, safety	Primary: Duloxetine was more effective than placebo on the primary efficacy measure (weekly mean 24-hour pain scores) beginning at week one and continuing through the treatment period (P<0.05). There was a significant reduction in the average pain score in the duloxetine group compared to the placebo group at each week. The mean change from baseline to endpoint in the 24-hour average pain score also showed a significant benefit for duloxetine over placebo (P=0.006). Analysis of the weekly 24-hour average pain score response rates (30% reduction in score from baseline to endpoint) showed a significant difference between duloxetine (59.3%) and placebo (44.5%; P=0.033). The 50% response rates revealed a similar pattern (duloxetine, 47.2%; placebo, 29.4%; P=0.006). Secondary: There was a significant improvement with duloxetine in most secondary endpoints compared to placebo. Mean changes in BDI-II and HADS-A did not differ significantly between treatment groups. For patients randomly re-assigned to duloxetine at week seven, there was a significant improvement in mean change in the weekly 24-hour average pain score in the duloxetine 120 mg/day group compared to the duloxetine 60 mg/day group (P=0.039). No significant differences were observed between the two duloxetine groups in the Mixed Model Repeated Measures analysis of the weekly 24-hour average pain score or the 30%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				and 50% response rates at endpoint. Adverse event rates did not differ significantly between treatment groups (49.5% for duloxetine and 40.8% for placebo). A total of 45.0% of patients reported ≥1 treatment-emergent adverse events.
Chappell et al.[204] (2010) Duloxetine 60 to 120 mg QD vs placebo	DB, MC, PC, RCT Patients ≥40 years of age with osteoarthritis of the knee and pain for ≥14 days/month	N=256 13 weeks	Primary: BPI 24-hour average pain rating Secondary: Weekly mean 24-hour average pain and worst pain rating, patients' perceived improvement as measured by PGI-I and on the change in patients' functioning as measured by the WOMAC physical functioning subscale, CGI-S, WOMAC pain and stiffness subscales, BPI-S and BPI-I, response to treatments, health outcomes, safety	Primary: There was a significant reduction in the BPI average pain rating with duloxetine compared to placebo at all time points (P≤0.001). The BPI average pain response rates (≥30% pain reduction from baseline to endpoint) were significantly higher with duloxetine (65.3%) compared to placebo (44.1%; P≤0.001). The 50% response rates of BPI average pain did not significantly differ between the treatment groups (duloxetine, 43.8%; placebo, 32.3%; P=0.068). Secondary: The least squares mean changes in the weekly mean 24-hour average pain rating was significantly reduced with duloxetine compared to placebo as early as at week two and remained significant at all time points. The weekly mean 24-hour worst pain ratings were significantly improved with duloxetine compared to placebo. Patients receiving duloxetine experienced greater improvements in many secondary endpoints compared to placebo, including CGI-S, BPI-S items, and BPI-I items (general activity and normal work). The other BPI-I items (mood, walking ability, relations with other people, sleep, enjoyment of life, and average interference) were not significantly different between the two treatment groups. No significant improvement in PGI-I was observed in the duloxetine group compared to the placebo group (P=0.164). The mean changes from baseline to endpoint were improved significantly for WOMAC total score (P=0.004) and physical functioning subscale (P=0.016) in patients treated with duloxetine compared to placebo. The other two WOMAC subscales (pain and stiffness) did not show significant improvement with duloxetine treatment.

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				Both the United Kingdome and the United States indexes of EQ-5D did not change significantly with either treatment. Physical component summary and three of the subscales of SF-36 were significantly improved with duloxetine compared to placebo. The other SF-36 items (mental component summary, general health, mental health, role-emotional, social functioning, and vitality) were not significantly improved with duloxetine compared to placebo. The frequency of nausea, constipation, and hyperhidrosis were significantly higher in the duloxetine group (P≤0.05). Significantly more duloxetine-treated patients discontinued therapy because of adverse events (P=0.002).
Frakes et al.[205] (2011) Duloxetine 60 to 120 mg QD vs placebo Patients were also required to take an NSAID and PPI.	DB, MC, PC, RCT Patients ≥40 years of age with osteoarthritis of the knee and pain for ≥14 days/month and who were using NSAIDs on most days of the week	N=524 10 weeks	Primary: Weekly mean of the daily average pain rating at week eight Secondary: Endpoint PGI-I, change in WOMAC physical function	Primary: Patients receiving duloxetine experienced significantly greater pain reduction at week eight than those receiving placebo. The estimated mean change was -2.46 for duloxetine compared to -1.55 for placebo (P<0.001). Duloxetine demonstrated greater improvement as early as week one (P<0.01), and at each subsequent week (P<0.001). Secondary: There was no significant difference in the use of acetaminophen as rescue medication for knee pain due to osteoarthritis (P=0.08). The mean PGI-I and the change in the WOMAC physical function scale were significantly different between the duloxetine and placebo groups (P<0.001 for each). Estimated mean improvement in diary-based night pain and worst pain ratings were significantly greater for duloxetine compared to placebo (P<0.001 for each). Duloxetine-treated patients showed greater reductions for each item on the pain and interference ratings on the BPI compared to placebo-treated patients (P<0.001 for each). Mean reductions for the total score and remaining subscale scores (pain and stiffness) of the WOMAC were significantly different (P<0.001 for

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				each). Treatment with duloxetine was associated with significantly more nausea, dry mouth, constipation, fatigue and decreased appetite than treatment with placebo (P<0.05). Discontinuation due to adverse events occurred more commonly in the duloxetine group than the placebo group (P=0.03).
Mazza et al.[206] (2010) Escitalopram 20 mg QD vs duloxetine 60 mg QD	RCT Adult patients with non-radicular chronic low back pain	N=85 13 weeks	Primary: Weekly mean of the 24-hour average pain ratings Secondary: CGI-S and the 36-item SF-36	Primary: The mean change in average weekly pain did not differ significantly between the escitalopram group and duloxetine group (P=0.15). The average weekly pain response rates (30% reduction from baseline to end point) showed no significant difference between the two groups (P=0.12). There were no significant differences between groups in 50% response rates. Secondary: Both escitalopram and duloxetine demonstrated significant improvement on CGI-S and SF-36. No patient experienced serious adverse events and the incidence of side effects did not differ significantly between treatment groups.
Obsessive-compulsive Disorder (OCD)				
Alaghband-Rad et al.[207] (2009) Fluoxetine 20 mg/day vs citalopram 20 mg/day	DB, RCT Children 8 to 17 years of age with OCD	N=29 6 weeks	Primary: CY-BOCS total score, CGI-OCD, adverse events Secondary; Not reported	Primary: After three weeks of treatment, obsessive-compulsive symptom severity for both groups decreased to a similar extent using the CY-BOCS total scores. Scores decreased for both obsessions and compulsions. CGI scores did not change significantly from baseline in either group. After six weeks of treatment, obsessive-compulsive symptom severity for both groups decreased to a similar extent using the CY-BOCS total scores. Scores decreased for both obsessions and compulsions (P<0.01). CGI scores did not change significantly from baseline in either group (P=NS). The most frequently reported adverse events were headache (3.4%), tremor (6.8%), insomnia (3.4%), hypomanic episode (3.4%) for fluoxetine. Headache (3.4%), hypomanic episode (3.4%) for citalopram.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary; Not reported
Koran et al.[208] (1996) Fluvoxamine 100 to 300 mg/day vs clomipramine 100 to 250 mg/day	DB, RCT Patients with OCD	N=79 10 weeks	Primary: Y-BOCS, CGI, HAM-D Secondary; Not reported	Primary: The mean reduction in Y-BOCS for the fluvoxamine group was 30.2% and for the clomipramine group 30.0% (P=NS). At the end of treatment, 56% of fluvoxamine patients were classified as responders (≥25% decrease in Y-BOCS score), compared to 54% of clomipramine patients. Both groups showed steady improvement throughout the study; no statistically significant differences were observed between the groups for any efficacy variable at any time. A similar percentage of patients in both groups withdrew because of adverse events. No serious adverse events related to drug occurred with either drug. Insomnia, nervousness, and dyspepsia were more statistically frequent with fluvoxamine; dry mouth and postural hypotension were more frequent with clomipramine. Secondary; Not reported
Mundo et al.[209] (1997) Fluvoxamine 100 to 300 mg daily vs paroxetine 20 to 60 mg daily vs citalopram 20 to 60 mg daily	RCT Patients with OCD	N=30 10 weeks	Primary: NIMH-OC, Y-BOCS, HAM-D, CGI Secondary; Not reported	Primary: No significant differences were noted between the treatment groups. Results performed on NIMH-OC and Y-BOCS obsessions, compulsions, and total scores did not show any significant effect of the variable group (treatment) but only a significant effect of time (NIMH-OC: P=0.000; Y-BOCS obsessions: P=0.000; Y-BOCS compulsions: P=0.000; Y-BOCS total: P=0.000) and no significant effect of their interaction. Similar results were derived from the ANOVA with repeated measures performed on HAM-D total scores (time effect: P=0.000). Secondary; Not reported
Denys et al.[210] (2003)	DB, PG, RCT	N=150	Primary: Y-BOCS	Primary: Both paroxetine and venlafaxine were efficacious with a mean decrease of

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Paroxetine 15 to 60 mg daily vs venlafaxine 75 to 300 mg daily	Patients with OCD	12 weeks	Secondary; Not reported	7.8 and 7.2 points, respectively, at the end of the study, as measured by the reduction in total Y-BOCS scores. Analyses of covariance, adjusted for the mean baseline Y-BOCS scores, revealed a highly significant treatment effect over the 12-week trial period for both treatment groups (P=0.001). A significant decrease in total Y-BOCS scores from baseline was found in the venlafaxine group at week three (P=0.008), whereas in the paroxetine group, a significant decrease in total Y-BOCS scores from baseline was evident as of the fifth week of treatment (P=0.018). Significant decreases in total Y-BOCS scores for both medications were observed until week 10, whereas from week 10 till week 12, no further decrease was detected. Secondary; Not reported
Panic Disorder				
Stahl et al.[211] (2003) Citalopram vs escitalopram vs placebo	DB, PC, RCT Patients 18 to 80 years of age diagnosed with panic disorder	N=366 10 weeks	Primary: Frequency of panic attacks at week 10 assessed by the Modified Sheehan Panic and Anticipatory Anxiety Scale Secondary; Not reported	Primary: A significant decrease in the frequency of panic attacks was observed in both the escitalopram and citalopram groups compared to placebo (P<0.05). Secondary; Not reported
Dannon et al.[212] (2007) Citalopram 10 to 40 mg/day vs	OL Adult patients with panic disorder or panic disorder with agoraphobia	N=200 12 months	Primary: Panic Self-Questionnaire, CGI-I Secondary; Not reported	Primary: Following 52 weeks of therapy, the clinical improvements observed were similar between the groups and there were no significant differences in treatment response as measured using the Panic Self-Questionnaire (P=0.13), VAS (P=0.43), or CGI-I (P=NS). There were no significant differences between the panic disorder and the panic disorder with agoraphobia groups in treatment response as measured

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fluoxetine 10 to 40 mg/day vs fluvoxamine 50 to 200 mg/day vs paroxetine 10 to 40 mg/day				at the 12 monthly follow-up visits. Secondary; Not reported
Rampello et al.[213] (2006) Escitalopram vs citalopram	OL Elderly patients diagnosed with panic attacks	N=40 8 weeks	Primary: Weekly rate of panic attacks Secondary: Change from base-line in HAMA, HAMD and Cooper Disability Scale scores	Primary: No significant difference was observed at eight weeks in the weekly rate of panic attacks. Secondary: No significant differences were observed at eight weeks in the HAMA or HAMD, or in the Cooper Disability Scale scores. A significant improvement from baseline in outcome measures was observed in the escitalopram at two weeks and in the citalopram group at four weeks (P<0.001 and P<0.01 respectively).
Van Ameringen et al.[214] (2007) Nefazodone 300 to 600 mg daily vs placebo	DB, MC, PC, RCT Patients 18 to 65 years of age with GSP diagnosis confirmed by DSM-IV for more than 1 year	N=105 14 weeks	Primary: Percent of responders at endpoint Secondary: Not reported	Primary: At endpoint, 31.4% of nefazodone-treated patients and 23.5% of placebo-treated patients were considered responders (P=0.38). Secondary: Not reported
Sheehan et al.[215] (2005) Paroxetine CR 25	DB, MC, PC, RCT Patients with DSM-IV panic disorder	N=889 10weeks	Primary: Patients free of panic attacks in the two weeks prior to	Primary: Paroxetine CR was statistically more effective compared to placebo on the primary outcome measure: 63 vs 53%; P<0.005.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
to 75 mg daily vs placebo	with or without agoraphobia		endpoint Secondary: CGI-I, HAMA	Secondary: Paroxetine CR was statistically more effective compared to placebo in the proportion of patients with improved CGI-I (79 vs 55%; P<0.001). Paroxetine CR was statistically more effective compared to placebo in alleviating general anxiety symptoms as measured by HAMA; P<0.001. Adverse events leading to study withdrawal occurred in 11% of patients in the paroxetine CR group and 6% of patients in the placebo group.
Ballenger et al.[216] (1998) Paroxetine 10 mg daily vs paroxetine 20 mg daily vs paroxetine 40 mg daily	DB, PG, PC, RCT Patients with panic disorder 18 years of age or older	N=278 10 weeks	Primary: Change in panic attacks from baseline, CGI-S Secondary: Marks-Sheehan Phobia Scale, HARS, MASDR	Primary: The percent of patients free of panic attacks were 86% (40 mg), 65.2% (20 mg), and 67.4% (10 mg) (P<0.019 at weeks four and 10). No significant differences were noted between groups in mean change from baseline in number of full panic attacks. No significant differences were reported between groups in percentage of patients with a 50% reduction from baseline in number of full panic attacks. The mean CGI global and severity ratings were 81.2% (40 mg), 75.4% (20 mg), 57.8% (10 mg), 51.5% (placebo) (significantly higher with 40 and 20 mg, P<0.019). Secondary: The mean score for public avoidance on the Marks-Sheehan Phobia Scale declined in all groups (P=NS). Significant improvement in the score on the HARS (total) was observed for the 40 mg paroxetine group (in the end-point but not in the completer analysis). Improvement in depressive symptoms (MADRS) was significantly greater for the 40 mg paroxetine group than for the placebo group at week 10.
Bandelow et al.[217] (2004)	DB, MC, PG, RCT Patients with panic	N=225 12 weeks	Primary: Clinician-rated PAS	Primary: Treatment with sertraline and paroxetine resulted in equivalent levels of improvement on the primary outcome measure from baseline, the PAS

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Sertraline 50 to 150 mg daily vs paroxetine 40 to 60 mg daily	disorder between 18 and 65 years of age		Secondary: CGI-I score	total score (P=0.749). The efficacy of sertraline and paroxetine was equivalent (P=0.487) with regard to the PAS across the agoraphobia and non-agoraphobia subtypes. Secondary: Global response (CGI-I score ≤2) was achieved by 82% of the efficacy-evaluable population treated with sertraline compared to 78% of patients treated with paroxetine (P=0.320).
Pollack et al.[218] (2007) Venlafaxine ER 75 mg/day vs venlafaxine ER 225 mg/day vs paroxetine 40 mg/day vs placebo	DB, MC, PC, RCT Outpatients ≥18 years of age with panic disorder (with or without agoraphobia)	N=653 12 weeks	Primary: Percentage of patients free from full-symptom panic attacks at endpoint (LOCF) Secondary: Changes from baseline in the Panic Disorder Severity Scale total score and panic attack frequency	Primary: Each of the active treatment groups had a significantly higher proportion of patients who were free of full-symptom panic attacks than in the placebo group (venlafaxine ER 75 mg, 64.7% [P≤0.001 vs placebo]; venlafaxine ER 225 mg, 70.0% [P≤0.001 vs placebo; P≤0.05 vs paroxetine]; paroxetine, 58.3% [P≤0.05 vs placebo]; placebo, 47.8%). Secondary: All three treatment groups had significantly greater mean reductions in Panic Disorder Severity Scale total score compared to the placebo group at study endpoint. The venlafaxine ER 225 mg group had a significantly lower Panic Disorder Severity Scale total score (4.78 vs 6.26; P<0.05) at endpoint than the paroxetine group. Each of the active treatment groups had significantly more CGI-I responders than the placebo group (venlafaxine ER 75 mg, 81.4%; venlafaxine ER 225 mg, 85.0%; paroxetine, 83.3%; placebo, 59.9%; P<0.001 vs placebo for all comparisons). The percentage of patients who experienced remission was higher in the active treatment groups (venlafaxine ER 225 mg, 50.0%; venlafaxine ER 75 mg, 41.0%; paroxetine 40 mg, 39.3%) than in the placebo group (26.8%).
Posttraumatic Stress Disorder (PTSD)				
Davidson et al.[219] (2005) Fluoxetine 10 to	OL, RCT Patients 18 to 70 years of age with	N=123 6 months	Primary: Rate of relapse defined by a change in CGI-I	Primary: On the CGI-I, there was a significantly higher number of relapses in the group who received placebo (50%) compared to the group that received fluoxetine (22.2%; P=0.029).

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60 mg daily vs placebo	PTSD		score that reverted back to no improvement relative to baseline or worse, CGI-I score which increased by at least two points Secondary: CGI-S	Secondary: Differences between the fluoxetine and the placebo group failed to meet significance for CGI-S (P=0.08).
Friedman et al.[220] (2007) Sertraline 250 to 200 mg daily vs placebo	DB, PC, RCT Patients with combat-related PTSD	N=169 12 weeks	Primary: Mean change in CAPS-2 total severity score from baseline to endpoint Secondary: IES, CGI-S	Primary: The adjusted mean changes on the CAPS-2 total severity score for the sertraline and placebo groups were –13.1 and –15.4, respectively; the difference was not statically different (P=0.26). Secondary: The adjusted mean changes for the IES total score were –8.7 and –8.1 for the sertraline and placebo groups, respectively. The difference was not statistically significant (P=0.28). For the CGI-S scale, there was no statically significant difference between treatment groups in changes from baseline to endpoint. The mean changes from baseline to endpoint were –0.5 and –0.6, respectively (P=0.41).
Premenstrual Dysphoric Disorder				
Pearlstein et al.[221] (2005) Paroxetine CR 12.5 mg daily or 25 mg daily vs placebo	DB, MC, PC, RCT Patients 18 to 45 years of age who had regular menstrual cycles with PMDD	N=47 3 menstrual cycles	Primary: VAS-Mood Secondary: VAS-Total	Primary: A statistically significant difference was observed in favor of paroxetine CR 25 mg vs placebo on the VAS-Mood (P<0.001) and for paroxetine CR 12.5 mg vs placebo (P=0.013). Secondary: Paroxetine CR demonstrated greater mean reduction in VAS-Total scores compared to placebo at each time point. At the treatment cycle three last-observation-carried-forward endpoint, statistically significant differences in mean changes were observed in favor of paroxetine CR 25 mg vs placebo (P<0.001) as well as for paroxetine CR 12.5 mg vs placebo (P=0.011).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Steiner et al.[222] (2005) Paroxetine CR 12.5 mg daily vs paroxetine CR 25 mg daily vs placebo	DB, MC, PC, RCT Patients 18 to 45 years of age who had regular menstrual cycles with PMDD	N=373 3 menstrual cycles	Primary: VAS-Mood Secondary: Change form baseline to treatment cycle three in the sum of the 11VAS symptoms; change from baseline in the SDS total score	Primary: A statistically significant difference was demonstrated in favor of paroxetine CR 25 and 12.5 mg compared to placebo (paroxetine CR 25 mg vs placebo: adjusted mean difference, –10.79 mm; 95% CI, –16.46 to –5.12; P<0.001; paroxetine CR 12.5 mg vs placebo: adjusted mean difference, –7.66 mm; 95% CI, –13.25 to –2.08; P=0.007) for change from baseline in mean luteal phase VAS-Mood score at the treatment cycle three last-observation-carried-forward endpoint. Secondary: The mean change from baseline in the VAS-Total score, (paroxetine CR 25 mg vs placebo, -77.82 mm; P=0.006, paroxetine CR 12.5 mg vs placebo, –73.13 mm; P=0.009) The mean change from baseline in the SDS total score (paroxetine CR 25 mg vs placebo, –2.74 mm; P=0.016, paroxetine CR 12.5 mg vs placebo, –2.33 mm; P=0.028) was greater compared to placebo.
Yonkers et al.[223] (2015) Sertraline 50 to 100 mg/day during the symptomatic interval vs placebo	DB, MC, PC, RCT Women 18 to 48 years of age with menstrual cycles of 21 to 35 days with PMDD	N=252 6 menstrual cycles	Primary: PMTS Secondary: IDS, DRSP, Michelson SSRI Withdrawal Scale	Primary: The difference between the sertraline and placebo groups in rates of change for the PMTS scores was not statistically significant (P=0.06). Secondary: Compared with the placebo group, participants in the sertraline group showed greater improvement in IDS scores over time (P=0.02). The mean changes in the total and Anger/Irritability subscale scores of the DRSP were greater for the sertraline than the placebo groups, with an estimated mean difference for change from baseline to the end point for the total DRSP (1.09; 95% CI, 0.96 to 1.25; P=0.02) and the Anger/Irritability subscale (1.22; 95% CI, 1.05 to 1.41; P<0.01) scores, but no differences were found between conditions in the Depressive Symptoms and Physical Symptoms subscales. Both groups acknowledged fewer and similar symptoms on the Michelson SSRI Withdrawal Symptoms Scale as the trial progressed.
Multiple Diseases				
Wernicke et al.[224] (2007)	MA (42 RCTs) Patients diagnosed	N=8,504 4 to 12 weeks	Primary: Vital signs, ECG findings,	Primary: Patients receiving duloxetine were noted to have statistically significant changes from baseline in ECG findings compared to patients receiving

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Duloxetine vs placebo	with either an MDD, diabetic peripheral neuropathy, fibromyalgia, GAD, or lower urinary tract infection		cardiovascular side effects of the study drug Secondary: Not reported	placebo (P<0.001). However, the differences in ECG findings of patients taking duloxetine were not judged to be of clinical significance. Demographic subgroup analysis suggests that there is no difference in risk of ECG abnormality or vital sign changes between patients ≥65 years of age and a younger population (P value not reported). Although patients receiving duloxetine experienced statistically significant pulse and blood pressure elevations compared to patients receiving placebo (P<0.001), those changes were transient returning to baseline values with sustained therapy. There was no statistically significant difference between placebo and duloxetine groups in sustained blood pressure (P=0.631), SBP (P=0.740), or DBP (P=1.00) measured during three consecutive visits. Patients randomized to duloxetine therapy experienced higher incidences of palpitations (P=0.004), tachycardia (P=0.007), orthostatic hypotension (P=0.004), increased blood pressure (P<0.001), blood total cholesterol (P=0.031), and peripheral coldness (P=0.044) compared to patients randomized to placebo. Secondary: Not reported
Mullins et al.[225] (2005) Sertraline vs paroxetine vs citalopram	RETRO Patients with depression, PTSD, or social anxiety disorder	N=14,933 Data gathered from 1/1/99 to 6/30/02	Primary: Persistence, switching, discontinuation Secondary: Not reported	Primary: Compared to patients receiving sertraline and citalopram, those receiving paroxetine had lower rates of persistence (23.79% for paroxetine vs 25.96% for sertraline [P=0.0093] and 26.56% for citalopram [P=0.0022]) and higher rates of switching (3.55% for paroxetine vs 3.32% for sertraline [P=0.5076] and 2.78% for citalopram [P=0.0359]) and discontinuation (72.66% for paroxetine vs 70.72% for sertraline [P=0.0258] and 70.66% for citalopram [P=0.0334]). Survival curves showed that persistence rates with sertraline and citalopram were significantly greater than with paroxetine (P<0.05). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Stein et al.[226] (2000) SSRIs, MAOIs, benzodiazepines, beta blockers, buspirone, gabapentin, olanzapine	MA Patients with social anxiety disorders	N=5,264 (36 trials) Variable duration	Primary: CGI-I scale Secondary: LSAS	Primary: Summary statistics for responder status (assessed using the CGI from 25 short-term comparisons demonstrated a higher degree of efficacy of various medications over placebo (RR of non-response, 0.63; 95% CI, 0.55 to 0.72). Response to treatment by SSRIs (N=11; RR, 0.67; 95% CI, 0.59 to 0.76), MAOIs (N=3; RR, 0.43; 95% CI, 0.24 to 0.76) supported the value of these agents. However, the SSRIs were significantly more effective than the other agents (P<0.00001). Secondary: LSAS showed a statistically significant difference between medication and placebo (weighed mean difference, –15.56; 95% CI, –17.95 to -13.16), with this effect once again most evident for the SSRIs. Medication was also significantly more effective compared to placebo in reducing symptom clusters, comorbid depressive symptoms, and associated disability. The value of long-term medication treatment in treatment responders was supported by three comparisons from maintenance studies (RR, 0.58; 95% CI, 0.39 to 0.85) and five comparisons from relapse prevention studies (RR, 0.33; 95% CI, 0.22 to 0.49).

Drug abbreviations: BID=twice daily, CR=controlled release, ER=extended release, QD=once daily, SR=sustained release, XR=extended release
Study abbreviations: AC=active control, CI=confidence interval, DB=double-blind, ES=extension study, FD=fixed dose, ITT=intention to treat, LOCF=last observation carried forward, LSM=least square mean, LSMD=least square mean difference, MA=meta-analysis, MC=multicenter, NI=non inferiority, NNH=number needed to harm, NNT=number needed to treat, OBS=observational, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk, SB=single blind, SC=single center, SMD=standard mean difference, SR=systemic review, XO=cross over
Diagnostic Criteria: DSM-III-R=Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised, DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th edition
Miscellaneous abbreviations: ASEX=Arizona Sexual Experience Scale, BAI=Beck Anxiety Inventory, BDI-FS=Beck Depression Inventory Fast Screen, BDI-II=Beck Depression Inventory-II, BPI=brief pain inventory, CAPS-S=Clinician-Administered PTSD Scale, CES-D=Center for Epidemiological Studies-Depression Scale, CGI-I=Clinical Global Impression, Improvement, CGI-S=Clinical Global Impression, Severity, CSFQ=Changes in Sexual Functioning Questionnaire, DBP=diastolic blood pressure, DRSP=Daily Record of Severity of Problems, DSST=digital symbol substitution test, ECG=electrocardiogram, EQ-5D=EuroQoL: 5 Dimensions Questionnaire, FIQ=Fibromyalgia Impact Questionnaire, GAD=Generalized Anxiety Disorder, GAF=Global Assessment of Functioning, GDS=Geriatric Depression Scale, GSP=Generalized Social Phobia, HADS-A=Hospital Anxiety and Depression Scale – Anxiety subscale, HAMA=Hamilton Rating Scale for Anxiety, HAM-D=Hamilton Rating Scale for Depression, HARS=Hamilton Anxiety Rating Scale, HDRS-17=17-item Hamilton Depression Rating Scale, HRQOL=health related quality of life, IDS=Inventory of Depressive Symptomatology-Clinician-Rated, IES=Impact of Event Scale, IU-GAM=Indiana University Generalized Anxiety Measurement Scale, LANSS=Leeds Assessment of Neuropathic Symptoms and Signs, LPS=Latency to Persistent Sleep, LSAS=Liebowitz Social Anxiety Scale, MADRS=Montgomery-Åsberg Depression Rating Scale, MAOIs=Monoamine Oxidase Inhibitors, MDD=major depressive disorder, MFI=Multidimensional Fatigue Inventory, MHID=Mantel-Haenszel Incidence Difference, MHRD=Mantel-Haenszel Exposure Time-adjusted Rate Difference, MRS=Menopause Rating Scale, NIMH-OC=National Institute of Mental Health-

Obsessive-Compulsive Scale, NSAID=nonsteroidal anti-inflammatory drug, OCD=obsessive compulsive disorder, PAS=Panic and Agoraphobia Scale, PGI-C=Patient Global Impression of Change, PGI-I=Patient Global Impressions of Improvement, PMDD=premenstrual dysphoric disorder, PMTS=Premenstrual Tension Scale, PPI=proton pump inhibitor, PTSD=Posttraumatic Stress Disorder, QIDS-SR16=16-item Quick Inventory of Depressive Symptomatology–Self-Rated, QOL=Quality of Life, Q-LES-Q=Quality of Life, Enjoyment, and Satisfaction Questionnaire, RAVLT=Rey Auditory Verbal Learning Test, REM=rapid eye movement, RMDQ-24=Roland Morris Disability Questionnaire, SBP=systolic blood pressure, SDS=Sheehan Disability Scale, SF-36=36-item Short-Form Health Status Survey, SNRI=serotonin norepinephrine reuptake inhibitor, SSI=28-item Somatic Symptom Inventory, SSRIs=Selective Serotonin-reuptake Inhibitors, TST=Total Sleep Time, UPDRS=Unified Parkinson's Disease Rating Scale, VAS=Visual Analog Scale, WASO=Wake Time After Sleep Onset, WHO-5=World Health Organization 5-item Well Being Index, WOMAC=Western Ontario and McMaster Universities, WTAS=Wake Time After Sleep, WTDS=Wake Time During Sleep, Y-BOCS=Yale-Brown Obsessive-Compulsive Scale

Additional Evidence

Dose Simplification
Claxton et al. evaluated compliance rates with fluoxetine 90 mg once weekly compared to fluoxetine 20 mg once daily in patients who had previously received four weeks of fluoxetine 20 mg once daily.[227] At the end of 12 weeks, compliance significantly declined from 87 to 79% with the once daily fluoxetine; however, the effect on clinical outcomes was not measured. More patients in the once-weekly group discontinued therapy due to lack of efficacy than in the once-daily group, but this difference was not statistically significant.

Stable Therapy
Brent et al. evaluated the efficacy of four treatment strategies in adolescents who continued to have depression despite initial treatment with a selective serotonin-reuptake inhibitor (SSRI).[228] The interventions included switching to a different SSRI, switching to a different SSRI plus cognitive behavioral therapy, switching to venlafaxine, or switching to venlafaxine plus cognitive behavioral therapy. The authors found that switching to a different treatment plus cognitive behavioral therapy was more effective than medication switch alone. A switch to another SSRI was as effective as switching to venlafaxine.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 12. Relative Cost of the Antidepressants

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Monoamine Oxidase Inhibitors				
Isocarboxazid	tablet	Marplan®	$$$$	N/A
Phenelzine	tablet	Nardil®*	$$$$	$$$$
Selegiline	transdermal patch	Emsam®	$$$$	N/A
Tranylcypromine	tablet	Parnate®*	$$$$	$$$$
Selective Serotonin- and Norepinephrine-reuptake Inhibitors				
Desvenlafaxine	extended-release tablet	Desvenlafaxine ER®, Pristiq®, Khedezla®*	$$$$$	N/A
Duloxetine	delayed-release capsule	Cymbalta®*, Irenka®*	$$$$$	$$$
Levomilnacipran	extended-release capsule	Fetzima®	$$$$$	N/A
Venlafaxine	extended-release capsule,	Effexor XR®*	$$$$$	$$

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
	extended-release tablet, tablet			
Selective Serotonin-reuptake Inhibitors				
Citalopram	solution, tablet	Celexa®*	$$$$	$
Escitalopram	solution, tablet	Lexapro®*	$$$$$	$
Fluoxetine	capsule, delayed-release capsule, solution, tablet	Prozac®*, Prozac Weekly®*, Sarafem®*	$$$$$	$
Fluvoxamine	extended-release capsule, tablet	N/A	N/A	$$$
Paroxetine	capsule, extended-release tablet, suspension, tablet	Brisdelle®, Paxil®*, Paxil CR®*, Pexeva®	$$$$$	$
Sertraline	oral concentrate, tablet	Zoloft®*	$$$$$	$
Serotonin Modulators				
Nefazodone	tablet	N/A	N/A	$$$
Trazodone	extended-release tablet, tablet	Oleptro®	$$$	$
Vilazodone	tablet	Viibryd®	$$$$$	N/A
Vortioxetine	tablet	Brintellix®	$$$$$	N/A
Tricyclics and Other Norepinephrine-reuptake Inhibitors-Single Entity Agents				
Amitriptyline	tablet	N/A	N/A	$
Amoxapine	tablet	N/A	N/A	$$
Clomipramine	capsule	Anafranil®*	$$$$$	$$$$$
Desipramine	tablet	Norpramin®*	$$-$$$$	$$$
Doxepin	capsule, oral concentrate, tablet	Silenor®	$$$$$	$
Imipramine	capsule, tablet	Tofranil®*, Tofranil-PM®*	$$$$$	$
Maprotiline	tablet	N/A	N/A	$$-$$$
Nortriptyline	capsule, solution	Pamelor®*	$$$$$	$
Protriptyline	tablet	N/A	N/A	$$$$$
Trimipramine	capsule	Surmontil®	$$$$$	N/A
Tricyclics and Other Norepinephrine-reuptake Inhibitors-Combination Products				
Amitriptyline and chlordiazepoxide	tablet	N/A	N/A	$$$
Antidepressants, Miscellaneous				
Bupropion	extended-release tablet, sustained-release tablet, tablet	Aplenzin®, Forfivo XL®, Wellbutrin®*, Wellbutrin SR®*, Wellbutrin XL®*	$$$$$	$$
Mirtazapine	orally disintegrating tablet, tablet	Remeron®*	$$$	$

*Generic is available in at least one dosage form or strength.
N/A=Not available.

X. Conclusions

The antidepressants are approved to treat a variety of mental disorders, including anxiety disorders, eating disorders (bulimia nervosa), mood disorders, premenstrual dysphoric disorder, and moderate to severe vasomotor symptoms associated with menopause.[1-34] Some of the agents are also approved for the treatment of nonpsychiatric conditions, such as chronic musculoskeletal pain, diabetic peripheral neuropathy, fibromyalgia, insomnia, nocturnal enuresis, and tobacco abuse.[1-34] The antidepressants are categorized into six different American Hospital Formulary Service (AHFS) subclasses, including monoamine oxidase inhibitors (MAOIs), selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs), selective serotonin-reuptake inhibitors (SSRIs), serotonin modulators, tricyclic antidepressants (TCAs), and miscellaneous agents. The agents which make up these subclasses differ with respect to their Food and Drug Administration (FDA)-approved indications, mechanism of action, pharmacokinetics, adverse events, and drug interactions. The majority of the products are

available in a generic formulation, and there is at least one generic product available in each antidepressant subclass.

Numerous clinical trials have been conducted with the antidepressants and comparative studies have demonstrated similar efficacy in patients with major depressive disorder.[36,57,60-61,77-79,83,89,91-98,102-103,106,108,156-158,160,162-163] Guidelines do not give preference to one agent over another.[36,37] Rather, the selection of an antidepressant should be based on adverse events, tolerability, and patient preference.[36,37]

Several antidepressants are approved for the treatment of anxiety disorders. The American Psychiatric Association recommends the initial use of either an SNRI or SSRI for the treatment of panic disorder due to their favorable safety and tolerability profiles.[39] The National Institute for Health and Clinical Excellence recommends the use of SSRIs as first-line therapy for the long-term treatment of generalized anxiety disorder.[38] SSRIs are also recommended for the initial treatment of obsessive-compulsive disorder.[40-41] The SNRIs, SSRIs, and TCAs have all been shown to be more effective than placebo for the treatment of anxiety disorders, and comparative studies have demonstrated similar efficacy among the antidepressants.[183,186,191,193,209-213,217] Guidelines do not give preference to one agent over another.[38-44] The choice of treatment should be based on safety, adverse events, drug interactions, prior response to treatment and comorbid conditions.[38-44]

Duloxetine has been approved by the FDA for the treatment of chronic musculoskeletal pain, in addition to depression, generalized anxiety disorder, diabetic peripheral neuropathic pain, and fibromyalgia.[8] It has been shown to be more effective than placebo in patients with chronic low back pain and osteoarthritis of the knee; however, the effects were modest.[199-200,203-205]

According to the boxed warning, antidepressants increased the risk of suicidal thinking and behavior in children, adolescents and young adults compared to placebo in short-term studies of major depressive disorder and other psychiatric disorders.[1-34] Short-term studies did not show an increase in the risk of suicidality in adults older than 24 years of age, and there was a reduction in risk in adults 65 years of age and older. Although the MAOIs are an effective treatment option for patients with major depressive disorder, drug interactions, dietary restrictions, and serious adverse events limit their use. It is recommended that MAOIs be reserved for patients who are not responding to other treatment options.[36]

There is insufficient evidence to support that one brand antidepressant is more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand antidepressants within the class reviewed, with the exception of the monoamine oxidase inhibitors, are comparable to each other and to the generics in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use. The monoamine oxidase inhibitors possess an extensive adverse effect profile compared to the other brands and generics in the class (if applicable) and should be managed through the existing medical justification portion of the prior authorization process.

XI. Recommendations

No brand antidepressant is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

No brand monoamine oxidase inhibitor is recommended for preferred status, regardless of cost.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Cerebral Stimulants/Agents Used for ADHD
Central Alpha-Agonists, AHFS Class 240816
Amphetamine Derivatives AHFS Class 282004
Respiratory and CNS Stimulants, AHFS Class 282032
Central Nervous System Agents, Miscellaneous, AHFS Class 289200
May 11, 2016

I. Overview

Attention-Deficit/Hyperactivity Disorder (ADHD) is a common psychiatric disorder that is often diagnosed during childhood; however, children with ADHD may continue to manifest symptoms into adulthood.[1-2] The key diagnostic feature is a persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development.[1] There are three subtypes of ADHD, including a predominantly inattentive subtype, a predominantly hyperactive-impulsive subtype, and a combined subtype in which both symptoms are displayed.[1] Untreated (or undertreated) ADHD is associated with adverse sequelae, including conduct disorder, antisocial personality traits, substance abuse, and other comorbidities.[1]

There are several central nervous system agents that are approved for the treatment of ADHD. This includes cerebral stimulants (amphetamines and methylphenidate derivatives), as well as atomoxetine, extended-release clonidine, and extended-release guanfacine.[3-22] The stimulants are thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space.[4-20] Due to their potential for abuse, the stimulants are classified as Schedule II controlled substances. Atomoxetine, extended-release clonidine, and extended-release guanfacine are not considered controlled substances and have no known potential for abuse or dependence. Their mechanism of action in the treatment of ADHD is unknown. Atomoxetine is a selective norepinephrine reuptake inhibitor, while clonidine and guanfacine are alpha$_2$-adrenergic agonists.[3,21,22]

Since the last review, two new agents have become available, including Evekeo® (amphetamine sulfate), which is a racemic mixture of amphetamine, and Aptensio XR® (methylphenidate extended release), which offers once daily dosing for patients six years and above and is composed of an immediate-release layer which contains approximately 40% of the methylphenidate dose and a controlled release layer which contains approximately 60% of the dose.[4,13]

The cerebral stimulants/agents used for ADHD that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Table 2 classifies the agents based on their duration of action. Many of the products are available in a generic formulation. This class was last reviewed in May 2014.

Table 1. Cerebral Stimulants/Agents Used for ADHD Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Central Alpha-Agonists			
Clonidine	sustained-release tablet	Kapvay®*	Kapvay®*†
Amphetamine Derivatives			
Amphetamine sulfate	tablet	Evekeo®	none
Amphetamine aspartate, amphetamine sulfate, and dextroamphetamine	extended-release capsule, tablet	Adderall®*, Adderall XR®*‡	Adderall XR®*†, amphetamine salts IR
Dextroamphetamine	sustained-release capsule, solution, tablet	Dexedrine®*, ProCentra®*, Zenzedi®*	dextroamphetamine
Lisdexamfetamine	capsule	Vyvanse®	Vyvanse®
Methamphetamine	tablet	Desoxyn®*	methamphetamine
Respiratory and CNS Stimulants			
Dexmethylphenidate	extended-release capsule, tablet	Focalin®*, Focalin XR®*	Focalin®*†, Focalin XR®*†

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Methylphenidate	chewable tablet, extended-release capsule, extended-release solution, extended-release tablet, sustained-release tablet, solution, tablet, transdermal patch	Aptensio XR®, Concerta®*, Daytrana®, Metadate CD®*, Metadate ER®*, Methylin®*, Ritalin®*, Ritalin LA®*, Quillivant XR®	methylphenidate, Ritalin®*
Central Nervous System Agents, Miscellaneous			
Atomoxetine	capsule	Strattera®	Strattera®
Guanfacine	extended-release tablet	Intuniv®*	Intuniv®†

*Generic is available in at least one dosage form or strength.
†Generic product requires prior authorization.
PDL=Preferred Drug List.

Table 2. Cerebral Stimulants/Agents Used for ADHD Classified by Duration of Action[3-24]

Generic Name(s)	Short-Acting	Intermediate-Acting	Long-Acting
Central Alpha-Agonists			
Clonidine			Kapvay®
Amphetamine Derivatives			
Amphetamine sulfate	Evekeo®		
Amphetamine aspartate, amphetamine sulfate, and dextroamphetamine	amphetamine aspartate, amphetamine sulfate, and dextroamphetamine, Adderall®*		amphetamine aspartate, amphetamine sulfate, and dextroamphetamine, Adderall XR®*
Dextroamphetamine	dextroamphetamine, ProCentra®*, Zenzedi®*	dextroamphetamine, Dexedrine®*	
Lisdexamfetamine			Vyvanse®
Methamphetamine		methamphetamine, Desoxyn®*	
Respiratory and CNS Stimulants			
Dexmethylphenidate	dexmethylphenidate, Focalin®*		Focalin XR®
Methylphenidate	methylphenidate, Methylin®*, Ritalin®*	methylphenidate SR, Metadate ER®*	methylphenidate, Aptensio XR®, Concerta®*, Daytrana®, Metadate CD®, Ritalin LA®*, Quillivant XR®
Central Nervous System Agents, Miscellaneous			
Atomoxetine			Strattera®
Guanfacine			Intuniv®*

*Generic is available in at least one dosage form or strength.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the cerebral stimulants/agents used for attention-deficit/hyperactivity disorder (ADHD) are summarized in Table 3.

Table 3. Treatment Guidelines Using the Cerebral Stimulants/Agents Used for ADHD

Clinical Guideline	Recommendation(s)
American Academy of Pediatrics: **Clinical Practice Guideline for the Diagnosis, Evaluation, and**	Preschool-aged children (four to five years of age) • The primary care clinician should prescribe evidence-based parent- and/or teacher-administered behavior therapy as the first-line of treatment. • Methylphenidate may be prescribed if the behavior interventions do not provide significant improvement and there is moderate-to-severe continuing disturbance

Clinical Guideline	Recommendation(s)
Treatment of Attention-Deficit Hyperactivity Disorder in Children and Adolescents (2011)[25]	in the child's function. <u>Elementary school-aged children (six to 11 years of age)</u> • The primary care clinician should prescribe Food and Drug Administration (FDA)-approved medications for attention deficit-hyperactivity disorder (ADHD) and/or evidence-based parent and/or teacher-administered behavior therapy as treatment for ADHD, preferably both. • The evidence is particularly strong for stimulant medications and sufficient but less strong for atomoxetine, extended-release guanfacine, and extended-release clonidine (in that order). <u>Adolescents (12 to 18 years of age)</u> • The primary care clinician should prescribe FDA-approved medications for ADHD with the assent of the adolescent and may prescribe behavior therapy as treatment for ADHD, preferably both. <u>General considerations</u> • Stimulant medications are highly effective for most children in reduction of core symptoms of ADHD. • Atomoxetine, extended-release guanfacine and extended-release clonidine reduce core symptoms; however, they have a smaller evidence base than stimulants. • Extended-release guanfacine and extended-release clonidine have evidence to support their use as adjunctive therapy with stimulant medications. • Before beginning medication treatment for adolescents with newly diagnosed ADHD, clinicians should assess these patients for symptoms of substance abuse. • Clinicians should monitor symptoms and prescription-refill requests for signs of misuse or diversion of ADHD medications and consider prescribing medications with no abuse potential, such as atomoxetine, extended-release guanfacine, or extended-release clonidine (which are not stimulants) or stimulant medications with less abuse potential, such as lisdexamfetamine, dermal methylphenidate, or osmotic-release oral system methylphenidate). • Primary care clinicians should titrate doses of medication for ADHD to achieve maximum benefit with minimum adverse effects.
Institute for Clinical Systems Improvement: **Diagnosis and Management of Attention Deficit Hyperactivity Disorder in Primary Care for School-Age Children and Adolescents (2012)**[26]	<u>Medication trials</u> • Prescribe FDA-approved treatments for ADHD in children, including psychostimulants and/or non-stimulants. • The decision to use medications should be made in conjunction with parents following a thorough discussion of expected benefits and potential risks. Factors such as the child's age, severity of symptoms and presence of comorbidity should also be considered and may involve decision-making regarding choice of medication. • Obtain cardiology consultation for patients with known structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems that could place patients at an increased risk to the sympathomimetic effects of central nervous system stimulants and/or atomoxetine. • Review the personal and family cardiovascular history, and complete a physical examination of each patient prior to starting stimulant therapy and/or atomoxetine. Medication history or physical exam changes consistent with possible cardiac disease during treatment with stimulant medication and/or atomoxetine may require additional evaluation by a cardiologist. • Optimal medication management alone is superior to other modalities for the core symptoms of ADHD. • Response to one stimulant does not predict response to the others. If a child is a non-responder to one stimulant, it is advisable to attempt a second or third trial

Clinical Guideline	Recommendation(s)
	with other stimulants. • Treatment with psychostimulants is often safe and effective in managing many children with ADHD with mild to moderate tics. Nevertheless, frequency and severity of tics should be carefully monitored in these patients. No routine blood work is necessary before or during psychostimulant therapy. • Current evidence does not support a higher risk of sudden cardiac death with stimulant medication compared to the general population; however, certain conditions may place a patient at higher risk for such an outcome. • Atomoxetine is a good option for patients with comorbid anxiety, sleep initiation disorder, substance abuse, or tics, or if initially preferred by parents and/or physician. Atomoxetine is a non-controlled substance that may make it preferable in certain clinical situations. • Extended-release guanfacine and extended-release clonidine are the first ADHD medications to achieve FDA approval as adjunctive therapy with stimulant medications. • Extended-release guanfacine is the first ADHD medication to look for improvement of oppositional symptoms in addition to ADHD core symptoms. <u>Alternative medications</u> • When adequate stimulant, atomoxetine or alpha adrenergic trials are unsuccessful due to either poor response or adverse effects, or if associated comorbidity is present, alternative medication trials should be considered. Second-line medications for ADHD therapy include tricyclic antidepressants (imipramine, desipramine), alpha adrenergic agonist (clonidine) a non- tricyclic antidepressant (bupropion), or immediate-release guanfacine.

National Institute for Health and Clinical Excellence:
Attention Deficit Hyperactivity Disorder: Diagnosis and Management of Attention Deficit Hyperactivity Disorder in Children, Young People, and Adults (2008)[27]
	<u>Treatment for children and adolescents with ADHD</u>
	• Methylphenidate, atomoxetine and dexamphetamine are recommended as options for the management of ADHD in children and adolescents.
	• The decision regarding which product to use should be based on the following:
	  o The presence of comorbid conditions.
	  o The different adverse effects of the drugs.
	  o Specific issues regarding compliance identified for the individual child or adolescent.
	  o The potential for drug diversion.
	  o The preferences of the child/adolescent and/or his or her parent or guardian.
	• Healthcare professionals should consider the following treatment recommendations:
	  o Methylphenidate for patients with ADHD without significant comorbidities.
	  o Methylphenidate for patients with ADHD with comorbid conduct disorder.
	  o Methylphenidate or atomoxetine when tics, Tourette's syndrome, anxiety disorder, stimulant misuse or risk of stimulant diversion are present.
	  o Atomoxetine if methylphenidate has been tried and has been ineffective at the maximum tolerated dose, or the child or young person is intolerant to low or moderate doses of methylphenidate.
	• Modified-release preparations should be considered for the following reasons:
	  o Convenience.
	  o Improving adherence.
	  o Reducing stigma (because the child or young person does not need to take medication at school).
	  o Reducing problems schools have in storing and administering controlled drugs.

Clinical Guideline	Recommendation(s)
	o Their pharmacokinetic profiles. • Immediate-release preparations may be considered if more flexible dosing regimens are required, or during initial titration to determine correct dosing levels. <u>Treatment of adults with ADHD</u> • Drug treatment is the first-line treatment for adults with ADHD with either moderate or severe levels of impairment. • Methylphenidate is recommended as the first-line drug. • If methylphenidate is ineffective or unacceptable, atomoxetine or dexamphetamine can be tried. • Caution should be exercised when prescribing dexamphetamine to those likely to be at risk of stimulant misuse or diversion.
British Association of Psychopharmacology: **Evidence-based guidelines for the pharmacological management of attention deficit hyperactivity disorder: Update on recommendations from the British Association for Psychopharmacology (2014)**[28]	<u>Treatment recommendations for children and adolescents</u> • All children with severe ADHD (conceptualized as hyperkinetic disorder) should be offered pharmacological treatment. In addition, consider pharmacological treatment for children with moderate symptoms of ADHD who have not responded to psychological interventions. • The treatment of choice for children with severe ADHD or moderate ADHD non-responsive to psychological treatments is psychostimulant medication. • Atomoxetine can be used instead when there is a risk of misuse of psychostimulants by children or the adults supporting the child. • Appropriate child and family-based psychological interventions should be available to all children with ADHD. These interventions should be tailored to the child's needs and not depend on the local availability of services. • Teachers should be given evidence-based information about ADHD. • Patient and parental preferences should be taken into account when designing a psychological intervention for ADHD. • Every effort should be made to facilitate the transition from adolescence to adulthood. This should include education of parents, children, and professionals involved in the care of these children and the development of appropriate services and shared care protocols to enable this transition. • Systems and protocols need to be implemented to allow early re-acces to services for young people who may have dropped out of treatment at an early age, but still have significant symptoms and impairment. <u>Treatment recommendations for adults</u> • Stimulant medications are the first-line drugs in adults with ADHD. • Although amphetamines, methylphenidate and atomoxetine are all effective in adults with ADHD, they cannot be considered equivalent because they have different mechanisms of actions and hazards. • Once methylphenidate, atomoxetine, and amphetamines have all been given a fair trial, third-line medications can be considered. These include bupropion, modafinil, tricyclic antidepressants, guanfacine and clonidine. • Co-administration of psychostimulant and other drugs (mainly atomoxetine) is an option for patients showing a limited or lack of clinical response. There is, however, limited evidence supporting either the efficacy or safety of combination therapy. • Psychological treatments are a complement to pharmacological treatment. • Different approaches have been used but the majority the evidence is for structured treatments employing a cognitive behavioral paradigm. • The use of different methods of delivery (group and individual therapy), different criteria for control groups and different outcome measures limit the generalization of results.

Clinical Guideline	Recommendation(s)
	Abuse potential • Abuse potential is related to drug action and formulation. Abuse is generally low among patients but it can occur with stimulants. Slow-release preparations of these agents or atomoxetine are preferred for patients with a history of substance abuse, or who are at risk for substance abuse.
American Academy of Sleep Medicine: **Practice Parameters for the Treatment of Narcolepsy and Other Hypersomnias of Central Origin (2007)**[29]	• Most of the agents used to treat excessive sleepiness have little effect on cataplexy or other rapid eye movement sleep associated symptoms. Most antidepressants and anticataplectics have little effect on alertness. However, some compounds act on both symptoms. Compounds should be selected depending on the diagnosis and the targeted symptoms. Coadministration of two or more classes of compounds may be needed in some patients to adequately address their symptoms. • Modafinil is effective for treatment of daytime sleepiness due to narcolepsy. • Sodium oxybate is effective for treatment of cataplexy, daytime sleepiness, and disrupted sleep due to narcolepsy. Sodium oxybate may be effective for treatment of hypnagogic hallucinations and sleep paralysis. • Amphetamine, methamphetamine, dextroamphetamine, and methylphenidate are effective for treatment of daytime sleepiness due to narcolepsy. • Selegiline may be an effective treatment for cataplexy and daytime sleepiness. • Tricyclic antidepressants, selective serotonin reuptake inhibitors, and venlafaxine may be effective treatment for cataplexy. • Scheduled naps can be beneficial to combat sleepiness, but seldom suffice as primary therapy for narcolepsy.
European Federation of Neurological Sciences: **Guidelines on Management of Narcolepsy in Adults (2011)**[30]	Excessive daytime sleepiness and irresistible episodes of sleep • Modafinil should be prescribed when excessive daytime sleepiness is present. Modafinil should be dosed as 100 to 400 mg/day, given once in the morning or twice daily. • Sodium oxybate may be used when excessive daytime somnolence coexists with cataplexy and poor sleep. Depressed patients should not receive sodium oxybate. • Sodium oxybate should be initiated with 4.5 g/night, increasing by increments of 1.5 g at four-week intervals and should not be used with other sedatives, respiratory depressants or muscle relaxants. Monitor patients for possible development of sleep-disordered breathing. Adverse effects may limit the dose, and require slower titration. • The optimal response on excessive daytime sleepiness may take up to 12 weeks. • Supplementation with modafinil is generally more successful than sodium oxybate alone. • Methylphenidate may be considered if modafinil is insufficient and sodium oxybate is not recommended. • The short-acting effect of methylphenidate is of interest when modafinil needs to be supplemented at a specific time of the day, or in situations where maximum alertness is required. Cataplexy • First-line pharmacological treatment of cataplexy is sodium oxybate at a starting dose of 4.5 g/night divided into two equal doses of 2.25 g/night. The dose may be increased to a maximum of 9 g/night, divided into two equal doses of 4.5 g/night, by increments of 1.5 g at two-week intervals. • Adverse effects may limit the dose, and require slower titration and the optimal response on excessive daytime sleepiness may take up to 12 weeks. • Antidepressants are recommended as second-line pharmacological treatment. Tricyclic antidepressants, particularly clomipramine (10 to 75 mg), are potent anticataplectic drugs; however, anticholinergic adverse effects are common. • Selective serotonin reuptake inhibitors are slightly less active but have fewer adverse effects.

Clinical Guideline	Recommendation(s)
	• Venlafaxine is widely used but clinical evidence supporting its use is limited. • Reboxetine and atomoxetine, also lack published clinical evidence. • Given the efficacy of sodium oxybate and antidepressants, the place for other compounds is fairly limited. • There is no accepted behavioral treatment of cataplexy. <u>Poor sleep</u> • Sodium oxybate appears to be the most appropriate to treat poor sleep. • Benzodiazepine or non-benzodiazepine hypnotics may be effective in consolidating nocturnal sleep, but objective evidence is lacking over intermediate- or long-term follow-up. • The improvement in poor sleep reported by some patients once established on modafinil is noteworthy. <u>Obstructive sleep apnea/hypopnea syndrome, periodic limb movements in sleep, neuropsychiatric symptoms</u> • Obstructive sleep apnea/hypopnea syndrome should be similarly in narcoleptic patients and general population, although continuous positive airway pressure does not improve excessive daytime sleepiness in most narcolepsy subjects. • There is usually no need to treat periodic limb movements in narcoleptic patients. Antidepressants and psychotherapy should be used in depressed narcoleptic patients as in non-narcoleptic depressed patients.
American Academy of Sleep Medicine: **Clinical Guideline for the Evaluation, Management and Long-term Care of Obstructive Sleep Apnea in Adults (2009)**[31]	<u>Weight reduction</u> • Successful dietary weight loss may improve the apnea-hypopnea index in obese obstructive sleep apnea patients. • Dietary weight loss should be combined with a primary treatment for obstructive sleep apnea. • Bariatric surgery may be adjunctive in the treatment of obstructive sleep apnea in obese patients. <u>Pharmacologic agents</u> • Modafinil is recommended for the treatment of residual excessive daytime sleepiness in obstructive sleep apnea patients who have sleepiness despite effective positive airway pressure treatment and who are lacking any other identifiable cause for their sleepiness. • Selective serotonin reuptake inhibitors, protriptyline, methylxanthine derivatives (aminophylline and theophylline), and estrogen therapy are not recommended for treatment of obstructive sleep apnea. <u>Supplemental oxygen</u> • Oxygen supplementation is not recommended as a primary treatment for obstructive sleep apnea. <u>Medical therapies intended to improve nasal patency</u> • Short-acting nasal decongestants are not recommended for treatment of obstructive sleep apnea. • Topical nasal corticosteroids may improve the apnea-hypopnea index in patients with obstructive sleep apnea and concurrent rhinitis, and thus may be a useful adjunct to primary therapies for obstructive sleep apnea. <u>Positional therapies</u> • Positional therapy is an effective secondary therapy or can be a supplement to primary therapies for obstructive sleep apnea in patients who have a low apnea-hypopnea index in the non-supine vs that in the supine position. vs
American Academy of	<u>Shift work disorder</u>

Clinical Guideline	Recommendation(s)
Sleep Medicine: **Practice Parameters for the Clinical Evaluation and Treatment of Circadian Rhythm Sleep Disorders (2007)**[32]	• Planned napping before or during the night shift is indicated to improve alertness and performance among night shift workers. • Timed light exposure in the work environment and light restriction in the morning, when feasible, is indicated to decrease sleepiness and improve alertness during night shift work. • Administration of melatonin prior to daytime sleep is indicated to promote daytime sleep among night shift workers. • Hypnotic medications may be used to promote daytime sleep among night shift workers. Carryover of sedation to the nighttime shift with potential adverse consequences for nighttime performance and safety must be considered. • Modafinil is indicated to enhance alertness during the night shift for shift work disorder. • Caffeine is indicated to enhance alertness during the night shift for shift work disorder.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the cerebral stimulants/agents used for attention deficit-hyperactivity disorder (ADHD) are noted in Table 4. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 4. FDA-Approved Indications for the Cerebral Stimulants/Agents Used for ADHD[3-23]

Generic Name(s)	Attention Deficit-Hyperactivity Disorder	Narcolepsy	Exogenous Obesity	Binge Eating Disorder
Central Alpha-Agonists				
Clonidine	✔ *			
Amphetamine Derivatives				
Amphetamine sulfate	✔	✔	✔ §	
Amphetamine aspartate, amphetamine sulfate, and dextroamphetamine	✔	✔ †		
Dextroamphetamine	✔	✔		
Lisdexamfetamine	✔			✔ ‖
Methamphetamine	✔		✔ §	
Respiratory and CNS Stimulants				
Dexmethylphenidate	✔			
Methylphenidate	✔	✔ †‡		
Central Nervous System Agents, Miscellaneous				
Atomoxetine	✔			
Guanfacine	✔ *			

*As monotherapy and as adjunctive therapy to stimulant medications.
†Immediate-release formulations.
‡Sustained-release formulations.
§As a short-term adjunct in a regimen of weight reduction based on caloric restriction, for patients in whom obesity is refractory to alternative therapy (e.g., repeated diets, group programs, and other drugs).
‖For use in moderate to severe Binge Eating Disorder. Not indicated for weight loss or treatment of obesity.

IV. Pharmacokinetics

The pharmacokinetic parameters of the cerebral stimulants/agents used for attention deficit-hyperactivity disorder (ADHD) are listed in Table 5.

Table 5. Pharmacokinetic Parameters of the Cerebral Stimulants/Agents Used for ADHD[3-24]

Generic Name(s)	Onset (hours)	Duration (hours)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Central Alpha-Agonists							
Clonidine	0.5 to 1.0	6 to 10	89	20 to 40	Liver (50)	Renal (40 to 60)	12 to 16
Amphetamine Derivatives							
Amphetamine sulfate	1 to 3	Up to 10	Well absorbed	20	Liver (not reported)	Renal (67 to 73)	7 to 34
Amphetamine aspartate, amphetamine sulfate, and dextroamphetamine	Not reported	IR: 4 to 6 XR: 10 to 12	Well absorbed	Not reported	Liver (not reported)	Renal (1 to 75)	9 to 14
Dextroamphetamine	2 to 3	IR: 4 to 6 SR: 6 to 8	Well absorbed	Not reported	Liver (not reported)	Renal (17 to 73)	10 to 12
Lisdexamfetamine	Not reported	10	Rapid	Not reported	Blood (not reported)	Renal (96.0) Feces (0.3)	<1
Methamphetamine	Not reported	Not reported	Rapid	Not reported	Liver (not reported)	Renal (62)	4 to 5
Respiratory and CNS Stimulants							
Dexmethylphenidate	1	IR: 5 to 6 XR: 12	22 to 25	12 to 15	Liver (not reported)	Renal (90)	2.0 to 4.5
Methylphenidate	IR: 2 SR: 4 to 7 ER: 1 to 2 XR: 0.5 to 1.0 TD: 2	IR: 3 to 6 SR: 8 ER: 10 to 12 XR: 8 to 12 TD: 10 to 12	10 to 52	10 to 33	Liver (not reported)	Renal (90) Fecal (1 to 3)	3 to 4
Central Nervous System Agents, Miscellaneous							
Atomoxetine	1 week	Not reported	63 to 94	98	Liver (not reported)	Renal (>80) Feces (<17)	5 to 22
Guanfacine	Not reported	Not reported	80	70	Liver (50)	Renal (50)	16

ER=extended-release (osmotic), IR=immediate-release, SR=sustained-release, TD=transdermal, XR=extended-release (non-osmotic)

V. Drug Interactions

Major drug interactions with the cerebral stimulants/agents used for attention deficit-hyperactivity disorder (ADHD) are listed in Table 6.

Table 6. Major Drug Interactions with the Cerebral Stimulants/Agents Used for ADHD[24]

Generic Name(s)	Interaction	Mechanism
Central Alpha-Agonists		
Clonidine	Beta-adrenergic blockers	Withdrawal hypertension may be more severe in patients receiving clonidine and beta-adrenergic blockers. This combination may, on occasion, cause paradoxical hypertension.
Clonidine	Tricyclic antidepressants	The antihypertensive effects of clonidine may be decreased by tricyclic antidepressants. Tricyclic antidepressants may worsen rebound reactions from abrupt clonidine withdrawal.
Clonidine	Non-dihydropyridine calcium channel blockers	Concurrent use of clonidine and non-dihydropyridine calcium channel blockers may result in increased incidence of sinus bradycardia.
Clonidine	Mirtazapine	Concurrent use of mirtazapine and clonidine may result in hypertension, decreased antihypertensive effectiveness.
Clonidine	Tizanidine	The potential for symptomatic additive hypotension exists when tizanidine is coadministered with clonidine.
Amphetamine Derivatives		
Amphetamines	MAOIs	Toxicity of amphetamines may be increased by MAOIs. Headache, hyperpyrexia, elevated blood pressure and bradycardia may occur. Amphetamines can liberate large quantities of intraneuronal norepinephrine that have accumulated during treatment with MAOIs.
Amphetamines	Furazolidone	Toxicity of amphetamines may be increased by furazolidone. Headache, hyperpyrexia, and elevated blood pressure may occur. Amphetamines can liberate large quantities of intraneuronal catecholamines that have accumulated during treatment with furazolidone, due to monoamine oxidase inhibition.
Amphetamines	Urinary alkalinizers	Interaction may lead to pH-dependent diminished urinary elimination of amphetamines and increases risk of amphetamine toxicity.
Amphetamines	Chlorpromazine	Concurrent use of amphetamine and chlorpromazine may result in decreased amphetamines and chlorpromazine effectiveness.
Respiratory and CNS Stimulants		
Methylphenidates	MAOIs	Pharmacologic effects of methylphenidates may be increased. Headache, gastrointestinal symptoms and hypertension may occur. The mechanism of this interaction is not clear. Liberation of intraneuronal catecholamine stores may play a role.

Generic Name(s)	Interaction	Mechanism
Methylphenidates	Bupropion	Caution is advised with concomitant use of bupropion and methylphenidates, as this may result in an increased risk of seizures, especially in patients with a seizure history. Both agents may lower the seizure threshold.
Central Nervous System Agents, Miscellaneous		
Atomoxetine	MAOIs	Toxic effects may be increased with concurrent administration of atomoxetine and MAOIs. Serious and sometimes fatal reactions have occurred. Pharmacologic effects of atomoxetine and MAOIs may be additive.

MAOIs=monoamine oxidase inhibitors

VI. Adverse Drug Events

The most common adverse drug events reported with the cerebral stimulants/agents used for attention deficit-hyperactivity disorder (ADHD) are listed in Tables 7 to 10. The boxed warnings for the cerebral stimulants/agents used for ADHD are listed in Tables 11 to 16. Methylphenidate and amphetamines increase dopamine levels in the brain similar to cocaine and methamphetamine. They are classified as Schedule II controlled substances by federal regulation. Long-term abusive use can lead to tolerance and psychological dependence. There is no evidence to suggest that drug abuse results from prescribed stimulants if they are properly monitored.[1,33-35] Methylphenidate is a less potent sympathomimetic amine than mixed amphetamine salts, which may be associated with a lower potential for abuse.[34] The osmotic-release formulation of methylphenidate cannot be crushed and may decrease the potential for abuse. It has also been proposed that transdermal methylphenidate may possess less potential for abuse compared to orally-administered cerebral stimulants. Atomoxetine, clonidine, and guanfacine are not controlled substances.

Table 7. Adverse Drug Events (%) Reported with the Central Alpha-Agonists[3]

Adverse Events	Clonidine
Cardiovascular	
Atrioventricular block	✔
Bradycardia	≤4
Cardiac arrhythmia	✔
Chest pain	✔
Congestive heart failure	✔
Electrocardiogram abnormalities	✔
Orthostatic hypotension	✔
Pallor	✔
Palpitations	1
Reynaud's phenomenon	✔
Syncope	✔
Tachycardia	1
Central Nervous System	
Abnormal sleep-related event	1 to 3
Aggressive behavior	✔
Agitation	✔
Anxiety	✔
Behavioral change	✔
Crying	1 to 3
Delirium	✔
Dizziness	2 to 5
Emotional disorder	3 to 4
Fatigue/lethargy	12 to 15
Fever	✔

Adverse Events	Clonidine
Hallucinations	✔
Headache	1 to 11
Insomnia	≤5
Irritability	3 to 6
Malaise	✔
Mental depression	1
Nervousness	1 to 3
Nightmares	✔
Paresthesia	✔
Restlessness	✔
Sleep terror	3
Somnolence	26 to 33
Tremor	✔
Vivid dreams	✔
Dermatological	
Flushing	✔
Rash	1
Urticaria	✔
Gastrointestinal	
Abdominal pain	≤3
Anorexia	1
Constipation	1 to 6
Diarrhea	≤1
Dry mouth	✔
Nausea	1 to 4
Thirst	1 to 3
Vomiting	✔
Weight gain	<1
Genitourinary	
Dysuria	✔
Enuresis	4
Erectile dysfunction	2 to 3
Gynecomastia	1
Libido decreased	✔
Nocturia	1
Pollakiuria	3
Sexual disturbances	3
Hepatic	
Hepatitis	✔
Liver function test abnormalities	≤1
Musculoskeletal	
Arthralgia	1
Leg cramps	≤1
Myalgia	1
Pain in extremities	✔
Weakness	10
Respiratory	
Asthma	4
Epistaxis	3
Lower respiratory tract infection	2
Nasal congestion	2 to 4
Nasal dryness	✔
Nasopharyngitis	2
Upper respiratory tract infection	2 to 7

Adverse Events	Clonidine
Special Senses	
Accommodation difficulties	✔
Blurred vision	✔
Dry eyes	✔
Eye pain	✔
Other	
Body temperature increase	≤2
Ear infection	✔
Ear pain	4
Flu-like syndrome	≤3
Throat pain	3 to 5
Thrombocytopenic purpura	✔
Viral infection	≤3

✔ Percent not specified.

Table 8. Adverse Drug Events (%) Reported with the Amphetamines[4-10]

Adverse Events	Amphetamine Sulfate	Amphetamine Aspartate/ Amphetamine Sulfate/ Dextroamphetamine	Dextroam-phetamine	Lisdexam-fetamine	Metham-phetamine
Cardiovascular					
Blood pressure increased	-	-	-	3	-
Cardiomyopathy	✔	✔ †	✔	✔	-
Heart rate increased	-	-	✔	2	✔
Hypertension	✔	✔ †	✔	✔	✔
Myocardial infarction	-	✔ *	✔	✔	✔
Palpitations	✔	✔ †, 2 to 4*	✔	✔	✔
Peripheral vascular disease	-	-	✔	-	-
Raynaud's disease	-	-	✔	-	✔
Sudden death	-	✔ *	✔	✔	✔
Tachycardia	✔	✔ †, 6*	✔	✔	✔
Central Nervous System					
Aggressive behavior	-	✔ †*	✔	-	-
Agitation	-	8*	-	3	-
Anxiety	-	8*	-	6	-
Depression	-	✔ †*	-	✔	-
Dizziness	✔	2 to 7*	✔	5	✔
Dyskinesia	✔	✔ †*	✔	✔	-
Dysphoria	✔	✔ †*	✔	✔	✔
Euphoria	✔	✔ †*	✔	✔	✔
Fever	-	5*	-	2	-
Headache	✔	✔ †, 26*	✔	12	✔
Insomnia	✔	12 to 27*	✔	13 to 27	✔
Irritability	-	✔ †*	-	10	-
Labile affect	-	-	-	3	-
Mania	-	-	✔	✔	✔
Nervousness	-	6 to 13*	-	-	-
Overstimulation	✔	✔ †	✔	✔	✔
Psychotic episodes	✔	✔ †	✔	✔	✔
Restlessness	✔	✔ †*	✔	3	✔
Seizures	-	✔ *	-	✔	✔
Somnolence	-	2 to 4*	-	2	-
Speech disorder	-	2 to 4*	-	-	-
Stroke	-	✔ *	✔	✔	✔
Tic exacerbation	✔	✔ †*	✔	2	✔
Tourette's exacerbation	✔	✔ †*	✔	✔	✔
Tremor	✔	✔ †*	✔	2	✔

Adverse Events	Amphetamine Sulfate	Amphetamine Aspartate/ Amphetamine Sulfate/ Dextroamphetamine	Dextroam-phetamine	Lisdexam-fetamine	Metham-phetamine
Twitching	-	2 to 4*	-	-	-
Dermatological					
Diaphoresis	-	2 to 4*	-	-	-
Hyperhidrosis	-	-	-	3	-
Photosensitivity	-	2 to 4*	-	-	-
Rash	-	✔ †*	✔	3	✔
Stevens-Johnson syndrome	-	✔ †*	-	✔	-
Toxic epidermal necrolysis	-	✔ †*	-	✔	-
Urticaria	✔	✔ †*	✔	✔	✔
Gastrointestinal					
Abdominal pain	-	11 to 14*	-	12	-
Anorexia	✔	-	✔	5	✔
Appetite decreased	-	22 to 36*	-	27 to 39	-
Constipation	✔	✔ †, 2 to 4*	✔	✔	✔
Diarrhea	✔	2 to 6*	✔	7	✔
Dry mouth	✔	2 to 35*	✔	4 to 26	✔
Dyspepsia	-	2 to 4*	-	-	-
Nausea	-	2 to 8*	-	6 to 7	✔
Other gastrointestinal disturbances	✔	-	✔	-	✔
Unpleasant taste	✔	✔ †*	✔	✔	✔
Vomiting	-	2 to 7*	-	9	✔
Weight loss	✔	4 to 11*	✔	9	✔
Genitourinary					
Changes in libido	✔	2 to 4*	✔	≤2	✔
Impotence	✔	2 to 4*	✔	✔	✔
Prolonged erections	✔	-	-	-	-
Urinary tract infection	-	5*	-	-	-
Other					
Anaphylaxis	-	✔ *	-	✔	-
Angioedema	-	-	-	✔	-
Blurred vision	-	✔ †*	✔	✔	-
Dysmenorrhea	-	2 to 4*	-	-	-
Dyspnea	-	2 to 4*	-	2	-
Growth suppression	-	-	✔	✔	✔
Hypersensitivity reactions	-	-	-	✔	-
Infection	-	2 to 4*	-	-	-
Rhabdomyolysis	✔	-	-	-	-
Tolerance	-	-	-	-	✔
Weakness	-	2 to 6*	-	-	-

†Immediate-release formulation.
*Extended-release formulation.
✔ Percent not specified.
-Event not reported or incidence <1%.

Table 9. Adverse Drug Events (%) Reported with the Respiratory and CNS Stimulants [11-20]

Adverse Events	Dexmethylphenidate	Methylphenidate
Cardiovascular		
Angina	✔	✔
Cardiac arrhythmia	✔	✔
Chest pain	-	✔
Hypertension	✔	✔
Hypotension	✔	✔
Myocardial infarction	-	✔
Palpitations	✔	✔
Pulse increase/decrease	✔	✔

Adverse Events	Dexmethylphenidate	Methylphenidate
Raynaud's phenomenon	-	✔
Sudden death	✔	-
Systolic blood pressure increased	-	-
Tachycardia	3	✔
Vasodilation	-	-
Central Nervous System		
Aggressive behavior	✔	✔
Agitation	-	-
Anxiety	5 to 11	-
Attention disturbance	-	-
Cerebral arteritis	✔	✔
Cerebral occlusion	✔	✔
Depression	✔	✔
Dizziness	6	✔
Drowsiness	✔	✔
Dyskinesia	✔	✔
Emotional instability	-	6†
Fatigue/lethargy	-	-
Fever	5	✔
Hallucinations	-	✔ †
Headache	25 to 39	✔, 28†
Hyperkinesia	-	-
Hypertonia	-	-
Insomnia	✔	✔, 13 to 30†
Jittery feeling	12	-
Labile affect	-	✔
Mania	-	✔
Migraine	-	-
Nervousness	✔	✔
Neuroleptic malignant syndrome	✔	✔
Overstimulation	-	-
Paresthesia	-	✔
Psychotic episodes	-	-
Restlessness	12	-
Seizures	-	✔ †
Somnolence	-	-
Tic	-	✔, 7†
Tourette's exacerbation	✔	✔
Toxic psychosis	✔	✔
Tremor	-	-
Vertigo	-	-
Dermatological		
Alopecia	-	✔
Application site reaction	-	✔ †
Dermatitis	-	-
Diaphoresis	-	-
Erythema	-	✔
Erythema multiforme	✔	✔
Exfoliative dermatitis	✔	✔
Hair loss	✔	✔
Herpes simplex	-	-
Hyperhidrosis	-	✔
Rash	✔	✔

Adverse Events	Dexmethylphenidate	Methylphenidate
Stevens-Johnson syndrome	-	-
Toxic epidermal necrolysis	-	✔
Urticaria	✔	✔
Gastrointestinal		
Abdominal pain	15	✔
Anorexia	5 to 7	✔, 5 to 46†
Appetite decreased	30	✔, 26†
Bruxism	-	✔
Constipation	-	✔
Diarrhea	-	✔
Dry mouth	7 to 20	✔
Dyspepsia	5 to 9	✔
Flatulence	-	-
Mouth ulceration	-	-
Nausea	9	✔, 12†
Stomach cramps	✔	-
Thirst	-	-
Unpleasant taste	-	-
Vomiting	-	✔, 10†
Weight loss	✔	✔, 9†
Genitourinary		
Abnormal urine	-	-
Erectile disturbance	-	✔
Hematuria	-	-
Libido decreased	-	✔
Polyuria	-	-
Pyuria	-	-
Hematologic		
Agranulocytosis	-	-
Anemia	✔	✔
Eosinophilia	-	-
Leukopenia	✔	✔
Pancytopenia	-	✔
Thrombocytopenic purpura	✔	✔
Hepatic		
Hepatic coma	✔	✔
Liver function test abnormalities	✔	✔
Musculoskeletal		
Arthralgia	✔	✔
Back pain	-	-
Respiratory		
Cough	-	✔
Dyspnea	-	✔
Epistaxis	-	-
Lung disorder	-	-
Nasal congestion	-	✔, 6†
Nasopharyngitis	-	✔, 5†
Pharyngitis	-	✔
Pharyngolaryngeal pain	4 to 7	✔
Respiratory tract infection	-	✔
Rhinitis	-	✔
Sinusitis	-	✔
Special Senses		

Adverse Events	Dexmethylphenidate	Methylphenidate
Abnormal vision	-	-
Accommodation difficulties	✔	✔
Amblyopia	-	-
Blurred vision	✔	✔
Dry eyes	-	✔
Eye pain	-	-
Mydriasis	-	✔
Other		
Accidental injury	-	✔
Allergic contact sensitization	-	✔ †
Anaphylaxis	-	✔ †
Dysmenorrhea	-	✔
Edema	-	-
Flu-like syndrome	-	-
Growth suppression	-	✔
Hypersensitivity reactions	✔	✔
Necrotizing vasculitis	✔	✔
Pain	-	-
Thirst	-	-
Viral infection	-	28†

†Transdermal formulation.
✔ Percent not specified.
- Event not reported or incidence <1%.

Table 10. Adverse Drug Events (%) Reported with the Central Nervous System Agents, Miscellaneous[21,22]

Adverse Events	Atomoxetine	Guanfacine
Cardiovascular		
Atrioventricular block	-	✔
Chest pain	-	-
Diastolic blood pressure increased	4 to 22	-
Flushing	≥2	-
Hypertension	1 to 9	✔
Hypotension	<2	4
Palpitations	3	-
QT prolongation	<1	-
Reynaud's phenomenon	✔	-
Sinus arrhythmia	-	✔
Stroke	✔	-
Systolic blood pressure increased	4 to 13	-
Tachycardia	2 to 24	-
Central Nervous System		
Abnormal dreams	4	-
Aggressive behavior	✔	-
Agitation	✔	✔
Akathisia	✔	-
Anxiety	✔	✔
Ataxia	-	-
Attention disturbance	-	-
Chills	3	-
Confusion	-	-
Crying	2	-
Depression	-	✔
Disorientation	-	-
Dizziness	5 to 6	6 to 8

Adverse Events	Atomoxetine	Guanfacine
Early morning awakening	<2	-
Fatigue/lethargy	6 to 9	14
Fever	3	-
Hallucinations	-	✔
Headache	2 to 19	21 to 24
Hostility	✔	-
Insomnia	2 to 15	12
Irritability	≤ 6	2
Jittery feeling	2	-
Mania	✔	-
Mood swings	1 to 2	-
Nervousness	-	-
Nightmare	-	✔
Panic disorder	✔	-
Paresthesia	4	-
Rigors	3	-
Seizure	-	✔
Sleep disorder	-	-
Sleep disturbance	3	-
Sleep paralysis	-	-
Sleep walking	-	-
Somnolence	4 to 11	18 to 38
Suicidal ideation	✔	-
Syncope	✔	✔
Tremor	2	-
Dermatological		
Dermatitis	2 to 4	-
Diaphoresis	2	-
Flushing	2	-
Hyperhidrosis	4	-
Rash	2	-
Urticaria	✔	-
Endocrine and Metabolic		
Dysmenorrhea	6	-
Hot flushes	8	-
Menstrual disturbances	2 to 3	-
Gastrointestinal		
Abdominal pain	7 to 18	10 to 11
Anorexia	<3	-
Appetite decreased	11 to 16	2
Constipation	1 to 9	3
Diarrhea	4	-
Dry mouth	4 to 21	3
Dyspepsia	4 to 6	✔
Fecal incontinence	-	-
Flatulence	2	-
Nausea	7 to 26	4
Stomach discomfort	-	✔
Vomiting	3 to 11	✔
Weight increase	-	✔
Weight loss	2 to 30	-
Genitourinary		
Dysuria	3	-
Ejaculatory disturbance	3	-

Adverse Events	Atomoxetine	Guanfacine
Enuresis	-	✔
Erectile disturbance	9	-
Impotence	3	-
Libido decreased	4	-
Orgasm abnormal	2	-
Prostatitis	2	-
Urinary incontinence	-	-
Urinary retention	7	-
Hepatic		
Hepatotoxicity	✔	-
Jaundice	✔	-
Hypoesthesia	-	-
Myalgia	-	-
Myasthenia	-	-
Weakness	-	-
Respiratory		
Asthma	-	✔
Bronchitis	-	-
Cough	11	-
Dyspnea	-	-
Nasopharyngitis	-	-
Rhinitis	-	-
Rhinorrhea	4	-
Sinus headache	3	-
Sinusitis	6	-
Upper respiratory infection	-	-
Special Senses		
Amblyopia	-	-
Blurred vision	-	-
Mydriasis	<2	-
Tinnitus	-	-
Other		
Accidental injury	-	-
Allergic contact sensitization	✔	-
Ear infection	3	-
Ear pain	-	-
Flu-like syndrome	✔	-
Hypersensitivity reactions	<1	✔
Influenza	3	-
Pain	-	-
Pallor	-	✔
Thirst	-	-
Viral infection	-	-

✔ Percent not specified.
- Event not reported or incidence <1%.

Table 11. Boxed Warning for the Amphetamines[23]

WARNING
Amphetamines have a high potential for abuse. Administration of amphetamines for prolonged periods of time may lead to drug dependence and must be avoided. Particular attention should be paid to the possibility of subjects obtaining amphetamines for non-therapeutic use or distribution to others, and the drugs should be prescribed or dispensed sparingly. Misuse of amphetamines may cause sudden death and serious cardiovascular adverse reactions.

Table 12. Boxed Warning for Atomoxetine[23]

WARNING
Suicidal ideation in children and adolescents: Atomoxetine increased the risk of suicidal ideation in short-term studies in children or adolescents with attention deficit hyperactivity disorder (ADHD). Anyone considering the use of atomoxetine in a child or adolescent must balance this risk with the clinical need. Closely monitor patients who are started on therapy for suicidality (suicidal thinking and behavior), clinical worsening, or unusual changes in behavior. Advise families and caregivers of the need for close observation and communication with the prescribing health care provider. Atomoxetine is approved for ADHD in children and adults. Atomoxetine is not approved for major depressive disorder (MDD). Pooled analysis of short-term (six- to 18-week), placebo-controlled trials of atomoxetine in children and adolescents (12 trials involving more than 2,200 patients, including 11 trials in ADHD and 1 trial in enuresis) has revealed a greater risk of suicidal ideation early during treatment in those receiving atomoxetine compared to placebo. The average risk of suicidal ideation in patients receiving atomoxetine was 0.4% (5/1,357 patients), compared to none in placebo-treated patients (0/851 patients). No suicides occurred in these trials

Table 13. Boxed Warning for Dexmethylphenidate[23]

WARNING
Drug dependence: Give dexmethylphenidate cautiously to patients with a history of drug dependence or alcoholism. Chronic, abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during drug withdrawal from abusive use because severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow-up.

Table 14. Boxed Warning for Lisdexamfetamine[23]

WARNING
Potential for misuse, abuse, addiction, and diversion: Lisdexamfetamine dimesylate is a Schedule II controlled substance. Stimulants, such as amphetamines and methylphenidates, are subject to misuse abuse, addiction, and criminal diversion. Misuse of amphetamines may cause sudden death and serious cardiovascular adverse reactions.

Table 15. Boxed Warning for Methamphetamine[23]

WARNING
Methamphetamine has a high potential for abuse. It should thus be tried only in weight reduction programs for patients in whom alternative therapy has been ineffective. Administration of methamphetamine for prolonged periods of time in obesity may lead to drug dependence and must be avoided. Particular attention should be paid to the possibility of subjects obtaining methamphetamine for nontherapeutic use or distribution to others, and the drug should be prescribed or dispensed sparingly.

Table 16. Boxed Warning for Methylphenidate[23]

WARNING
Drug dependence: Give methylphenidate cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during withdrawal, because severe depression as well as the effects of chronic overactivity can be unmasked. Withdrawal following long-term therapeutic use may unmask symptoms of the underlying disorder that may require follow-up.

VII. Dosing and Administration

The usual dosing regimens for the cerebral stimulants/agents used for attention deficit-hyperactivity disorder (ADHD) are listed in Table 17.

Table 17. Usual Dosing Regimens for the Cerebral Stimulants/Agents Used for ADHD[3-23]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Central Alpha-Agonists			
Clonidine	Safety and efficacy has not been established in adults.	ADHD in patients ≥6 years of age: Tablet (SR): initial, 0.1 mg at bedtime; increase by 0.1 mg/day every seven days until desired response; doses should be administered twice daily; maximum, 0.4 mg/day	Tablet (SR): 0.1 mg
Amphetamines			
Amphetamine sulfate	Exogenous obesity: Tablet: usual dosage is up to 30 mg daily, taken in divided doses of 5 to 10 mg, 30 to 60 minutes before meals Narcolepsy: Tablet: 5 to 60 mg/day in divided doses	ADHD in children three to five years of age: Tablet: initial, 2.5 mg once daily, daily dosage may be raised in increments of 2.5 mg at weekly intervals until optimal response ADHD in children six years of age or older: Tablet: initial, 5 mg once or twice daily, daily dosage may be raised in increments of 5 mg at weekly intervals until optimal response Exogenous obesity in children ≥12 years of age: Tablet: usual dosage is up to 30 mg daily, taken in divided doses of 5 to 10 mg, 30 to 60 minutes before meals Narcolepsy in children six to 12 years of age: Tablet: initial, 5 mg daily, daily dose may be raised in increments of 5 mg at weekly intervals until optimal response Narcolepsy in children 12 years of age and older: Tablet: initial, 10 mg once daily, daily dosage may be raised in increments of 10 mg at weekly intervals until optimal response	Tablet: 5 mg 10 mg
Amphetamine aspartate,	ADHD: Capsule (ER): 20 mg once	ADHD: Capsule (ER), ≥six years of	Capsule (ER): 5 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
amphetamine sulfate, and dextroamphetamine	daily in the morning Tablet: 2.5 to 5 mg once or twice daily; maintenance, up to 40 mg/day Narcolepsy: Capsule (ER), tablet: 5 to 60 mg daily in divided doses	age: 10 mg once daily in the morning; maximum, 30 mg/day Tablet, ≥three years of age: 2.5 to 5 mg once or twice daily; maintenance, up to 40 mg/day Narcolepsy in children six to 12 years of age: Capsule (ER), tablet: 5 mg once daily; may increase by 5 mg weekly until optimal response Narcolepsy in children 12 years of age and older: Capsule (ER), tablet: 10 mg once daily; may increase by 10 mg weekly until optimal response	10 mg 15 mg 20 mg 25 mg 30 mg Tablet: 5 mg 7.5 mg 10 mg 12.5 mg 15 mg 20 mg 30 mg
Dextroamphetamine	ADHD: Solution, tablet: initial, 2.5 to 5 mg once or twice daily; maintenance, up to 40 mg/day Capsule (SR): initial, 5 mg once or twice daily; maintenance, up to 40 mg/day Narcolepsy: Capsule (SR), solution, tablet: 5 to 60 mg/day administered in divided doses	ADHD in children six years of age and older: Solution, tablet: initial, 2.5 to 5 mg once or twice daily; maintenance, up to 40 mg/day Capsule (SR): initial, 5 mg once or twice daily; maintenance, up to 40 mg/day ADHD in children three to five years of age: Solution, tablet: initial, 2.5 mg once daily; maintenance, up to 40 mg daily Narcolepsy in adolescents 12 years of age and older: Capsule (SR), solution, tablet: initial, 10 mg once daily; maintenance, 5 to 60 mg/day administered in divided doses Narcolepsy in children six to 12 years of age: Capsule (SR), solution, tablet: initial, 5 mg once daily; maintenance, 5 to 60 mg/day administered in divided doses	Capsule (SR): (Dexedrine® Spansule) 5 mg 10 mg 15 mg Solution: (Procentra®) 5 mg/5 mL Tablet: (Dexedrine®, Zenzedi®) 2.5 mg 5 mg 7.5 mg 10 mg
Lisdexamfetamine	ADHD: Capsule: initial, 30 mg once daily in the morning; maximum, 70 mg/day	ADHD in children six years of age and older: Capsule: initial, 30 mg once daily in the morning; maximum, 70 mg/day	Capsule: 10 mg 20 mg 30 mg 40 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Binge eating disorder: Capsule: initial, 30 mg once daily in the morning; maximum, 70 mg/day		50 mg 60 mg 70 mg
Methamphetamine	Exogenous obesity: Tablet: 5 mg taken 30 minutes before each meal ADHD: Tablet: initial, 5 mg once or twice daily; maintenance, 20 to 25 mg/day	Exogenous obesity in children 12 years of age and older: Tablet: 5 mg taken 30 minutes before each meal ADHD in children six years of age and older: Tablet: initial, 5 mg once or twice daily; maintenance, 20 to 25 mg/day	Tablet: 5 mg
Respiratory and CNS Stimulants			
Dexmethylphenidate	ADHD: Capsule (ER) (new starts): initial, 5 to 10 mg once daily in the morning; maximum, 40 mg/day Capsule (ER) (patients currently receiving methylphenidate): initial, half the dose of racemic methylphenidate Tablet (new starts): initial, 2.5 mg twice daily; maximum, 10 mg twice daily Tablet (patients currently receiving methylphenidate): initial, half the dose of racemic methylphenidate; maximum, 10 mg twice daily	ADHD in children six years of age and older: Capsule (ER) (new starts): initial, 5 to 10 mg once daily in the morning; maximum, 30 mg/day Capsule (ER) (patients currently receiving methylphenidate): initial, half the dose of racemic methylphenidate Tablet (new starts): initial, 2.5 mg twice daily; maximum, 10 mg twice daily Tablet (patients currently receiving methylphenidate): initial, half the dose of racemic methylphenidate; maximum, 10 mg twice daily	Capsule (ER): 5 mg 10 mg 15 mg 20 mg 25 mg 30 mg 35 mg 40 mg Tablet: 2.5 mg 5 mg 10 mg
Methylphenidate	Treatment of ADHD: Chewable tablet, solution, tablet: 20 to 30 mg/day administered in two or three divided doses Capsule (ER) (new starts): initial, 10 or 20 mg once daily in the morning; maximum, 60 mg/day Capsule (ER) (patients currently receiving methylphenidate): administer equivalent total daily doses Suspension (ER): initial, 20	ADHD in children six years of age and older: Chewable tablet, solution, tablet: initial, 5 mg twice daily; maintenance, increase dose gradually Tablet (ER) (new starts): initial, 18 mg once daily in the morning; maximum, 54 (children) and 72 mg/day (adolescents) Tablet (ER) (patients currently receiving methylphenidate): dosing is based on current dose regimen and clinical	Capsule (ER): (Aptensio XR®, Metadate CD®, Ritalin LA®) 10 mg 15 mg 20 mg 30 mg 40 mg 50 mg 60 mg Suspension (ER): (Quillivant XR®) 25 mg/5 mL Chewable tablet:

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	mg once daily in the morning; maximum, 60 mg/day Tablet (ER) (new starts): initial, 18 to 36 mg/day; maximum, 72 mg/day Tablet (ER) (patients currently receiving methylphenidate): dosing is based on current dose regimen and clinical judgment Tablet (ER): may be used in place of tablets when the eight hour dosage of the tablet (ER) corresponds to the titrated eight hour dosage with the tablets Tablet (SR): may be used in place of tablets when the eight hour dosage of the tablet (SR) corresponds to the titrated eight hour dosage with the tablets Transdermal patch: initial, 10 mg; maintenance, titrate to effect <u>Narcolepsy:</u> Chewable tablet, solution, tablet (adults): 20 to 30 mg/day administered in two or three divided doses Tablet (ER): may be used in place of tablets when the eight hour dosage of the tablet (ER) corresponds to the titrated eight hour dosage with the tablets Tablet (SR): may be used in place of tablets when the eight hour dosage of the tablet (SR) corresponds to the titrated eight hour dosage with the tablets	judgment Tablet (ER): may be used in place of tablets when the eight hour dosage of the tablet (ER) corresponds to the titrated eight hour dosage with the tablets Tablet (SR): may be used in place of tablets when the eight hour dosage of the tablet (SR) corresponds to the titrated eight hour dosage with the tablets Transdermal patch: initial, 10 mg; maintenance, titrate to effect <u>Narcolepsy in children six years of age and older:</u> Chewable tablet, solution, tablet: initial, 5 mg twice daily; maintenance, increase dose gradually Tablet (ER): may be used in place of tablets when the eight hour dosage of the tablet (ER) corresponds to the titrated eight hour dosage with the tablets Tablet (SR): may be used in place of tablets when the eight hour dosage of the tablet (SR) corresponds to the titrated eight hour dosage with the tablets	(Methylin®) 2.5 mg 5 mg 10 mg Solution: (Methylin®) 5 mg/5 mL 10 mg/5 mL Tablet (ER): (Concerta®, Metadate ER®) 10 mg 18 mg 20 mg 27 mg 36 mg 54 mg Tablet: (Methylin®, Ritalin®) 5 mg 10 mg 20 mg Tablet (SR): 20 mg Transdermal patch: 10 mg/9 hours 15 mg/9 hours 20 mg/9 hours 30 mg/9 hours
Central Nervous System Agents, Miscellaneous			
Atomoxetine	<u>ADHD:</u> Capsule (>70 kg and adults): initial, 40 mg/day; maintenance, 80 mg/day; maximum, 100 mg/day	<u>ADHD in children six years of age and older:</u> Capsule (≤70 kg): initial, 0.5 mg/kg/day; maintenance, 1.2 mg/kg/day; maximum, 1.4	Capsule: 10 mg 18 mg 25 mg 40 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
		mg/kg/day Capsule (>70 kg and adults): initial, 40 mg/day; maintenance, 80 mg/day; maximum, 100 mg/day.	60 mg 80 mg 100 mg
Guanfacine	ADHD as monotherapy and as adjunctive therapy to stimulant medications: Tablet (ER): initial, 1 mg once daily; maintenance, 1 to 4 mg/day	ADHD as monotherapy and as adjunctive therapy to stimulant medications in children six years of age and older: Tablet (ER): initial, 1 mg once daily; maintenance, 1 to 4 mg/day	Tablet (ER): 1 mg 2 mg 3 mg 4 mg

ADHD=attention deficit hyperactivity disorder, ER=extended-release, SR=sustained-release

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the cerebral stimulants/agents used for attention deficit hyperactivity disorder (ADHD) are summarized in Table 18.

Table 18. Comparative Clinical Trials with the Cerebral Stimulants/Agents Used for ADHD

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Attention Deficit Hyperactivity Disorder				
McCracken et al.[36] (2003) AMP-IR (Adderall®) 10 mg daily vs AMP-XR (Adderall XR®) 10 to 30 mg daily vs placebo	DB, PC, RCT, XO Children six to 12 years of age diagnosed with ADHD (combined or hyperactive-impulsive subtype)	N=51 5 weeks	Primary: SKAMP scales Secondary: Examination of the time course of AMP-XR	Primary: AMP-IR and AMP-XR were judged to have similar efficacy, and both exceeded placebo on attention and deportment SKAMP scales (P<0.0001). Secondary: The AMP-XR group displayed continued efficacy (in SKAMP score improvements) at time points beyond that of the AMP-IR group (i.e., 12 hours post dose).
Pliszka et al.[37] (2000) AMP-IR (Adderall®) 12.5 mg daily vs MPH-IR 25 mg daily vs	DB, PC, PG, RCT Children in grades one through five diagnosed with ADHD	N=58 3 weeks	Primary: CGI-S (parent and teacher) Secondary: Not reported	Primary: More responders were reported with AMP-IR than MPH-IR or placebo on both CGI-S scores (P<0.05). Behavioral effects of AMP-IR appeared to persist longer than with MPH-IR. Fourteen (70%) patients in the AMP-IR group required only a single morning dose, and 17 (85%) patients in the MPH-IR group received two or more doses per day (P=0.003). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				
Pelham et al.[38] (1999) AMP-IR (Adderall®) 7.5 or 12.5 mg twice daily vs MPH-IR (Ritalin®) 10 or 17.5 mg twice daily vs placebo	DB, PC, RCT, XO Children five to 12 years of age diagnosed with ADHD	N=25 6 weeks	Primary: Time course and dose-dependent response information Secondary: Not reported	Primary: Both doses of AMP-IR were generally more efficacious in reducing negative behaviors and improving academic productivity than low-dose MPH-IR (10 mg BID) throughout the course of the entire day. The differences were more pronounced when the effects of MPH-IR were wearing off at midday and late afternoon/early evening (P<0.025). Conversely, AMP-IR 7.5 mg BID and MPH-IR 17.5 mg BID produced equivalent behavioral changes throughout the entire day. The doses of AMP-IR that were assessed produced greater improvement than did the assessed doses of MPH-IR, particularly the lower dose of MPH-IR (P<0.01). Both drugs produced low and comparable levels of clinically significant side effects. Secondary: Not reported
Faraone et al.[39] (2002) AMP-IR (Adderall®) vs MPH-IR	MA (4 trials) Patients diagnosed with ADHD	N=216 3 to 8 weeks	Primary: CGI-S (parent, teacher and investigator) Secondary: Not reported	Primary: Combined results showed slightly greater efficacy with AMP-IR vs MPH-IR in clinician and parent ratings (P<0.05). No statistically significant difference was found in CGI-S scores with teacher ratings (P≥0.26). Secondary: Not reported
Biederman et al.[40] (2002) AMP-XR (Adderall XR®) 10 to 30 mg daily	DB, MC, PC, RCT Children six to 12 years of age diagnosed with ADHD (hyperactive-	N=584 3 weeks	Primary: CGI-S (teachers and parents) Secondary: Variation in responses based on	Primary: Each AMP-XR treatment group had a statistically significant improvement in both CGI-S teacher and parent scales (P<0.001). Secondary: The CGI-S teacher scores calculated for the morning and afternoon assessments showed all doses of AMP-XR to be more effective than

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	impulsive or combined subtypes)		morning and afternoon assessments	placebo (P<0.001) at each assessment. The CGI-S teacher scores in the AMP-XR group were statistically significantly improved at all time points compared to those in the placebo group (P<0.001).
Goodman et al.[41] (2005) AMP-XR (Adderall XR®) 10 to 60 mg daily	MC, OL, PRO Adults ≥18 years of age diagnosed with ADHD (any subtype)	N=725 10 weeks	Primary: ADHD-RS, CGI-I Secondary: SF-36	Primary: At the end of the study, the mean ADHD-RS scores significantly decreased in the AMP-XR group regardless of dose compared to baseline (P<0.0001). Statistical analysis comparing the individual AMP-XR doses was not performed. At the end of the study, most patients obtained CGI-I ratings of much/very much improved (522/702; 74.4%). Secondary: At the end of the study, the AMP-XR groups reported significant improvements in all quality of life measurements (P<0.0001 for all) measured by the SF-36, including physical functioning and mental health parameters.
Biederman et al.[42] (2002) Atomoxetine 1.2 to 1.8 mg/kg/day vs placebo	2 DB, MC, PC, RCT Females seven to 13 years of age diagnosed with ADHD	N=51 9 weeks	Primary: ADHD-RS Secondary: CPRS-R, CGI-S (parents)	Primary: Atomoxetine significantly decreased ADHD-RS scores compared to placebo (P<0.05) for the entire duration of the study. Secondary: Atomoxetine statistically significantly decreased the parent-rated CPRS-R index scores compared to placebo (10.3 vs 1.0; P<0.001). Atomoxetine also statistically significantly decreased the parent-rated CGI-S scores compared to placebo (1.5 vs 0.6; P<0.001).
Durell et al.[43] (2013) Atomoxetine vs placebo	DB, PC, RCT Young adults 18 to 30 years of age with ADHD	N=445 12 weeks	Primary: CAARS-Inv: SV total ADHD symptoms score with adult prompts Secondary: AAQoL-29, CGI-	Primary: Compared to placebo, treatment with atomoxetine resulted in a greater improvement in CAARS: Inv: SV (-13.6±0.8 vs -9.3±0.8; 95% CI, -6.35 to -2.37; P<0.001). Secondary: Compared to placebo, treatment with atomoxetine resulted in a greater improvement in CGI-S (-1.1±0.1 vs -0.7±0.1; 95% CI, -0.63 to -0.24;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			S, Patient Global Impression-Improvement, CAARS self report, BRIEF-Adult Version Self Report and assessments of depression, anxiety, sleepiness, driving behaviors, social adaptation and substance abuse	P<0.001) and CAARS Self-Report (-11.9±0.8 vs -7.8±0.7; 95% CI, -5.94 to -2.15; P<0.001) but not on the Patient Global Impression-Improvement score. Treatment with atomoxetine was superior to placebo on the AAQoL-29 and BRIEF-Adult Version Self-Report.
Michelson et al.[44] (2001) Atomoxetine 1.2 to 1.8 mg/kg/day vs placebo	MC, OL, PC, RCT Children eight to 18 years of age diagnosed with ADHD	N=297 8 weeks	Primary: ADHD-RS Secondary: CPRS-R, CHQ	Primary: Significant reduction in ADHD-RS was seen in both active groups (P<0.001). No difference was seen between the 1.2 and the 1.8 mg/kg/day treatment arms. Secondary: Atomoxetine 1.2 mg/kg showed significant decreases in all scales of CPRS-R (P<0.05). Atomoxetine 1.8 mg/kg showed significant increase in all scales of CHQ (P<0.05).
Kratochvil et al.[45] (2011) Atomoxetine 0.5 to 1.8 mg/kg/day vs placebo	DB, MC, PC, RCT Children five to six years of age diagnosed with ADHD	N=101 8 weeks	Primary: ADHD-RS Secondary: CGI-S, CGI-I	Primary: Atomoxetine significantly reduced mean parent (P<0.009) and teacher (P=0.02) ADHD-RS total score compared to placebo. Secondary: A total of 40% of children treated with atomoxetine and 22% of children who received placebo had CGI-I scores much too very much improved (P=0.1) with no significant differences between groups. A total of 62% of children treated with atomoxetine had CGI-S scores

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				of moderately or severely ill at the end of the study compared to 77% of children who received placebo. Common adverse events included decreased appetite, gastrointestinal upset, and sedation. Most adverse events were considered mild or moderate by the study investigator.
Spencer et al.[46] (2002) Atomoxetine up to 90 mg daily vs placebo	DB, MC, PC, RCT (pooled data) Children seven to 13 years of age diagnosed with ADHD	N=291 9 weeks	Primary: ADHD-RS Secondary: CPRS-R:S, CGI-S	Primary: Significant mean reductions in both active groups in all scales were reported (both studies) for ADHD-RS (P<0.001) and CPRS-R:S (P=0.023 for study one and P<0.001 for study two). Secondary: Atomoxetine displayed a significant mean reduction in CPRS-R:S index over placebo in both studies (study 1: -5.7 vs -2.6; P=0.023 and study 2: -8.8 vs -2.1; P<0.001). Atomoxetine displayed a statistically significant mean change in CGI-S scores over placebo in both studies (study 1: -1.2 vs -0.5; P=0.023 and study 2: -1.5 vs -0.7; P=0.001).
Adler et al.[47] (2014) Atomoxetine 20 to 50 mg twice daily vs placebo	DB, MC, PC, RCT Patients 18 to 30 years of age with ADHD	N=445 12 weeks	Primary: BRIEF-A Secondary: Not reported	Primary: Significantly greater mean reductions were seen in the atomoxetine vs placebo group for the BRIEF-A GEC, Behavioral Regulation Index, and Metacognitive Index scores, as well as the Inhibit, Self-Monitor, Working Memory, Plan/Organize and Task Monitor subscale scores (P<0.05), with decreases in scores signifying improvements in executive functioning. Changes in the BRIEF-A Initiate (P=0.051), Organization of Materials (P=0.051), Shift (P=0.090), and Emotional Control (P=0.219) subscale scores were not statistically significant. The validity scales: Inconsistency (P=0.644), Infrequency (P=0.097), and Negativity (P=0.456) were not statistically significant, showing scale validity. Secondary: Not reported
Dittmann et al.[48] (2011)	DB, PC, RCT Patients six to 17	N=181 9 week	Primary: SNAP-ODD, SNAP-ADHD	Primary: Treatment with atomoxetine once daily at week nine, using either fast or slow titration to a target dose of 1.2 mg/kg/day, was significantly

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Atomoxetine 0.5 mg/kg/day for seven days, then 1.2 mg/kg/day (fast titration) vs atomoxetine 0.5 mg/kg/day for seven days, then 0.8 mg/kg/day for seven days, then 1.2 mg/kg/day (slow titration) vs placebo	years of age ADHD with comorbid ODD or conduct disorder		Secondary: CGI-S	better compared to placebo in reducing ODD symptoms measured by SNAP-ODD scores (P<0.001). Comparing fast and slow titration separately, the decrease in ODD symptoms severity was significant for both individual titration groups (atomoxetine-fast: 8.6; 95% CI, 7.2 to 9.9; atomoxetine-slow: 9.0; 95% CI, 7.7 to 10.3; and placebo: 12.0; 95% CI, 10.6 to 13.5). Atomoxetine was significantly more effective than placebo in reducing the severity of ADHD symptoms measured by SNAP-ADHD scores. Scores reflecting severity of conduct disorder symptoms, attention-deficit and disruptive behavior, were significantly reduced after nine weeks of atomoxetine treatment. Secondary: CGI-S and individual treatment behaviors showed were significantly reduced after treatment with atomoxetine. The most common adverse events included fatigue, sleep disorders, nausea, and gastrointestinal complaints and were reported the first three weeks of treatment in 60.0% of atomoxetine-fast, 44.3% of atomoxetine-slow, and 18.6% of placebo group study patients.
Hammerness et al.[49] (2009) Atomoxetine 0.5 to 1.4 mg/kg/day	OL, PRO Children six to 17 years of age diagnosed with ADHD who had a prior trial of stimulant treatment	N=34 6 weeks	Primary: ADHD-RS, CGI Secondary: Not reported	Primary: There was a significant reduction in ADHD RS symptoms compared to baseline. There was a significant reduction in ADHD-RS symptoms score from baseline to the second week of atomoxetine treatment. There was a significant reduction in ADHD symptoms of inattention (-8.1; P<0.001) and hyperactivity (-5.7; P<0.001) at the end of atomoxetine treatment. A total of 56% of patients met criteria for the a priori definition of response; much or very much improved on the CGI plus >30% reduction in ADHD-RS symptoms.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Commonly reported adverse events (>10%) included gastrointestinal problems, headache and sedation. Secondary: Not reported
Adler et al.[50] (2008) Atomoxetine 60 to 120 mg/day	MC, OL Adults diagnosed with ADHD	N=384 4 years	Primary: CAARS-Inv:SV total ADHD symptom score Secondary: CAARS-Self:SV, CGI-ADHD-S, HAM-D-17, HAMA, WRAADDS, SDS	Primary: The mean CAARS-Inv:SV total ADHD symptom scores decreased 30.2% from baseline to endpoint (-8.8; P<0.001). Secondary: Significant decreases were found on the CAARS-Inv:SV subscales, and the CAARS-Self:SV total and subscales (P<0.001). CGI-ADHD-S and WRAADDS scores improved significantly from baseline (-1.1 and -5.0, respectively; P<0.001 for both). SDS total and subscale scores improved 25.3% (-3.8; P<0.001). A slight increase was noted in HAM-D-17 scores (0.8; P=0.004), but this small change is not likely clinically relevant. There was no significant change in HAMA scores (0.4; P=0.216). HR, DBP, SBP increased. Weight loss over the course of the study was statistically significant (-0.94 kg; P<0.001).
Wietecha et al.[51] (2012) Atomoxetine 40 mg daily titrated to 100 mg daily after two weeks vs placebo	DB, PC, RCT Adults with ADHD having both a spouse/partner and child	N=502 24 weeks	Primary: CAARS-Inv: SV and CGI-S Secondary: Not reported	Primary: Treatment with atomoxetine resulted in a greater improvement in CAARS-Inv: SV (-16.43 vs -8.65; P<0.001) and CGI-S compared to placebo at week 24 (P<0.001). Secondary: Not reported
Biederman et al.[52]	DB, FD, MC, RCT	N=57	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2006) Atomoxetine 0.5 mg to 1.2 mg/kg daily vs AMP-XR (Adderall XR®) 10 to 30 mg daily	Females six to 12 years of age diagnosed with ADHD	18 days	SKAMP-A SKAMP-D Academic testing Secondary: Adverse events	The AMP-XR group experienced significantly greater mean changes in SKAMP-D scores from baseline compared to the atomoxetine group (-0.48 vs -0.04; P<0.001). The AMP-XR group experienced significantly greater mean changes in SKAMP-A scores from baseline compared to the atomoxetine group (-0.45 vs -0.05; P<0.001). Both AMP-XR and atomoxetine groups experienced a significant increase in the mean number of math problems attempted and answered correctly from baseline (P<0.001), but patients in the AMP-XR group attempted a significantly greater number of math problems than those in the atomoxetine group (P=0.04). Secondary: Both AMP-XR and atomoxetine were well tolerated. The number of adverse events was similar in both groups. Most adverse events reported were of mild or moderate severity.
Kemner et al.[53] (2005) Atomoxetine 0.5 mg/kg once daily vs MPH-ER (Concerta®) 18 mg once daily	MC, OL, PRO, RCT Children six to 12 years of age diagnosed with ADHD	N=1,323 3 weeks	Primary: Investigator-related ADHD-RS and CGI-I, performed at weeks one, two, and three; PSQ Secondary: Not reported	Primary: The ADHD-RS change from baseline measured at each time point showed that both treatments were effective. MPH ER produced significantly greater improvements in ADHD-RS scores at weeks, one, two, and three (P<0.001). At week three, rates of treatment response (i.e., ≥25% reduction in ADHD-RS score) were significantly greater with MPH ER than were seen with atomoxetine (P<0.001). Significantly more children treated with MPH ER than with atomoxetine achieved a CGI-I score ≤2 after week three (P<0.001). Parent-rated PSQ scores revealed statistically significantly greater improvements with MPH ER than with atomoxetine. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Newcorn al.[54] (2008) Acute Comparison Trial Atomoxetine 0.8 mg to 1.8 mg/kg/day administered twice daily vs MPH-ER (Concerta®) 18 mg to 54 mg once daily vs placebo XO Trial Atomoxetine 0.8 mg to 1.8 mg/kg/day administered twice daily Patients on MPH-ER were switched to atomoxetine during the XO trial.	DB, PC, RCT, XO Children six to 16 years of age diagnosed with ADHD (any subtype)	Acute Comparison Trial: N=516 6 weeks XO Trial: N=178 6 weeks	Primary: ADHD-RS Secondary: CGI-S, CPRS, CHQ, and Daily Parent Ratings of Evening and Morning Behavior-Revised	Acute Comparison Trial Primary: The proportion of patients responding to atomoxetine (45%) was significantly higher than the rate for placebo (24%; P=0.003). MPH-ER (56%) was also more effective than placebo (24%; P≤0.001). MPH-ER was found to be more effective than atomoxetine (P=0.02). Secondary: Atomoxetine and MPH-ER produced greater improvements in CGI-S, CPRS and CHQ compared to placebo. MPH-ER also produced greater improvements compared to atomoxetine on CGI-S, CPRS and CHQ (P=0.004, P=0.003, P=0.02, respectively). XO Trial The responses to the two treatments in these patients were as follows: 34% responded to either atomoxetine or MPH-ER, but not both; 44% responded to both treatments; 22% did not respond to either treatment. Of the 70 patients who did not respond to MPH-ER in the initial trial, 43% subsequently responded to atomoxetine in the XO trial. Of the 69 patients who did not respond to atomoxetine in the second trial, 42% had previously responded to MPH-ER. Of the patients classified as MPH-ER, 36% showed significantly worse response on atomoxetine, 18% showed significantly better response on atomoxetine, and 46% showed roughly the same response to treatment with atomoxetine. Of the 70 patients classified as MPH-ER nonresponders, 10% showed significantly worse response, 51% showed significantly better response, and 39% showed roughly the same response to treatment with atomoxetine.
Starr et al.[55] (2005)	OL, RCT African-American	N=183 3 weeks	Primary: Investigator-related ADHD-RS and	Primary: For the ADHD-RS scores, both treatment groups achieved significant improvements from baseline at all time points (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Atomoxetine 0.5 mg/kg once daily vs MPH-ER (Concerta®) 18 mg once daily	children six to 12 years of age diagnosed with ADHD		CGI-I, performed at weeks one, two, and three; PSQ Secondary: Not reported	Improvements from baseline, defined as ADHD-RS score reductions of ≥30% or ≥50%, were significantly greater in the MPH ER group starting at week three (P<0.03 for ≥30% reduction, P<0.006 for ≥50% reduction). Significantly more children treated with MPH ER than atomoxetine achieved a CGI-I score ≤2 after week three (P<0.01). Parent-rated PSQ scores revealed statistically significantly greater improvements with MPH ER than with atomoxetine. Secondary: Not reported
Wang et al.[56] (2007) Atomoxetine 0.8 mg to 1.8 mg/kg/day vs MPH-IR 0.2 mg to 0.6 mg/kg/day in two divided doses	DB, MC, RCT Children six to 16 years of age diagnosed with ADHD	N=330 8 weeks	Primary: ADHD-RS Secondary: CPRS-R:S, CGI-S, treatment-emergent adverse events, weight	Primary: Atomoxetine was not significantly different than MPH in improving ADHD symptoms based on ADHD-RS scores (atomoxetine, 77.4%; MPH, 81.5%; P=0.404). Secondary: Both atomoxetine and MPH-IR treatment groups significantly improved CPRS-R:S and CGI-S scores from baseline (P<0.001 for all), the groups were not statistically significant from each other in both measures (P>0.05). Treatment-emergent adverse events that occurred significantly more frequently in the atomoxetine group, compared to the MPH group, included anorexia (37.2 vs 25.3%; P=0.024), nausea (20.1 vs 10.2%; P=0.014), somnolence (26.2 vs 3.6%; P<0.001), dizziness (15.2 vs 7.2%; P=0.024) and vomiting (11.6 vs 3.6%; P=0.007), most of which were of mild or moderate severity. Patients in the atomoxetine group experienced a small but significantly greater mean weight loss at the end of eight weeks compared to those in the MPH group (-1.2 vs -0.4 kg; P<0.001).compared to
Kratochvil et al.[57] (2002)	MC, OL	N=228	Primary: ADHD-RS	Primary: Both atomoxetine and MPH-IR were associated with marked

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Atomoxetine titrated up to 2 mg/kg/day vs MPH-IR titrated up to 60 mg daily	Males seven to 15 years of age and females seven to nine year of age diagnosed with ADHD	10 weeks	Secondary: CPRS-R, CGI-S, safety	improvement in inattentive and hyperactive-impulsive symptom clusters but were not statistically different (P=0.66). Secondary: There were no statistically significant differences between treatment groups on all of the CPRS-R and CGI-S outcome measures (P<0.001). Tolerability was also similar between the two drugs with no statistical differences in discontinuations (P=0.18). Statistically significant increases in pulse and BFI were seen with both atomoxetine and MPH-IR (P<0.05).
Sutherland et al.[58] (2012) Atomoxetine 40 mg to 100 mg/day vs atomoxetine 40 mg to 100 mg/day and buspirone 15 mg to 45 mg/day vs placebo	DB, MC, PC, RCT Men and women 18 to 60 years of age diagnosed with ADHD	N=241 8 weeks	Primary: AISRS Secondary: Not reported	Primary: There was a significantly greater decrease in the AISRS total score for atomoxetine plus buspirone than placebo at weeks one to seven, with an estimated mean difference of -4.80 (P=0.001). There was a greater decrease in the AISRS total score for atomoxetine plus buspirone than for atomoxetine at weeks one to seven, but only statistically significant at week four (P<0.09). The most commonly reported adverse events from both treatment groups included insomnia, dry mouth, headache, and asthenia. Dizziness was most commonly reported for the atomoxetine plus buspirone treatment group. Discontinuations due to treatment-related adverse events were 15.5% for atomoxetine plus buspirone, 11.3% for atomoxetine and 14.9% for placebo. Secondary: Not reported.
Ni et al.[59] (2013) Atomoxetine titrated up to 1.2	OL, RCT Patients 18 to 50 years of age diagnosed with	N=63 8 to 10 weeks	Primary: ASRS, CGI-ADHD-S, AAQoL, WFIS-S and safety	Primary: At visit one (weeks four and five), both the MPH-IR and atomoxetine treatment groups experienced statistically significant reductions from baseline in ASRS scores for inattention (-5.77 and -8.93, respectively; P<0.001 for both) and hyperactivity-impulsivity (-3.69 and -8.11,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/kg/day vs MPH-IR titrated up to 60 mg/day	ADHD		Secondary: Not reported	respectively; P<0.001). The differences between the treatment groups was significant, favoring treatment with atomoxetine (P<0.05). Significant reductions from baseline in ASRS scores were apparent at visit two (eight to 10 weeks) for both the inattention (-9.25 and -10.20, respectively; P<0.001) and hyperactivity-impulsivity subtypes (-6.21 and -7.80, respectively; P<0.001); however, differences between treatment groups were not statistically significant. Both treatment groups experienced improved CGI-ADHD-S scores at all time points compared to baseline values (P<0.001 for all); however, differences between groups were not statistically significant. The mean AAQoL scores significantly increased from baseline to visit one (weeks four and five) and visit two (weeks eight to 10) for both treatment groups. The effect sizes as assessed by Cohen's d ranged from 0.59 to 1.63 (P<0.01). Both treatment groups experienced significant improvements in the severity of functional impairment (WFIS-S) from baseline to visit one (weeks four to five) or (weeks eight to 10). Cohen's d ranged from 0.49 to 1.70 for the MPH-IR group and 0.42 to 1.11 for the atomoxetine group. Differences between the treatment groups were not statistically significant. Decreased appetite, vomiting and palpitation were frequently reported in both treatment groups. There was no significant difference in the occurrence of adverse events between treatment groups. Moreover, there was no significant change in body weight, BP, or HR during the study period (P>0.05 for all). Secondary: Not reported
Sutherland et al.[60] (2012) Atomoxetine 40 to	DB, MC, PC, RCT Patients 18 to 60 years of age	N=241 8 weeks	Primary: AISRS Secondary:	Primary: There was a significantly greater decrease in the AISRS total score for atomoxetine plus buspirone than placebo at weeks one to seven, with an estimated mean difference -4.80 (P=0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
100 mg daily vs atomoxetine 40 to 100 mg daily plus buspirone 15 to 45 mg daily vs placebo	diagnosed with ADHD		Not reported	There was a greater decrease in the AISRS total score for atomoxetine plus buspirone than for atomoxetine at weeks one to seven, but only statistically significant at week four (P<0.09). The most commonly reported adverse events from both treatment groups included insomnia, dry mouth, headache, and asthenia. Dizziness was most commonly reported for the atomoxetine plus buspirone treatment group. Discontinuations due to treatment-related adverse events were 15.5% for atomoxetine plus buspirone, 11.3% for atomoxetine, and 14.9% for placebo. Secondary: Not reported
Prasad et al.[61] (2007) Atomoxetine 0.5 mg to 1.8 mg/kg/day vs standard current therapy	MC, OL, RCT Children seven to 15 years of age diagnosed with ADHD	N=201 10 weeks	Primary: CHIP-CE Secondary: ADHD-RS, CGI-S, CGI-I, HSPP, FBIM	Primary: Quality of life greatly improved over the 10 weeks in the atomoxetine group vs the standard current therapy group as demonstrated by the significant increase in CHIP-CE (P<0.001). Secondary: ADHD-RS, CGI-S, and CGI-I scores were significantly improved in the atomoxetine group over the standard current therapy group (P<0.001 for all). The atomoxetine group was significantly better in improving the HSPP Social Acceptance domain over the standard current therapy group (P=0.03), but the groups were not significantly different in the other five HSPP domains (P>0.05). There was not a statistically significant difference between groups in reduction in FBIM scores (P>0.05).
Cheng et al.[62] (2007) Atomoxetine	MA (9 trials) Patients diagnosed with ADHD	N=1,828 Variable duration	Primary: ADHD-RS Secondary:	Primary: Atomoxetine significantly improved ADHD-RS scores compared to placebo (P<0.01 for all).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo			CTRS-RS, CPRS-R:S, CGI-S, CHQ	Secondary: Atomoxetine significantly improved CTRS-RS, CPRS-R:S, and CGI-S scores compared to placebo (P<0.01 for all). Atomoxetine significantly improved quality of life as measured by the CHQ compared to placebo (P<0.01).
Hazell et al.[63] (2003) Clonidine 0.1 to 0.2 mg/day vs placebo	PC, RCT, TB Children six to 14 years of age with ADHD and co-morbid ODD or conduct disorder	N=67 6 weeks	Primary: CBC (subscales conduct and hyperactive index) Secondary: Not reported	Primary: Significantly more children treated with clonidine than placebo improved on the CBC-Conduct scale (21 of 37 vs 6 of 29; P<0.01) but not the Hyperactive Index (13 of 37 vs 5 of 29; P=0.16). Compared to placebo, clonidine was associated with a greater reduction in standing SBP measured and with transient sedation and dizziness. Study patients treated with clonidine have a greater reduction in a number of unwanted effects associated with psychostimulant treatment compared to placebo. Secondary: Not reported
Jain et al.[64] (2011) Clonidine XR 0.2 mg/day vs Clonidine 0.4 mg/day vs placebo	DB, PC, RCT Patients six to 17 years of age diagnosed with ADHD	N=236 8 weeks	Primary: ADHD-RS (total score) Secondary: ADHD-RS (inattention and hyperactivity), CPRS-R:S, CGI-S, CGI-I, PGA, treatment-emergent adverse events	Primary: Improvement from baseline to week five in ADHD-RS total score was significantly greater in both clonidine ER groups vs placebo (P<0.001). A significant improvement in ADHD-RS total score occurred beginning week one for the clonidine ER 0.2 mg/day group (P=0.02) and week two for the clonidine ER 0.4 mg/day group (P<0.0001) as compared to the placebo group and continued throughout the treatment period. Secondary: A significant improvement in mean change in ADHD-RS inattention score at week five vs baseline was -7.7 for both clonidine ER groups vs -3.4 for the placebo group (P<0.001 for clonidine ER 0.2 mg/day; P<0.006 for clonidine ER 0.4 mg/day).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Improvements from baseline to week five in ADHD-RS hyperactivity score were -4.1 in the placebo group, -7.9 in the clonidine ER 0.2-mg/day group, and -8.8 in the clonidine ER 0.4-mg/day group (P<0.0012). Mean improvement in CPRS-R total score was significantly greater than placebo in both clonidine ER groups (P<0.01) at weeks three and five. Improvement in CGI-S and CGI-I from baseline to week five was significantly greater in both treatment groups vs placebo (P<0.0001 for CGI-S and P<0.003 for CGI-I). Significant improvement in PGA score from baseline in both treatment groups vs placebo was observed at week two (P<0.001) and was maintained through week seven (P<0.02) in the clonidine ER 0.2 mg/day group and through week five in the clonidine ER 0.4 mg/day group (P<0.009). The most common treatment-emergent adverse event was mild-to-moderate somnolence. Changes on ECG were minor and due to the pharmacology of clonidine.
Kollins et al.[65] (2011) Clonidine-XR 0.1 mg to 0.4 mg/day and psychostimulant vs placebo and psychostimulant	DB, MC, PC, RCT Children and adolescents diagnosed with hyperactive or combined subtype ADHD who had inadequate response to their psychostimulant therapy	N=198 8 weeks	Primary: ADHD-RS (total score) Secondary: ADHD-RS (hyperactivity and inattention), CPRS, CGI-S, CGI-I, PGA	Primary: At week five, study patients in the clonidine ER plus psychostimulant group experienced a greater improvement in ADHD-RS total score compared to patients in the placebo plus psychostimulant group (P=0.009). Secondary: Scores from baseline ADHD-RS hyperactivity and inattention subscale (P=0.014 and P=0.017, respectively), CPRS (P<0.062), CGI-S (P=0.021), CGI-I (P=0.006), and PGA (P=0.001) were significantly improved in the clonidine ER plus psychostimulant group compared to the placebo plus psychostimulant group. The most commonly treatment-emergent adverse event reported were

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				mild to moderate in severity and included somnolence, headache, fatigue, upper abdominal pain, and nasal congestion.
Wigal et al.[66] (2004) DXM (Focalin®) 2.5 to 10 mg twice daily vs MPH-IR 5 to 20 mg twice daily vs placebo	DB, MC, PC, RCT Children six to 17 years of age diagnosed with ADHD (any subtype)	N=132 4 weeks	Primary: SNAP-T Secondary: SNAP-P, CGI-I Math test performance (clinic and home)	Primary: Both DXM and MPH-IR significantly improved SNAP-T scores compared to placebo (P=0.004 and P=0.0042, respectively) Secondary: The DXM group decreased SNAP-P scores at both 3 and 6 PM assessments compared to placebo (P<0.0001 and P=0.0003 respectively). The MPH-IR group significantly decreased 3 PM SNAP-P assessments compared to the placebo group (P=0.0073) but did not reach statistical significance at the 6 PM assessment (P=0.064). Both DXM and MPH-IR improved CGI-I scores in significantly more patients than the placebo group (67% [P=0.0010] and 49% [P=0.0130] compared to 22%, respectively). Both DXM and MPH-IR significantly improved clinic-based math test scores compared to placebo (P=0.001 and P=0.0041 respectively). DXM significantly improved home-based math test scores compared to placebo (P=0.0236). MPH-IR did not reach statistical significance compared to placebo.
Greenhill et al.[67] (2006) DXM-XR (Focalin XR®) 5 to 30 mg daily vs placebo	DB, MC, PC, RCT Children six to 17 years of age diagnosed with ADHD (any subtype)	N=97 7 weeks	Primary: CADS-T Secondary: CADS-P, CGI-I, CGI-S, CHQ (physical and psychosocial)	Primary: DXM-XR significantly increased CADS-T scores from baseline compared to placebo (16.3 vs 5.7; P<0.001). Secondary: DXM-XR significantly increased CADS-P scores from baseline compared to placebo (17.6 vs 6.5; P<0.001). DXM-XR improved overall CGI-I scores in a greater percent of patients compared to placebo (67.3 vs 13.3%; P<0.001). DXM-XR significantly improved CGI-S scores in a greater percent of patients than placebo (64.0 vs 11.9%; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There was not a statistical difference between DXM-XR and placebo on the mean change in CHQ physical scores. DXM-XR did significantly improve mean CHQ psychosocial scores compared to placebo (11.9 vs 4.3; P<0.001).
Spencer et al.[68] (2007) DXM-XR (Focalin XR®) 20 to 40 mg daily vs placebo	DB, MC, PC, RCT Adults 18 to 60 years of age diagnosed with ADHD (any subtype), childhood onset of symptoms, and a baseline ADHD-RS score ≥24	N=184 5 weeks	Primary: ADHD-RS Secondary: ADHD-RS, CGI-I, CGI-S, CAARS, Q-LES-Q	Primary: All doses of DXM-XR significantly improved ADHD-RS scores from baseline compared to placebo (P<0.05). Secondary: The 20 and 40 mg doses of DXM-XR achieved improved ADHD-RS scores ≥30% and were significant compared to placebo, the 30 mg group did not reach statistical significance. The percent of patients who achieved ≥30% were as follows: DXM-XR 20 mg, 57.9% (P=0.017); DXM-XR 30 mg, 53.7% (P=0.054); DXM-XR 40 mg, 61.1% (P=0.007); and placebo, 34.0%. All doses DXM-XR significantly improved CGI-I scores over placebo (P<0.05 for all). The 20 and 40 mg doses of DXM-XR improved CGI-S scores in a greater percent of patients compared to placebo, but the 30 mg group did not reach statistical significance. The percents of patients were as follows: 20 mg, 68.4% (P=0.09); 30 mg, 61.1% (P value not significant); 40 mg, 64.8% (P=0.031); and placebo, 41.5%. All doses of DXM-XR significantly improved CAARS scores compared to placebo (P<0.05 for all). None of the groups improved Q-LES-Q scores from baseline nor were there significant differences between groups.
Adler et al.[69] (2009) DXM-XR (Focalin XR®) 20 to 40 mg/day	DB, MC, RCT Patients 18 to 60 years of age diagnosed with ADHD	N=103 6 months	Primary: Long-term safety and tolerability Secondary: ADHD-RS, CGI-I	Primary: DXM-XR was well tolerated; the most common adverse events were headache (27.6%), insomnia (20.0%), and decreased appetite (17.6%). Most adverse events were considered mild or moderate by the study investigator. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo After completion of DB phase, patients could enter an OL extension phase with flexible dosing 20 to 40 mg/day for six months.				Mean improvements in ADHD-RS scores were -10.2 for study patients switched from placebo to DXM-XR and -8.4 for those maintained on DXM-XR. Improvements in CGI-I scores were reported in 95.1% of study patients switched from placebo to DXM-XR and 95.0% of study patients maintained on DXM-XR.
Brams et al.[70] (2012) DXM-XR 20 mg daily vs DXM-XR 30 mg daily vs placebo	DB, RCT, XO Children 6 to 12 years of age with ADHD previously stabilized on MPH (40 mg to 60 mg/day) or DXM (20 mg to 30 mg/day)	N=165 3 weeks	Primary: Change in average SKAMP-combined score from pre-dose to 10, 11 and 12 hours post-dose Secondary: Not reported	Primary: The mean change from pre-dose in SKAMP-combined score was significantly greater in the DXM-XR 30 mg group compared to the DXM-XR 20 mg group (-4.47 vs -2.02; P=0.002). Significantly greater improvement in ADHD symptoms was observed in the DXM-XR 30 mg group compared to the DXM-XR 20 mg group at hours 10 through 12. Secondary: Not reported
Stein et al.[71] (2011) DXM-XR (Focalin XR®) 10 to 30 mg/day vs AMP-XR	DB, PC, RCT Patients nine to 17 years of age with ADHD	N=56 8 weeks	Primary: ADHD-RS, CGI-I, CGI-S, WFIS, SSERS Secondary: Not reported	Primary: There were significant dose-related decreases in total and hyperactive-impulsive symptom scores (P<0.001 and P<0.001, respectively) that did not differ by type of stimulant. There were significant dose-related decreases for Inattention symptoms (P<0.001) that were more modest and did not differ by type of stimulant. There were significant dose-related decreases in CGI-S scores

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(Adderall XR®) 10 to 30 mg/day				(P<0.001) that did not differ by type of stimulant. There were significant effects of dose on the WFIS total score (P=0.008), on the Family (P=0.010), Learning (P=0.002), Social Activities (P=0.018), and Risk Taking (P=0.050) subscales, but not on the Living Skills or Self-Esteem subscales. The most common adverse events were mild to moderate in severity and included decreased appetite and insomnia. Adverse events were more common at higher dose levels for both stimulants. Secondary: Not reported
Muniz et al.[72] (2008) DXM-XR (Focalin XR®) 20 mg/day vs DXM-XR (Focalin XR®) 30 mg/day vs MPH-ER (Concerta®) 36 mg/day vs MPH-ER (Concerta®) 54 mg/day	DB, MC, RCT Children six to 12 years of age diagnosed with ADHD and stabilized on MPH ≥2 weeks	N=84 10 weeks	Primary: SKAMP Secondary: Not reported	Primary: Mean change in combined SKAMP score at two hours post-dose was significantly larger for MPH-ER 20 vs 36 mg/day (P<0.001). MPH-ER 20 and 30 mg doses have a more rapid onset and a greater effect in the morning relative to MPH-ER 36 and 54 mg doses while MPH-ER 36 and 54 mg had a greater effect at the end of the 12 hour day. All active treatments provided a significant benefit over placebo at most time points to 12 hours post-dosing. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				
Scahill et al.[73] (2001) Guanfacine 0.5 mg at bedtime, day four added 0.5 mg in the morning, day eight added 0.5 mg afternoon dose vs placebo	DB, PC, PG, RCT Children seven to 15 years of age diagnosed with ADHD and tic disorder	N=34 8 weeks	Primary: ADHD-RS, CGI-I, CPRS-R (hyperactivity index), YGTSS, CPT Secondary: Not reported	Primary: Guanfacine was associated with a mean improvement of 37% in the teacher-rated ADHD-RS total score compared to 8% improvement for placebo (P<0.01). Nine of 17 patients who received guanfacine were rated on the CGI-I as either much improved or very much improved, compared to 0 of 17 patients who received placebo. The mean CPRS-R on the parent-rated hyperactivity index improved by 27% in the guanfacine group and 21% in the placebo group, not a significant difference. Tic severity decreased by 31% in the guanfacine group, compared to 0% in the placebo group (P=0.05). For CPT, commission errors decreased by 22% and omission errors by 17% in the guanfacine group, compared to increases of 29% in commission errors and of 31% in omission errors in the placebo group. No significant adverse events were observed; one study patient taking guanfacine withdrew with sedation. Guanfacine was associated with an insignificant decrease in BP and pulse. Secondary: Not reported
Kollins et al.[74] (2011) Guanfacine ER 1 to 3 mg once daily vs	DB, MC, PC, RCT Patients six to 17 years of age diagnosed with ADHD	N=182 6 weeks	Primary: CANTAB-CRT Secondary: CANTAB-SWM, DSST, PERMP	Primary: There were no significant differences between guanfacine ER and placebo groups on measures of psychomotor functioning or alertness on the CANTAB-CRT (mean difference, 2.5; P=0.8 for CRT, 2.5; P=0.84 for correct responses, 15.5; P=0.30 for movement time, and -8.2; P=0.72 for total time).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				Secondary: Guanfacine ER treatment was associated with significant improvement in ADHD symptoms (P=0.001) Most sedative adverse events were mild to moderate and occurred during dose titration, decreased with dose maintenance, and resolved during the study period.
Sallee et al.[75] (2009) Guanfacine ER 1 to 4 mg once daily vs placebo	DB, MC, PC, RCT Patients six to 17 years of age with ADHD and a baseline score of 24 on the ADHD-RS-IV	N=324 9 weeks	Primary: ADHD-RS-IV total score Secondary: CPRS-R, CGI-I, PGA	Primary: The mean reduction in ADHD-RS-IV total scores from baseline to endpoint across all guanfacine ER dose groups was -19.6 compared to -12.2 for the placebo group. The placebo-adjusted mean endpoint changes from baseline were -6.75 (P=0.0041), -5.41 (P=0.0176), -7.34 (P=0.0016), and -7.88 (P=0.0006) in the guanfacine ER 1, 2, 3, and 4 mg groups, respectively. Placebo-adjusted mean baseline-to-endpoint changes for symptoms of inattentiveness were: -4.2 (P=0.002), -3.0 P=0.02), -3.5 (P=0.007), and -4.0 (P=0.002) for guanfacine ER 1, 2, 3, and 4 mg, respectively. Placebo-adjusted mean baseline-to-endpoint changes for symptoms of hyperactivity/impulsivity were: -2.7 (P=0.028), -2.5 (P=0.03), -3.9 (P=0.001), and -4.0 (P=0.0008) for guanfacine ER 1, 2, 3, and 4 mg, respectively. Secondary: Using placebo-adjusted LSMD in change from baseline at endpoint in CPRS-R total scores, the 4 mg guanfacine ER dose demonstrated significant efficacy at eight hours (-10.2; P=0.004) and 12 hours (-7.5; P=0.04). The 3 mg guanfacine ER dosage group demonstrated significant improvements in CPRS-R results at eight (-11.8; P=0.002), 12 (-9.6; P=0.01), and 14 hours (-9.8; P=0.0156) postdose. The 2 mg guanfacine ER dosage group demonstrated significant improvements in CPRS-R scores at eight hours (-9.0; P=0.01) postdose. For the 1 mg guanfacine ER dosage group, the placebo-adjusted LSMD in CPRS-R at eight, 12, 14, and 24 hours were -12.8 (P=0.0004), -11.4 (P=0.002), -10.4 (P=0.0077), and -8.9 (P=0.02), respectively. Based on CGI-I scores, the percentages of the patients showing clinical

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				improvement were 30% (placebo), 54% (guanfacine ER 1 mg; P=0.007 vs placebo), 43% (guanfacine ER mg; P=0.1404 vs placebo), 55% (guanfacine ER mg; P=0.006 vs placebo), and 56% (guanfacine ER mg; P=0.004 vs placebo). Improvements in PGA scores were 30% (placebo), 51% (guanfacine ER 1 mg; P=0.030 vs placebo), 36% (guanfacine ER 2 mg; P=0.4982 vs placebo), 62% (guanfacine ER mg; P=0.002 vs placebo), and 57% (guanfacine ER 4 mg; P=0.0063 vs placebo). Mild to moderate treatment-emergent adverse events in patients taking guanfacine ER were somnolence, headache, fatigue, sedation, dizziness, irritability, upper abdominal pain, and nausea. There were no significant differences in sleepiness between the patients taking placebo and guanfacine ER. Guanfacine ER was not associated with abnormal changes in height or weight. SBP, DBP, and pulse rate decreased as the guanfacine ER dose increased and then increased during dose maintenance and tapering. The range of mean changes from baseline for seated SBP for the placebo group was -1.30 to -0.48 mm Hg and -7.38 to 0.54 mm Hg for the guanfacine ER randomized dose groups.
Sallee et al.[76] (2009) Guanfacine ER 1 to 4 mg once daily	ES, OL Patients six to 17 years of age with ADHD and a baseline score of 24 on the ADHD-RS-IV	N=257 24 months	Primary: ADHD-RS-IV, CPRS-R, CGI-I, CHQ-PF50, CTRS-R, PGA Secondary: Not reported	Primary: Somnolence (30.5%), headache (24.3%), upper respiratory tract infection (17.8%), nasopharyngitis (14.3%), fatigue (13.9%), upper abdominal pain (12.7%) and sedation (11.2%) were the most frequently reported adverse events. The majority of somnolence, sedation, or fatigue events was moderate or mild in severity and resolved by end of treatment. Hypotension was reported in 5.0% of patients. Decreased DBP was found in 3.5% of patients, decreased BP in 2.7% of patients, and decreased SBP in 2.3% of patients. Decreased appetite (13.2%), irritability (13.2%), and pharyngitis (11.3%) were among the most common treatment-emergent adverse events that differed in the subgroup coadministered psychostimulants relative to monotherapy or the overall safety population.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Mean changes in ADHD-RS-IV total score from baseline to end point showed significant improvement: overall, -20.1 (P<0.001), and for all guanfacine ER dose groups, -23.8, -22.5, -20.0, and -18.4 for the 1, 2, 3, and 4 mg dose groups, respectively (P<0.001 for each). CPRS-R mean changes from baseline to end point were statistically significant in the overall treatment group (-18.2; P<0.001). The overall mean change from baseline demonstrated significant improvement in CPRS-R scores at each postdose assessment (P<0.001). Investigator-rated CGI-I scores at end point showed that investigators rated the majority of patients very much improved (29.3%) or much improved (28.8%). For the PGA, 59.7% of patients were rated as very much or much improved at end point. Mean changes in CHQ-PF50 Physical Summary Scores from baseline to end point were not statistically significant. CHQ-PF50 Psychosocial Summary Scores demonstrated significant improvement from baseline to end point for the overall full analysis set (P<0.001). Secondary: Not reported
Sallee et al.[77] (2012) Guanfacine ER 1 to 4 mg daily vs placebo	DB, PC, RCT (Post-hoc analysis) Patients 6 to 17 years of age with ADHD	N=631 Variable duration	Primary: Change in ADHD-RS total scores Secondary: Not reported	Primary: For patients with the predominantly inattentive subtype of ADHD, patients treated with guanfacine ER achieved significantly greater mean reductions from baseline in ADHD-RS total scores compared to placebo (P≤0.020). For patients with combined-type ADHD, patients treated with guanfacine ER achieved significantly greater reductions in ADHD-RS total score from baseline compared to placebo at treatment weeks one through five and at study end (P≤0.011). Secondary: Not reported
Connor et al.[78]	DB, MC, PC, RCT	N=217	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2010) Guanfacine ER 1 to 4 mg once daily vs placebo	Patients six to 12 years of age with a diagnosis of ADHD and the presence of oppositional symptoms	9 weeks	Change from baseline to endpoint in the oppositional subscale of the CPRS-R:L Secondary: Change in ADHD-RS-IV total score and safety	The mean change from baseline in the oppositional subscale of the CPRS-R:L was -10.9 for those receiving guanfacine ER and -6.8 for those receiving placebo (P<0.001). The mean percentage reductions from baseline were 56.3% with guanfacine ER and 33.4% with placebo (P<0.001). Secondary: The mean decrease from baseline to endpoint in ADHD-RS-IV total score was 23.8 points for guanfacine ER compared to 11.5 for placebo (P<0.001). The mean percentage reductions from baseline were 56.7% with guanfacine ER and 26.5% with placebo (P<0.001). Adverse events were reported in 84.6% of those receiving guanfacine ER group and 60.3% of those receiving placebo. Treatment-emergent adverse events occurred more frequently with guanfacine ER than with placebo (83.8 vs 57.7%, respectively). The most common treatment-emergent adverse events in the guanfacine ER group were somnolence (50.7%), headache (22.1%), sedation (13.2%), upper abdominal pain (11.8%) and fatigue (11.0%).
Biederman et al.[79] (2008) Guanfacine ER 2 to 4 mg once daily vs placebo	DB, MC, PC, RCT Patients six to 17 years of age with ADHD combined subtype, predominantly inattentive subtype, or predominantly hyperactive-impulsive subtype	N=345 8 weeks	Primary: ADHD-RS-IV total score observed during the last treatment week of the dosage escalation period (weeks one to five) Secondary: CGI-S, CGI-I, PGA, CPRS-R, and CTRS-R observed during the last treatment week of the dosage escalation period (weeks one to five)	Primary: The mean reduction in ADHD-RS-IV score at end point across all guanfacine ER groups was -16.7 compared to -8.9 for placebo. Placebo-adjusted LS mean end point changes from baseline in the guanfacine ER 2, 3, and 4 mg groups were -7.70 (P=0.0002), -7.95 (P=0.0001), and -10.39 (P<0.0001), respectively. Mean changes from baseline in hyperactivity/impulsivity in the placebo and guanfacine ER 2, 3, and 4 mg groups were -3.51, -7.33 (P=0.0002 vs placebo), -7.32 (P=0.0002 vs placebo), and -9.31, (P<0.0001 vs placebo) respectively. Mean changes from baseline in inattentiveness were -4.92, -8.7 (P=0.0011 vs placebo), -9.11 (P=0.0006 vs placebo), and -9.44 (P=0.0002 vs placebo), respectively. Secondary: Significant improvement in CGI-I scores at end point was shown in 25.64, 55.95, 50.00, and 55.56% of patients in the placebo and guanfacine ER 2, 3, and 4 mg groups, respectively. Improvement in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				CGI-I scores was significant in the guanfacine ER 2 mg group compared to the placebo group by week two (P=0.0194) and in all guanfacine ER groups by week three continuing through week five (P<0.05). Significant improvement in PGA scores at end point was shown in 23.08, 62.12, 50.82, and 66.10% of patients in the placebo and guanfacine ER 2, 3, and 4 mg groups, respectively. On the CPRS-R, placebo-adjusted LS mean day total end point changes from baseline were -6.55 in the 2 mg group (P=0.0448), -7.36 in the 3 mg group (P=0.0242), and -12.70 in the 4 mg group (P<0.0001). On the CTRS-R, placebo-adjusted LS mean day total end point changes from baseline were -11.57 (P<0.0001), -13.48 (P<0.0001), and -12.53 (P<0.0001), for the 2, 3, and 4 mg doses, respectively. The most commonly reported treatment-emergent adverse events were somnolence, fatigue, upper abdominal pain and sedation. The incidence of somnolence in patients who were receiving guanfacine ER 1, 2, 3, and 4 mg doses was 12.7, 11.4, 20.9, and 17.5%, respectively. SBP, DBP, and pulse rate decreased as guanfacine ER dosages increased, then increased as dosages stabilized and tapered down. The greatest mean changes from baseline in SBP and DBP for patients who were receiving guanfacine ER 2, 3, and 4 mg doses were -7.0 mm Hg (week 3) and -3.8 mm Hg (week 2), -7.0 mm Hg (week 3) and -4.7 mm Hg (weeks three and five), and -10.1 mm Hg (week four) and -7.1 mm Hg (week four), respectively. The greatest mean changes from baseline in pulse rate for patients who were receiving guanfacine ER 2, 3, and 4 mg doses were -5.7 beats per minute (week three), -8.1 beats per minute (week three), and -8.0 beats per minute (week four), respectively. Mean changes in height and weight from baseline to end point were not significant across the treatment groups.
Hervas et al.[80] (2014)	DB, MC, PC, PG, RCT	N=337 10 to 13	Primary: ADHD-RS	Primary: The placebo-adjusted difference in LS mean change from baseline in ADHD-RS total score for guanfacine ER was −8.9 (95% CI, −11.9 to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Guanfacine ER vs placebo An atomoxetine arm was included to provide reference data against placebo.	Patients six to 17 years of age with a diagnosis of ADHD of at least moderate severity	weeks: 4 to 7 weeks of dose optimization, 6 weeks of DB maintenance, 2 week tapering, follow up 1 week after last dose	Secondary: CGI-I, WFIS-parent report	−5.8; P<0.001). Secondary: Compared with placebo, the difference in the percentage of patients showing improvement in CGI-I rating was 23.7 (95% CI, 11.1 to 36.4; P<0.001) for guanfacine ER and 12.1 (−0.9 to 25.1; P=0.024) for atomoxetine. The placebo-adjusted difference in LS mean change from baseline in WFIRS-parent report learning and school domain at study end for guanfacine ER was −0.22 (95% CI, −0.36 to −0.08; P=0.003) and for WFIRS-parent score family domain at study end was −0.21 (95% CI, −0.36 to −0.06; P=0.006). The corresponding values for atomoxetine were −0.16 (95% CI, −0.31 to −0.02; P=0.026) and −0.09 (95% CI, −0.24 to −0.06; P=0.242), respectively.
Biederman et al.[81] (2008) Guanfacine ER 2 to 4 mg once daily	ES, OL Patients six to 17 years of age with ADHD combined subtype, predominantly inattentive subtype, or predominantly hyperactive-impulsive subtype	N=240 24 months	Primary: Safety Secondary: ADHD-RS-IV, PGA, CHQ-PF50	Primary: Somnolence (30.4%), headache (26.3%), fatigue (14.2%), and sedation (13.3%) were the most frequently reported adverse events. Changes from baseline to endpoint in SBP, DBP, and pulse rate were -0.8 mm Hg, -0.4 mm Hg, and -1.9 beats per minute, respectively. Mean changes in pulse rate and QRS intervals were generally unchanged across study visits. Hypotension was reported in 2.9% of patients and bradycardia was reported in 2.1% of patients. There were no unexpected changes in mean height or weight. Approximately 7.0% of patients reported weight increase possibly or probably related to study drug. Weight decrease was not reported. Appetite increase was reported by 2.1% of patients, appetite decrease by 3.3% of patients, and anorexia by 0.8% of patients. Secondary: The mean ADHD-RS-IV total score was significantly reduced from baseline to endpoint (-18.1; P<0.001 vs baseline).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Mean reductions in ADHD-RS-IV scores were significant for both the inattention (-9.5; P<0.001 vs baseline) and the hyperactivity/impulsivity (-8.5; P<0.001 vs baseline) subscales. For PGA scores, 58.6% of patients were 'improved' at endpoint compared to baseline of the preceding study. For the CHQ-PF50, physical summary scores did not change significantly from baseline to endpoint overall or in any dose or age group.
Spencer et al.[82] (2009) Guanfacine ER 1 mg to 4 mg once daily added to existing stimulant therapy	MC, OL Patients six to 17 years of age with ADHD (combined, predominantly inattentive, or predominantly hyperactive-impulsive subtype) and who were on a stable regimen of either MPH or AMP ≥1 month with suboptimal control of ADHD symptoms	N=75 9 weeks	Primary: ADHD-RS-IV, CPRS-R, CGI-I, CGI-S, CHQ-PF50, and PGA Secondary: Not reported	Primary: The most common treatment-related adverse events were fatigue (34.7%), headache (33.3%), upper abdominal pain (32.0%), irritability (32.0%), somnolence (18.7%), and insomnia (16.0%). Most adverse events were mild to moderate in severity. The incidences of the treatment-emergent adverse events were comparable between both psychostimulant subgroups except for fatigue (28.6% in the guanfacine ER plus MPH subgroup vs 18.2% in the guanfacine ER plus AMP subgroup) and irritability (14.3% in the guanfacine ER plus MPH subgroup vs 33.3% in the guanfacine ER plus AMP subgroup). Twenty patients have a decrease in BP judged to be of clinical interest. Twelve patients exhibited orthostatic BP decreases. None of the patients with BP decreases reported syncope or lightheadedness. At baseline, the mean PDSS score was 15.0. Decreases were observed at visit six (-4.8) and end point (-3.1). During treatment, there was an increase from screening in the number of patients reporting clinically significant dullness, tiredness, and listlessness on the PSERS. There was a decrease in the number of patients with clinically significant loss of appetite and trouble sleeping. The psychostimulant subgroups were generally comparable. Significant decreases from baseline (psychostimulant only) to end

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				point in ADHD-RS-IV total score were observed overall and in both psychostimulant combination subgroups, indicating improvement in ADHD symptoms (overall, -16.1; guanfacine ER plus MPH group, -17.8; guanfacine ER plus AMP group, -13.8; *P*<0.0001 for all). The mean percentage reduction from baseline to end point in ADHD-RS-IV score overall was 56.0%. Improvement was significant for the mean day CPRS-R total score (-19.8; *P*<0.0001), as well as for all three time points (-23.2 at 12 hours postdose, -18.5 at 14 hours postdose, and -17.8 at 24 hours postdose; *P*<0.0001 for all). The percentage of patients showing improvement at end point on the CGI was 73.0%. On the PGA, 84.1% of patients showed improvement. No significant improvement occurred at end point in the CHQ-PF50 physical summary score. Mean improvement for the CHQ-PF50 psychosocial score was 10.2 (*P*<0.0001). Secondary: Not reported
Wilens et al.[83] (2012) Guanfacine ER 1 to 4 mg/day in the morning and placebo at bedtime vs placebo in the morning and guanfacine ER 1 mg to 4 mg/day in the afternoon	DB, MC, PC, RCT Children and adolescents six to 17 years of age diagnosed with ADHD	N=461 9 weeks	Primary: ADHD-RS Secondary: CGI-S, CGI-I	Primary: At the end of the study, guanfacine ER treatment groups showed significantly greater improvement from baseline ADHD-RS total scores compared to placebo plus psychostimulant (guanfacine ER in the morning; P=0.002; guanfacine ER in the evening; P<0.001). Secondary: Significant benefits of guanfacine ER treatment compared to placebo plus psychostimulant were observed on the CGI-S (guanfacine ER in the morning; P=0.013, guanfacine ER in the evening; P<0.001) and CGI-I (guanfacine ER in the morning; P=0.024, guanfacine ER in the evening; P=0.003). At study endpoint, small mean decreases in pulse, SBD, and DBP were observed in guanfacine ER treatment groups compared to placebo plus psychostimulant group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo Patients continued stable dose of psychostimulant given in the morning.				The most common treatment-emergent adverse events were mild to moderate in severity and included headache, somnolence and upper respiratory infections.
Cutler et al.[84] (2014) Guanfacine ER 1 to 4 mg/day in the morning and placebo at bedtime vs placebo in the morning and guanfacine ER 1 mg to 4 mg/day in the afternoon vs placebo Patients continued stable dose of psychostimulant given in the morning.	Post hoc analysis of Wilens et al, 2012 Children and adolescents six to 17 years of age diagnosed with ADHD	N=461 9 weeks	Primary: Response (≥40% or ≥50% reduction in ADHD-RS scores), remission (symptomatic: ADHD-RS score ≤18; syndromal: ADHD-RS score ≤18 and CGI-S score ≤2) Secondary: Not reported	Primary: With response defined as ≥40% reduction, 69.8% of participants in the guanfacine ER morning group and 70.3% of participants in the guanfacine ER evening group achieved response, vs 57.9% of placebo participants. The percentage of responders in both guanfacine ER groups was higher (P=0.032 for the morning group; P=0.026 for the evening group) compared with placebo. With response defined as ≥50%, response rates were 63.1% for the guanfacine ER morning group, 64.9% for the guanfacine ER evening group, and 43.4% for placebo (P<0.001 for the morning group; P<0.001 for the evening group compared with placebo). At final on-treatment assessment, more participants receiving morning guanfacine ER (61.1%; P=0.010) and evening guanfacine ER (62.2%; P=0.005) achieved symptomatic remission compared with the placebo group (46.1%). Similarly, more participants receiving guanfacine ER (morning group [40.3%; P=0.053] or evening group [46.6%; P=0.002]) achieved syndromal remission compared with participants receiving placebo (29.6%). Secondary: Not reported
Faraone et al.[85] (2010)	MA Patients six to 17	N=813 6 to 9 weeks	Primary: Predictors of efficacy and	Primary: Actual Dose Model The presence or absence of ADHD symptoms was influenced by the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Guanfacine ER 1 to 4 mg once daily	years of age with ADHD (combined subtype, predominantly inattentive subtype, or predominantly hyperactive-impulsive subtype)		sedation using various models Secondary: Not reported	actual doses of medication received by the participants (P=0.006). In participants with residual ADHD symptoms, greater total ADHD-RS symptom scores were significantly related to shorter treatment duration (P<0.001) and higher baseline total ADHD-RS symptom scores (P<0.001). The only significant influence on the frequency of sedation-related adverse events was treatment duration (P=0.034). mg/kg Dose Model: The presence or absence of ADHD symptoms was significantly influenced by the dose of medication received by the participant as expressed in mg/kg (P=0.001). Treatment duration (P<0.001) and baseline total ADHD-RS symptom scores (P<0.001) were predictors of weekly total ADHD-RS symptom scores. The only significant influence on the frequency of sedation-related adverse events was treatment duration (P=0.034). Titration Rate Dose Model: The presence or absence of ADHD symptoms was significantly influenced by the titrated dose of medication received by the participant (P=0.005). The number of symptoms was significantly influenced by treatment duration (P<0.001) and baseline total ADHD-RS scores (P<0.001). The only significant influence on the frequency of sedation-related adverse events was treatment duration (P=0.034). Secondary: Not reported
Adler et al.[86] (2013) LDX 30 to 70 mg daily	DB, PC, RCT Adults 18 to 55 years of age with a primary diagnosis	N=161 10 weeks	Primary: BRIEF-A scales (GEC, index and clinical subscales)	Primary: At week 10 or early termination, treatment with LDX was associated with significantly greater reductions from baseline in mean BRIEF-A GEC T-scores compared to placebo (P<0.0001) and significantly greater reductions from baseline in mean T-scores for both BRIEF-A index

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	of ADHD and executive function deficits (assessed by baseline BRIEF-A GEC T-scores ≥65)		Secondary: Not reported	scales (metacognition scale) and all nine clinical subscales (P≤0.0056 for all). At week 10 or early termination, patients treated with LDX had mean T-scores for BRIEF-A indices and clinical subscales that were below levels of clinically significant deficits in executive function. The mean GEC T-scores were 57.2 and 68.3 for the LDX and placebo groups, respectively. Secondary: Not reported
Babcock et al.[87] (2012) LDX 30 to 70 mg daily vs placebo	DB, MC, RCT (Post-hoc analysis) Adults with ADHD who remained symptomatic on AMP therapy prior to enrollment in a four-week trial	N=36 4 weeks	Primary: Mean change in ADHD-RS score from baseline Secondary: Change in CGI-S, CGI-I	Primary: At study end, the change from baseline in mean ADHD-RS scores for LDX-treated patients was similar in the AMP group and the overall study group. The prior AMP non-responders in the placebo group had a change from baseline in ADHD-RS total score of -13.5. In the overall efficacy population, the placebo group experienced a change from baseline of -7.8. Secondary: Mean CGI scores were similar between the prior AMP subgroup and overall efficacy population in the LDX groups. In addition, the percentage of clinical responders and symptomatic remitters was comparable at all time points assessed in both LDX groups.
Biederman et al.[88] (2007) LDX 30 to 70 mg daily vs placebo	DB, MC, PC, RCT Children six to 12 years of age diagnosed with ADHD and with an ADHD-RS score ≥28	N=209 4 weeks	Primary: ADHD-RS Secondary: CPRS-R, CGI-S, CGI-I	Primary: ADHD-RS scores were significantly greater with each of the three LDX doses compared to placebo (P<0.001). The greatest efficacy was seen in the 70 mg group with a mean ADHD-RS change of -4.91 from baseline between the 30 and 70 mg groups (P<0.05). Secondary: Each LDX group significantly improved CPRS-R scores throughout the day compared to the placebo group (P<0.01 for all). Mean CGI-S scale scores significantly improved from baseline to treatment end point for all LDX groups compared to the placebo group (P<0.001 for all). CGI-I ratings were either “very much improved” or “much improved”

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				in ≥70% of patients in the LDX groups compared to 18% of patients in the placebo group (P<0.001 for all).
Biederman et al.[89] (2007) LDX 30 to 70 mg daily vs placebo (AMP-XR 10 to 30 mg was used as a control arm)	DB, MC, PC, RCT, XO Children six to 12 years of age diagnosed with ADHD	N=52 12 weeks	Primary: SKAMP scale Secondary: PERMP, CGI-I	Primary: SKAMP scores significantly improved in both the LDX and AMP-XR groups compared to the placebo group (P<0.0001 for both). Secondary: PERMP scores for both the LDX and AMP-XR groups significantly decreased compared to the placebo group (P<0.0001 for both). The CGI-I scores significantly improved in the both LDX and AMP-XR groups compared to the placebo group (P<0.0001).
Brams et al.[90] (2012) LDX 30 to 70 mg daily vs placebo	DB, RCT Withdrawal study Adults 18 to 55 years of age with baseline ADHD-RS with adult prompt total scores <22 and CGI-S ratings of 1, 2 or 3	N=116 6 weeks	Primary: Proportion of patients with symptom relapse (≥50% increase in ADHD-RS score and ≥2 rating-point increase in CGI-S score) Secondary: Not reported	Primary: At study end, 8.9% of patients in the LDX group and 75.0% of patients in the placebo group experienced symptom relapse (P<0.0001), with most patients showing relapse after one and two weeks of the randomized withdrawal period. Secondary: Not reported
Coghill et al.[91] (2013) LDX 30 to 70 mg daily vs MPH-ER	DB, MC, PC, PG, RCT Children and adolescents six to 17 years of age diagnosed with ADHD	N=336 7 weeks	Primary: ADHD-RS Secondary: CGI-I	Primary: The LS mean change from baseline in ADHD-RS total score was significantly greater for patients treated with LDX (-24.3±1.2) and MPH-ER (-18.7±1.1) compared to placebo (-5.7±1.1; P<0.001 for both). The LS mean change from baseline in ADHD-RS total score was significantly greater with LDX or MPH-ER compared to placebo at every time point evaluated (P<0.001 for all visits). Effect sizes based

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(Concerta®) 18 to 54 mg daily vs placebo				on the difference in LS mean change in ADHD-RS total score from baseline to endpoint were 1.80 and 1.26 for LDX and MPH-ER, respectively. The decreases in both the ADHD-RS hyperactivity/impulsivity and inattention subscale scores from baseline were also significantly greater for patients treated with LDX or MPH-ER compared to placebo. The LS mean change from baseline to endpoint in hyperactivity/impulsivity was significantly greater with LDX compared to placebo (-8.7; 95% CI -10.3 to -7.2; P<0.001) as was the change in inattention score (-9.9; 95% CI, -11.5 to -8.3; P<0.001). The LS mean change from baseline to endpoint significantly favored MPH-ER compared to placebo for hyperactivity/impulsivity (-6.0; 95% CI, -7.5 to -4.5; P<0.001) and inattention (-7.0; 95% CI, -8.6 to -5.4; P<0.001) scores. Secondary: The proportions of patients with a CGI-I rating of 'very much improved' or 'much improved' after seven weeks of treatment were 78 and 61% for patients treated with LDX or MPH-ER, respectively, compared to 14% of patients treated with placebo (P<0.001 for both).
Findling et al.[92] (2011) LDX 30 to 70 mg daily vs placebo	DB, PC, RCT Adolescents 13 to 17 years of age diagnosed with ADHD	N=314 4 weeks	Primary: ADHD-RS Secondary: CGI-I, YQOL-R, treatment-emergent adverse events	Primary: Differences in ADHD-RS total scores favored all LDX doses compared to placebo at all weeks (P<0.0076). Secondary: Patients were rated much or very much improved at the end of the study with all doses of LDX (69.1%) compared to placebo (39.5%; P<0.0001). YQOL-R scores at the end of the study indicated improvement with LDX treatment, but did not result in significant differences compared to placebo. The most common treatment-emergent adverse events for all combined LDX doses included decreased appetite, headache, insomnia, decreased weight, and irritability. The severity of treatment-

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				emergent adverse events was generally mild or moderate Clinically insignificant mean increases in pulse, BP and ECG changes were noted with LDX.
Findling et al.[93] (2008) LDX 30 to 70 mg daily	MC, OL, SA Children six to 12 years of age diagnosed with ADHD	N=274 12 months	Primary: ADHD-RS Secondary: CGI-S	Primary: Mean ADHD-RS total score improved by 27.2 points (P<0.001). Mean ADHD-RS inattentive subscale score improved by 13.4 points (P<0.001). Mean ADHD-RS hyperactivity score improved by 13.8 points (P<0.001). After improvements during the first four weeks, improvements in ADHD-RS scores were maintained throughout eleven months of treatment. Secondary: Improvement in scale scores seen in >80% of study patients at endpoint and >95% of completers at 12 months were rated as improved. Adverse event included insomnia and vomiting and considered mild or moderate by the study investigator. There were no clinical meaningful changes in BP or electrocardiographic parameters.
Jain et al.[94] (2013) LDX 20 to 70 mg daily vs placebo	OL, PC, RCT, SA, XO (Post-hoc analysis) Children 6 to 12 years of age with ADHD and baseline ADHD-RS IV total score ≥28 who had received MPH within six months of study enrollment	N=150 Variable duration	Primary: Study 1 Change in ADHD-RS total score from baseline Study 2 Mean SKAMP-D subscore over the course of a laboratory school day Secondary:	Study 1 Primary: Of patients treated with LDX, the mean change from baseline in ADHD-RS total score was similar for the overall study population and the prior MPH group, with a 64.9% improvement observed in the prior MPH group. Secondary: Of patients treated with LDX, the mean change in BRIEF scores from baseline were similar for the overall study population and the prior MPH group. The mean change in CGI-I scores, EESC total scores and the BRIEF index subscale scores from baseline were similar between the overall study population and the prior MPH group. In addition, the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Study 1 CGI-S, EESC, BRIEF-Parent form Study 2 SKAMP-A, PERMP math scores, ADHD-RS and CGI scores	BRIEF index subscale scores were normalized at endpoint. The rates of symptomatic remission were similar between the overall study population and the prior MPH group; however, the prior MPH group had numerically lower remission rates compared to the overall group. A clinical response was achieved in 89.6% and 86.7% of the overall population and the prior MPH group, respectively. Study 2 Primary: Improvements in SKAMP-D subscores were similar for both the overall study population and the prior MPH group. For both groups, SKAMP-D scores were improved at all post-dose time points from 1.5 hours to 13 hours with LDX vs placebo ($P \leq 0.0046$ and $P \leq 0.0284$ for all time points in the overall study population and prior MPH group, respectively). Secondary: Improvements in SKAMP-A scores were similar in the overall study population and prior MPH group from 1.5 hours to 13 hours post-dose with LDX vs placebo ($P<0.0001$ and $P \leq 0.0114$ for all time points in the overall study population and prior MPH group, respectively). The PERMP-A and PERMP-C scores were improved to a similar degree in both the overall study population and the prior MPH group at all post-dose time points from 1.5 to 13.0 hours with LDX vs placebo ($P<0.0001$ for all time points in the overall study population and prior MPH group, respectively, for both PERMP-A and PERMP-C). The change from baseline in mean ADHD-RS total scores for the overall study population and the prior MPH groups were similar when taking LDX and placebo during the XO phase (57.1 and 18.1% for patients who had previously received MPH in the LDX group and the placebo group, respectively). At visit five during the XO period, mean CGI-I scores were 1.7 and 3.5 for patients taking LDX and placebo, respectively, for the overall study population and 1.7 and 3.7, respectively, for the prior MPH group who had received $\geq$1 mg/kg/day of MPH.
Mattingly et al.[95] (2013)	Post-hoc analysis of Weisler et al.	N=345	Primary: ADHD-RS-IV	Primary: Baseline ADHD-RS-IV total scores were lower in the predominantly

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
LDX 30 to 70 mg daily vs placebo	Adults aged 18 to 55 years of age diagnosed with ADHD who had completed ≥2 weeks of treatment with LDX	12 months	Secondary: Not reported	inattention and hyperactivity/impulsivity symptom cluster subgroups. LDX decreased ADHD-RS-IV total scores in all predominant symptom cluster subgroups. Mean percent reduction from baseline to endpoint was 55.9, 71.0, and 62.6% for the predominantly inattention, hyperactivity/impulsivity, and combined symptom cluster subgroups, respectively, and was 61.1% for the overall population. At trial end, 285/345 patients were classified as clinical responders (ADHD-RS-IV total score decrease of ≥30% from baseline and CGI-I score of one or two). Of the 93 patients with predominantly inattention symptom cluster at baseline, 74 were classified as clinical responders at trial end. All 13 patients who had predominantly hyperactivity/impulsivity symptom cluster at baseline were classified as clinical responders at endpoint. At endpoint, 236 of patients who had combined type ADHD at baseline, 196 were classified as clinical responders. Secondary: Not reported
Weisler et al.[96] (2009) LDX 30 to 70 mg daily	DB, PC, RCT, SA Adults aged 18 to 55 years of age diagnosed with ADHD	N=349 12 months	Primary: ADHD-RS Secondary: CGI-S, CGI-I	Primary: Mean ADHD-RS total scores improved at week one of treatment and sustained throughout the eleven month treatment period (P<0.001). Mean ADHD-RS total scores improved by 24.8 points from baseline to study endpoint (P<0.001). Secondary: All study patients rated as moderately ill with a mean CGI-S of 4.8 with improvement in their mean score of 1.7 at endpoint. At weeks one, two, three, and four, the proportion of study patients rated as improved on the CGI-I was 43.9, 68.3, 83.4 and 89.1%, respectively. At month 12, 92.6% were improved on the CGI-I. Common adverse events included upper respiratory tract infection, insomnia, headache, dry mouth, decreased appetite and irritability. Most adverse events were considered mild or moderate by the study

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				investigator. Small but statistically significant increases in pulse and BP noted at treatment endpoint.
Wigal et al.[97] (2011) MPH-ER (Concerta®) 18 to 54 mg daily vs placebo	DB, PC, RCT Children nine to 12 years of age diagnosed with ADHD	N=78 5 months	Primary: PERMP, SKAMP, TOVA, Finger Windows forward and backward subtest Secondary: Not reported	Primary: MPH-ER significantly improved performance on the number of problems attempted and number of problems correctly answered on the PERMP compared to placebo (P<0.001). MPH-ER significantly improved performance on inattention, deportment, and total ratings of the SKAMP measure (P<0.001) as compared to placebo. Children taking MPH-ER had statistically significantly better scores than children taking placebo on response time (P<0.000). MPH-ER significantly improved performance on memory as compared to placebo. Most common adverse effects included decreased appetite, upper abdominal pain, headache and irritability. Most adverse events were considered mild or moderate by the study investigator. Secondary: Not reported
Casas et al.[98] (2011) MPH-ER (Concerta®) 54 mg to 72 mg/day vs placebo	DB, MC, PC, RCT Men and women 18 to 65 years of age diagnosed with ADHD	N=279 13 weeks	Primary: CAARS-Inv: SV Secondary: CGI-S, CGI-C, CAARS-Self: SV, SDS, AIMA-A	Primary: Improvements in CAARS-Inv:SV were significantly greater with MPH-ER 72 mg compared to placebo (P=0.0024). There was no significant difference between MPH-ER 54 mg and placebo. Secondary: Mean improvement in CGI-S score was significantly greater with MPH-ER 72 mg than placebo (P<0.001); however, there was no significant difference with MPH-ER 54 mg compared to placebo. Median improvement in CGI-C score was significantly greater with MPH-ER 72 mg (2.0) compared to placebo (3.0; P=0.0018); however, there was no significant difference with MPH-ER 54 mg (2.5) compared to placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				CAARS-Self:SV scores decreased significantly compared to placebo in both MPH-ER treatment groups (P<0.05). There was no significant change in SDS score from baseline in either treatment group. Significant benefit compared to placebo was observed on several AIM-A subscales, which included performance and daily functioning, communication and relationships, living with ADHD and general well-being. The most common adverse events with MPH-ER were mild to moderate in severity and included headache, decreased appetite, dry mouth and nausea.
Wigal et al.[99] (2013) MPH-ER suspension (Quillivant XR®) 20 to 60 mg daily vs placebo	DB, MC, PC, RCT, XO Children six to 12 years of age diagnosed with ADHD	N=45 2 weeks	Primary: SKAMP combined score Secondary: Onset of action and duration of clinical effect, subscale scores for SKAMP, PERMP, CGI-S and CGI-I	Primary: Children treated with MPH-ER suspension experienced a statistically significant improvement in SKAMP combined score at four hours post-dose compared to children treated with placebo. The LS mean SKAMP combined score was 7.12 in children receiving MPH-ER suspension compared to 19.58 in children receiving placebo (LS mean difference, -12.46; P<0.0001). Secondary: There were statistically significant improvements from baseline with MPH-ER suspension compared to placebo at each time point tested (45 minutes, two, four, eight, 10 and 12 hours), with the onset of action at 45 minutes post-dose and a duration of effect continuing to be significant compared to placebo at 12 hours post-dose. The results of the remaining secondary endpoints were not presented in this study.
Wilens et al.[100] (2004) MPH-ER (Concerta®)	MC, OS, PRO Children six to 13 years of age diagnosed with	N=432 1 year	Primary: HR and BP after one year Secondary:	Primary: Compared to baseline, MPH-ER was associated with minor clinical, although statistically significant, DBP elevations (1.5 mm Hg; P<0.001), SBP elevations (3.3 mm Hg; P<0.001) and HR (3.9 beats per minute; P<0.0001) at the 12-month end point.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
18 to 54 mg daily	ADHD		Not reported	Secondary: Not reported
Mattos et al.[101] (2012) MPH-ER (Concerta®) 18 mg to 72 mg/day	MC, OL Men and women 18 to 65 years of age diagnosed with ADHD	N=60 12 weeks	Primary: ASRS, AAQoL, STAI, HAMD, CGI-I Secondary: Not reported	Primary: ADHD symptom severity improved with the ASRS scores (total score, inattention and hyperactivity) significantly reduced from baseline to weeks four, eight, and 12 (P<0.001). AAQoL subscales (P<0.001), as well as AAQoL total score (P<0.001), significantly improved from baseline to week 12. A significant reduction in STAI, CGI-I, and HAMD, scores were observed (P<0.0001). The most common adverse events included appetite changes (25%), dry mouth (16.7%), headache (11.7%), irritability (5%) and insomnia (5%). Adverse events were mild to moderate in severity as reported by the study investigators. Secondary: Not reported
Cox et al.[102] (2006) MPH-ER (Concerta®) 36 mg once daily on days one to five, then 72 mg once daily on days 6 to 17 vs AMP-XR (Adderall XR®) 15 mg once daily on	DB, PC, RCT, XO Adolescents 16 to 19 years of age diagnosed with ADHD and licensed to drive	N=35 21 to 38 days	Primary: IDS, assessed using an Atari Research Driving Simulator on days 10 and 17; subjective ratings of driving performance by participants and investigators Secondary: Not reported	Primary: Overall IDS values were significantly better than with placebo with MPH-ER (P<0.001), but not with AMP-ER (P=0.24). Simulator-rated driving performance as indicated by IDS was also significantly better in the MPH-ER group than in those receiving AMP-ER (P=0.03). MPH-ER was significantly better than placebo in the categories off-road excursions (P=0.02), speeding (P=0.01), SD speed (P=0.02), and time at a stop sign deciding where to turn (P=0.003). AMP-ER was significantly better than placebo in the category of inappropriate braking (P=0.04). Subjective ratings of driving performance by participants and investigators rated MPH-ER as better for driving performance

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
days one to five, then 30 mg once daily on days 6 to 17 vs placebo				(P=0.008). Secondary: Not reported
Yang et al.[103] (2011) MPH-ER 18 mg to 54 mg/day vs atomoxetine 0.5 mg to 1.4 mg/kg/day	RCT, SB Children and adolescents seven to 14 years of age diagnosed with ADHD	N=142 4 to 6 weeks	Primary: RCFT, Digit span, Stroop color word test Secondary: Not reported	Primary: Both MPH-ER and atomoxetine significantly improved visual memory, verbal memory, and word inference time. Visual and verbal memory was not significantly different from the control group at post-treatment assessment (P>0.05). Although word interference time was more improved than the control group, there was no statistically significant difference (P>0.05). Secondary: Not reported
Wolraich et al.[104] (2001) MPH-ER (Concerta®) 18 to 54 mg daily vs MPH-IR 5 to 15 mg three times daily vs placebo	DB, PC, PG, RCT Children six to 12 years of age diagnosed with ADHD (any subtype)	N=282 28 days	Primary: Iowa Conners I/O and O/D rating scale (parents and teachers) Secondary: SNAP-IV scores (teachers and parents), CGI-I scores (investigators), global assessment of efficacy (parents and teachers)	Primary: Both MPH-ER and MPH-IR demonstrated a statistically significant improvement in the Iowa Conners I/O and O/D rating scale scores compared to placebo at week one and at the end of the study (P<0.001). There was no significant difference in the mean Iowa Conners scale scores between the MPH-ER and MPH-IR groups at week one (P=0.838) or at the end of the study (P=0.539). Secondary: Teacher and parent SNAP-IV scores were significantly better for patients in the MPH-ER and MPH-IR groups than for those in the placebo group (P<0.001). There was not a significant difference in SNAP-IV scores between the MPH-ER and MPH-IR groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				CGI-I scores significantly improved in the MPH-ER and MPH-IR groups compared to the placebo group (P<0.001). Both the parent and teacher global assessment of efficacy scores were significantly higher with the MPH-ER and MPH-IR groups than the placebo group (P<0.001).compared to
Pelham et al.[105] (2001) MPH-ER (Concerta®) 18 to 54 mg daily vs MPH-IR 5 to 15 mg three times daily vs placebo	DB, PC, RCT, XO Children six to 12 years of age diagnosed with ADHD (any subtype) who were taking MPH prior to study entry	N=68 1 week	Primary: Iowa Conners I/O and O/D rating scales (teacher and parents), SKAMP scale (teacher) Secondary: Not reported	Primary: MPH-ER and MPH-IR were better than placebo in the Iowa Conners I/O and O/D rating scale scores from teachers and parents (P<0.05). MPH-ER scored significantly better than MPH-IR in the parent Iowa Conners I/O rating scales (P<0.05). In the SKAMP scales, MPH-ER and MPH-IR were similar in efficacy, but both were significantly better than placebo. Secondary: Not reported
Gau et al.[106] (2006) MPH-ER (Concerta®) 18 to 36 mg daily vs MPH-IR 5 to 10 mg three times daily	OL, RCT Children six to 15 years of age diagnosed with ADHD (any subtype) who were taking MPH (10 to 40 mg/day)	N=64 28 days	Primary: CTRS-RS, CPRS-RS, SKAMP-A, SKAMP-D Secondary: SAICA, CGI	Primary: Each of the four groups displayed a significant decrease in all measures of CTRS-RS, CPRS-RS, SKAMP-A, SKAMP-D at each of the follow-up visits (P<0.001 for all) compared to baseline, but there were no significant differences between the groups (P>0.05 for all). Secondary: Patients in both the MPH-XR and MPH-IR groups experienced significant improvements from baseline in academic performance and less severe problems at school (P<0.05). Patients in the MPH-XR group also significantly improved from baseline in attitude toward their teachers, school social interaction, and relationships with peers and siblings (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The MPH-XR group had a significantly greater number of patients being very much or much improved (84.4%) than the MPH-IR group (56.3%) (P=0.014) based on the CGI score.
Lopez et al.[107] (2003) MPH-ER (Concerta®) 18 to 36 mg daily vs MPH-XR (Ritalin LA®) 20 mg daily vs placebo	DB, PC, RCT Children six to 12 years of age diagnosed with ADHD who were previously stabilize on MPH (equivalent dose of 10 mg BID)	N=36 28 days	Primary: SKAMP scales Secondary: Not reported	Primary: Both MPH-ER and MPH-XR statistically improved SKAMP scale scores compared to placebo (P<0.001). Secondary: Not reported
Swanson et al.[108] (2004) MPH-ER (Concerta®) 18 to 54 mg daily vs MPH-XR (Metadate CD®) 20 to 60 mg daily vs placebo	DB, MC, PC, RCT, XO Children six to 12 years of age diagnosed with ADHD (inattentive type, hyperactive-impulsive type, or combined type) being treated with MPH in doses of 10 to 60 mg/day	N=184 7 weeks	Primary: SKAMP scales, PERMP Secondary: Not reported	Primary: MPH-ER and MPH-XR demonstrated similar efficacy, and both were better than placebo in SKAMP and PERMP scores (P<0.016). Secondary: Not reported
Silva et al.[109]	MC, RCT, SB, XO	N=54	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2005) MPH-ER (Concerta®) 18 mg vs MPH-ER (Concerta®) 36 mg vs MPH ER 20 mg vs MPH ER 40 mg vs placebo All medications were dosed once per study day (six consecutive Saturdays). Patients continued their regular ADHD medications on Sunday through Thursday of the study weeks, with	Children six to 12 years of age diagnosed with ADHD and stabilized on MPH (20 to 40 mg/day)	6 weeks	SKAMP-A rating subscale Secondary: SKAMP-D and SKAMP-C rating subscales and written math tests	All doses of the study medications significantly improved SKAMP-A scores from baseline at all time points, compared to placebo (P<0.038). ER-MPH 20 and 40 mg showed significantly greater differences from predose on the SKAMP-A than did MPH ER, 36 mg at two hours postdose, and also when scores were integrated over zero to four hours (P=0.022 for the 20 mg dose and P=0.001 for the 40 mg dose), but showed no significant improvement over eight to 12 hours. Secondary: Single morning doses of ER-MPH and MPH ER, were effective in improving SKAMP-D scores and academic productivity for the majority of the 12-hour classroom session.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
no medications allowed on Friday.				
Jahromi et al.[110] (2009) MPH-IR 0.125 mg/kg/dose twice daily for one week (low dose) vs MPH-IR 0.25 mg/kg/dose twice daily for one week (medium dose) vs MPH-IR 0.50 mg/kg/dose twice daily for one week (high dose) vs placebo for one week	DB, RCT, XO Children five to 13 years of age with PDD and hyperactivity	N=33 4 weeks	Primary: JAMES, Caregiver-Child Interaction measure (competing demands and clean-up task) captured social communication, self-regulation and affective behavior Secondary: Not reported	Primary: Significant positive effect of MPH was seen on social communication (P<0.05); comparing each of the three MPH doses of MPH compared to placebo, the low dose showed significant improvement compared to placebo (P<0.05); no significant differences found between placebo and the medium or high doses. No significant improvement in self-regulation for the competing demands task when comparing best dose MPH to placebo (P=0.09); significant improvement in self-regulation behaviors comparing low dose MPH (P<0.05) and medium dose effect (P<0.01) compared to placebo; no improvement found in high dose MPH over placebo. No significant improvement in self-regulation behaviors for the clean-up task for any of the three dose levels of MPH compared to placebo, or between placebo and the best dose of MPH (P>0.05). Significant improvement in affective behavior for the competing demands task when comparing medium MPH dose (P <0.05) and high MPH dose compared to placebo (P<0.05); no improvement found in best dose of MPH compared to placebo (P=0.09); or low dose (P=0.07). No significant improvement on affective behavior for the clean-up task and any MPH dose (P>0.05). Secondary: Not reported
Spencer et al.[111] (2011) MPH-IR three times daily vs	PG, RCT, SB Patients 19 to 60 years of age diagnosed with ADHD who were on stable therapy	N=61 6 weeks	Primary: AISRS Secondary: Not reported	Primary: MPH-IR responders randomized to MPH-IR or MPH-ER had no effect on AISRS score at the study endpoint (11.2 vs 10.7; P=0.80). Study patients stabilized on MPH-IR and switched to MPH-ER remained satisfied over 71% of the time.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
MPH-ER once daily (OROS-MPH)	with MPH-IR			MPH-IR treatment group missed significantly more doses than the MPH-ER treatment group (7.3 vs 3.3; P=0.02). Secondary: Not reported
Efron et al.[112] (1997) MPH-IR 0.3 mg/kg/dose twice daily vs DEX-IR 0.15 mg/kg/dose twice daily Patients received one drug for two weeks then crossed over to the other stimulant for two weeks.	DB, RCT, XO Children five to 15 years of age diagnosed with ADHD	N=125 4 weeks	Primary: SERS Secondary: Not reported	Primary: There was a statistically significant decrease in the mean number of side effects in the MPH-IR group vs the DEX-IR group (8.19 vs 7.19; P=0.03) based on the results of the SERS questionnaire which assess the 17 most common side effects of stimulants including trouble sleeping, decreased appetite and anxiousness. Mean severity of side effects statistically significantly improved in the MPH-IR group compared to the DEX-IR group (3.24 vs 3.73; P<0.01). A majority of parents rated their children as improved compared to their “usual selves” in both of the treatment groups (68.8% in the DEX-IR groups and 72% in the MPH-IR). Secondary: Not reported
Pelham et al.[113] (1990) MPH-IR 10 mg twice daily vs MPH-SR (Ritalin SR®) 20 mg daily vs	DB, PC, RCT, XO Males eight to 13 years of age diagnosed with ADHD	N=22 8 weeks	Primary: Evaluated social behavior during activities, classroom performance, and performance on a continuous performance task Secondary: Not reported	Primary: Each of the active treatment groups were more effective than placebo on most measures of social behavior from the medication assessment (P<0.05). DEX-SR and pemoline tended to produce the most consistent effects. The continuous performance task results showed that all four medications had an effect within two hours, and the effects lasted for nine hours vs placebo (P<0.025). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
DEX-SR (Dexedrine®) 10 mg daily vs pemoline 56.25 mg daily vs placebo				
Palumbo et al.[114] (2008) MPH-IR 5 mg to 60 mg/day vs clonidine 0.05 mg to 0.6 mg/day vs MPH-IR and clonidine vs placebo	DB, MC, PC, RCT Children seven to 12 years of age diagnosed with ADHD	N=122 16 weeks	Primary: CASQ-T Secondary: CASQ-P, CGAS	Primary: For CASQ-T, clonidine did not improve ADHD symptoms. Study patients treated with MPH showed significant improvement compared to those not treated with MPH. Secondary: Study patients treated with clonidine had greater improvements on the CASQ-P and CGAS, but a higher rate of sedation compared to patients not treated with clonidine.
Huss et al.[115] (2014) MPH-LA 40 mg/day	DB, MC, PC, RCT Adult patients 18 to 60 years of age with a diagnosis of	N=725 40 weeks (9 week double-blind dose-	Primary: ADHD-RS, SHS, percentage of treatment failures	Primary: Improvement from baseline in ADHD-RS (P<0.0001 for all comparisons) and SDS (40 mg, P=0.0003; 60 mg, P=0.0176; 80 mg, P<0.0001) total scores was significantly greater vs placebo for all MPH-LA doses. Treatment failure rate was significantly lower with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs MPH-LA 60 mg/day vs MPH-LA 80 mg/day vs placebo	ADHD	confirmation phase; 5 week real-life dose-optimization phase; 6 month double-blind maintenance of effect phase)	Secondary: CGI-I, CGI-S, CAARS- observer, ASRS	MPH-LA (21.3%) versus placebo (49.6%) during the six-month maintenance of effect phase. By the end of the nine-week double-blind dose-confirmation phase, improvement from baseline in ADHD-RS total score for all MPH-LA dose levels was significantly greater than placebo (all comparisons: P<0.0001). Similarly, functional improvement, as assessed by change from baseline in the SDS total score, was significantly greater for all MPH-LA dose levels compared to placebo (40 mg, P=0.0003; 60 mg, P=0.0176; 80 mg, P<0.0001). During the six-month double-blind maintenance of effect phase, significantly less patients treated with MPH-LA were required to discontinue the study due to treatment failure (21.3%, n=75) compared to those treated with placebo (49.6%, n=57). Patients treated with placebo had more than three times higher chance of being required to discontinue the study due to treatment failure compared to patients treated with MPH-LA (OR, 0.3; 95% CI, 0.2 to 0.4). Secondary: The percentage of patients with improvement on the CGI-I scale for all three MPH-LA dose levels was significantly higher compared to placebo. Similarly, the percentage of patients with improvement for all three MPH-LA dose levels on CGI-S was significantly higher compared to the placebo group. Consistent results were seen for the observer-rated CAARS and self-rated ASRS: improvement from baseline for all dose levels of MPH-LA was significantly greater than placebo.
Ginsberg et al.[116] (2014) MPH-LA (40 to 80 mg/day)	ES (of Huss et al, 2014), OL Adult patients 18 to 60 years of age with a diagnosis of ADHD	N=298 1 year (6 month double-blind maintenance of effect phase and 6 month extension)	Primary: Safety Secondary: Efficacy (ADHD-RS, SDS, CGI-I, CGI-S)	Primary: Overall, the incidence of adverse events was comparable between patients receiving placebo (79.3%) and those receiving MPH-LA (81.0%) during the maintenance of effect phase of the core study. The incidence of adverse events occurring in the extension study was 69.8%. Incidence of adverse events was comparable between MPH-LA mean daily dosage groups (69.4; 75.0; and 65.1% in the ≤40, >40 to 60, and >60 mg dosage groups, respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: The mean improvement in total score of ADHD-RS from the maintenance of effect phase baseline to the end of the extension study was 0.9. The mean improvement in SDS total score from the maintenance of effect phase baseline to the end of the extension study was 1.4. A total of 91 (31.4%) patients showed improvement in CGI-S score from the maintenance of effect phase baseline to the end of the extension study (MPH-LA, 32.1%; placebo, 29.5%). The mean improvement in total score of ADHD-RS and SDS from extension baseline to the end of the study was 7.2 and 4.8, respectively. Overall, 69.4% of patients showed improvement in CGI-I rating (MPH-LA, 65.3%; placebo, 80.2%), and 52.1% of patients showed improvement in CGI-S scale (MPH-LA, 42.9%; placebo, 76.9%) from the extension study baseline to the end of the study.
Greenhill et al.[117] (2002) MPH-XR (Metadate CD®) 20 to 60 mg daily vs placebo	DB, MC, PC, RCT Children six to 16 years of age diagnosed with ADHD	N=321 3 weeks	Primary: CGI-S (teacher) Secondary: CGI-S (parents), CGI-I scores, adverse events	Primary: CGI-S teacher scores significantly improved in the MPH-XR group (12.7±7.2 to 4.9±4.7) compared to the placebo group (11.5±7.3 to 10.3±6.9; P<0.001). Secondary: CGI-S parent scores significantly improved from 13.6±6.6 to 7.4±5.9 with MPH-XR vs 12.9±7.6 to 10.1±6.7 with placebo (P<0.001 for both scales). Eighty-one percent of the patients in the MPH-XR group compared to 50% of the patients in the placebo group were classified as responders based on their CGI-I scores (P<0.001). In the MPH-XR group, 52% of children reported at least one adverse event vs 38% from the placebo group (P=0.014). The rate of anorexia was more significant in the MPH-XR group vs the placebo group (9.7 vs 2.5%; P=0.007).
McGough et al.[118] (2006) MTS 10 to 27 mg	OL, RCT (first five weeks) then DB, PC Children six to 12	N=80 7 weeks	Primary: Evaluate time course effects of MPH transdermal	Primary: Mean SKAMP-D scores were improved with MPH transdermal patch vs placebo (mean score, 3.2 vs 8.0) and at all time points assessed including 12 hours post-application (P<0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
daily vs standard current therapy	years of age diagnosed with ADHD		patch vs placebo transdermal patch via SKAMP-A, SKAMP-D, PERMP, ADHD-RS-IV, CPRS-R, CGI-I, and PGA rating scales Secondary: Acute efficacy and tolerability of MPH transdermal patch	Mean (SKAMP-A) scores were improved with MPH transdermal patch vs placebo (6.2±0.50 vs 9.9±0.50, respectively; P<0.0001). PERMP scale results: Mean number of math problems attempted and math problems correct were significantly higher with MPH transdermal patch vs placebo (113.8 vs 86.2 and 109.4 vs 80.7, respectively; P<0.0001). Across the double-blind period, mean scores for the ADHD-RS-IV and CPRS-R scales were significantly improved with MPH transdermal patch vs placebo (P<0.0001). Those in the MPH transdermal patch group (79.8%) were more likely to be deemed improved on clinician rated CGI-I scores vs those in the placebo group (79.85 and 11.6%, respectively; P<0.0001). Statistically significant differences were observed with PGA ratings; 71.1% of MPH transdermal patch participants and 15.8% of placebo participants were rated as improved (P<0.0001). Secondary: More treatment-emergent adverse events were recorded with MPH transdermal patch therapy (39 events, 24 participants) vs placebo therapy (25 events, 18 participants). The most common treatment-related adverse events were decreased appetite, anorexia, headache, insomnia, and upper abdominal pain, all reported by less than 5% of study participants.
Pelham et al.[119] (2005) MPH transdermal patches: 6.25 cm^2 (0.45 mg/hour), 12.5 cm^2 (0.9 mg/hour) and 25	DB, DR, MC, RCT Children seven to 12 years of age diagnosed with ADHD	N=36 8 days	Primary: MPH transdermal patch efficacy and influence of exposure time on morning effects Secondary:	Primary: All doses of MPH transdermal patches were significantly improved vs placebo on measures of social behavior in recreational settings, classroom functioning, and parent ratings of evening behavior (P<0.05). Beneficial effects of MPH transdermal patches were observed at all time points after application of the patch and were still seen for three

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
cm^2 (1.8 mg/hour), worn for at least 12 hours daily Each participant received single applications of MPH transdermal patches 6.25 cm^2, 12.5 cm^2 or 25 cm^2 patches or placebo in a random order on separate days and at two time points (6:00 AM or 7:00 AM).			Not reported	hours after the patch had been removed (i.e., throughout the 12-hour assessment). Incidence of skin rash was reported as 40 to 50%. Secondary: Not reported
Pelham et al.[120] (2005) MPH transdermal patches: 12.5 cm^2, 25 cm^2 and 37.5 cm^2 plus behavior modification Each participant had two days on each treatment without concomitant plus behavior modification and four days on each treatment with plus behavior modification.	DR, RCT Children aged six to 12 years diagnosed with ADHD	N=27 6 weeks	Primary: Proportion that reached individual target goals in Daily Report Card scores Secondary: Not reported	Primary: The percentage of individualized target criteria met by children in their Daily Report Card assessment was significantly ($P<0.05$ for all) higher with MPH transdermal patch 12.5, 25, and 37.5 cm^2 vs placebo, both without behavior modification (41.9, 63.1, and 66.2 vs 20.8%) and with behavior modification (73.7, 87.5, and 86.2 vs 54.7%; all $P<0.05$). Response rates were higher in the MPH transdermal patches 25 cm^2 group than in the 12.5 cm^2 group, both with and without behavior modification ($P<0.05$ for both); increasing the size of the patch to 37.5 cm^2 added no further advantage. Secondary: Not reported
Faraone et al.[121]	DB, MC, PC, RCT	N=268	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2009) MPH transdermal patches 10 to 30 mg daily worn for nine hours per day or MPH-ER (Concerta®) 18 to 54 mg daily vs placebo	Children six to 12 years of age diagnosed with ADHD (predominantly hyperactive-impulsive, predominantly inattentive, or combined type)	5 weeks	CSHQ Secondary: Not reported	No significant difference in the severity of sleep problems was observed among the treatment and placebo groups (P≥0.233). No significant differences in the numbers of sleep problems were observed between MPH transdermal patch/MPH-ER and placebo (P≥0.554). There was no significant effect of MPH dosage on sleep problems (P=0.135). The effects of each MPH treatment and the various doses of these treatments on each CSHQ subscale were identical to the effects observed for the total CSHQ scale. Secondary: Not reported
Findling et al.[122] (2008) MTS 10 to 30 mg daily or OROS-MPH 18 to 54 mg daily vs placebo	DB, PC, RCT Children six to 12 years of age diagnosed with ADHD	N=282 7 weeks	Primary: ADHD-RS Secondary: CTRS-R, CPRS-R, CGI-S, CGI-I	Primary: Mean total ADHD-RS scores were similar between MPH transdermal patch, MPH-ER, and placebo at baseline (43.0, 43.8, and 41.9, respectively), but not at endpoint (18.8, 21.8, and 32.1, respectively). Mean change from baseline in ADHD-RS scores was greater in study patients receiving MPH transdermal patch and MPH-ER compared to patients receiving placebo (P<0.001). There was a two-fold improvement of ADHD symptoms in active treatments compared to placebo from baseline to study endpoint. Secondary: MPH transdermal patch and MPH-ER showed improvements over placebo in mean total parent and teacher scores from baseline to endpoint. More study patients receiving MPH transdermal patch and MPH-ER compared to placebo were rated as improved by clinicians and parents (P<0.001). Adverse events included decreased appetite, nausea, vomiting and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				insomnia. Most adverse events were considered mild or moderate by the study investigator.
Chou et al.[123] (2012) MPH-ER (Concerta®) 18, 36, or 54 mg once daily	OS Children six to 19 years of age with ADHD who have received MPH-IR for ≥1 month	N=521 10 weeks (six weeks forced-titration phase to achieve remission, followed by a four week maintenance phase)	Primary: Symptomatic remission Secondary: Changes in efficacy and satisfaction, safety	Primary: Using the forced-titration of MPH-ER dosage to increase the dosage during the first six weeks, the remission rate significantly increased with time from 4.8% (at baseline), 25% (week two), 44.2% (week four), 58.8% (week six), up to 59.6% (week 10) among 507 ITT patients. Among 439 patients who completed the 10 week follow-up assessments, 290 (66.1%) patients achieved symptomatic remission (95% CI, 61.6 to 70.5). The non-remission group had higher mean daily doses compared to the remission group from visit two to trial end. Secondary: Among the 439 patients who completed the treatment, there was a significant decrease in the total score and three sub-scores of the Chinese SNAP-IV (P<0.001), CGI-ADHD-S (P<0.001), and CGI-ADHD-I (P<0.001) as intra-individual comparison from the baseline to each visit through the trial period. Among the items on the Barkley SERS, poor appetite was the only one exacerbated on visit three, but improved on later visits. The other side effects gradually decreased in intensity throughout the trial period, and the difference from baseline reached significance from visit three to trial end. At trial end, there was a decrease in both mean body weight (-0.85 kg) and mean respiratory rate (-0.44/minute), and an increase in mean pulse rate (5.09 beats per minute) in comparison with baseline with significance (P<0.001). Five percent of patients withdrew from the trial because of adverse events, and these patients mostly left due to poor appetite and insomnia. Three patients experienced at least one serious adverse event that was not deemed to be treatment-related.
Faraone et al.[124] (2006)	MA (29 trials)	N=2,988	Primary: Effect sizes	Primary: All of the drugs groups produced a significant measure of effect

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
AMP-IR, AMP-XR, atomoxetine, bupropion, DEX-IR, DEX-ER, DEX-IR, modafinil, MPH-ER, MPH-IR, MPH-XR, MPH transdermal patches, pemoline	Patients diagnosed with ADHD	Variable duration	Secondary: Not reported	compared to the placebo group (P<0.0001). The effect sizes for non stimulant medications were significantly less than those for immediate-release stimulants (P<0.0001) or long-acting stimulants (P=0.0008). The two classes of stimulant medications (short acting and long acting) did not differ significantly from one another (P=0.14). Secondary: Not reported
Schelleman et al.[125] (2011) ADHD medications vs nonusers	RETRO Children three to 17 years of age who were dispensed a prescription for an AMP, atomoxetine, or MPH	N=241,417 Variable duration	Primary: Sudden cardiac death, or ventricular arrhythmia, stroke, MI Secondary: All-cause death	Primary and Secondary: No statistically significant difference between incident users and nonusers was observed in the rate of validated sudden death or ventricular arrhythmia (HR, 1.6; 95% CI, 0.19 to 13.60) or all-cause death (HR, 0.76; 95% CI, 0.52 to 1.12). None of the strokes identified during exposed time to ADHD medications were validated. No MIs were identified in study patients who used ADHD medication. No statistically significant difference between prevalent users and nonusers was observed for validated sudden death or ventricular arrhythmia (HR, 1.43; 95% CI, 0.31 to 6.61); stroke (HR, 0.89; 95% CI, 0.11 to 7.11); stroke/MI (HR, 0.72; 95% CI, 0.09 to 5.57); or all-cause death (HR, 0.77; 95% CI, 0.56 to 1.07).
Olfson et al.[126] (2012) AMP and MPH vs	RETRO Patients six to 21 years of age diagnosed with ADHD who were prescribed AMP or	N=171,126 Variable duration	Primary: Cardiac events (inpatient diagnosis of chest pain, cardiac dysrhythmia or transient cerebral	Primary: There were 0.92 new cardiac events and 3.08 new cardiac symptoms per 1,000,000 days of current stimulant use. Current stimulant use compared to no stimulant use was not associated with less severe cardiovascular event (adjusted OR, 0.69; 95% CI, 0.42 to 1.12).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
nonusers	MPH		ischemia) and cardiac symptoms (tachycardia, palpitations, or syncope) Secondary: Not reported	Past stimulant use compared to no stimulant use was not associated with less severe cardiovascular event (adjusted OR, 1.18; 95% CI, 0.83 to 1.66). The adjusted ORs for cardiac symptoms were 1.18 (95% CI, 0.89 to 1.59) for current and 0.93 (95% CI, 0.71 to 1.21) for past stimulant use when compared to no stimulant use. Current and past stimulant use was not associated with cardiac symptoms. No significant differences were observed in risks of cardiovascular events (adjusted OR, 2.14; 95% CI, 0.82 to 5.63) or symptoms (adjusted OR, 1.08; 95% CI, 0.66 to 1.79) for current MPH use compared to AMP use. Secondary: Not reported
Schelleman et al.[127] (2012) AMP, atomoxetine, MPH	RETRO Patients three to 17 years of age with a prescription for an AMP, atomoxetine, or MPH	N=219,954 Variable duration	Primary: Sudden death, ventricular arrhythmia, stroke, MI Secondary: Not reported	Primary: No significant difference between incident users and nonusers was observed in the rate of sudden death or ventricular arrhythmia (HR, 1.60; 95% CI, 0.19 to 3.60) or all-cause death (HR, 0.76; 95% CI, 0.52 to 1.12). None of the strokes identified during exposed time to ADHD medications were validated. No MIs were identified in ADHD medication users. No significant difference between prevalent users and nonusers was observed (HR for validated sudden death or ventricular arrhythmia, 1.43; 95% CI, 0.31 to 6.61; stroke, 0.89; 95% CI, 0.11 to 7.11; stroke/MI, 0.72; 95% CI, 0.09 to 5.57; and all-cause death, 0.77; 95% CI, 0.56 to 1.07). Secondary: Not reported
Hanwella et al.[128]	MA (five trials)	N=2,762	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2011) Atomoxetine vs MPH	Children and adolescents six to 16 years of age diagnosed with ADHD	Variable duration	ADHD-RS Secondary: Not reported	The MA did not find a significant difference in efficacy between MPH and atomoxetine when comparing SMD in ADHD-RS scores (SMD, 0.09; 95% CI, -0.08 to 0.26). There was no significant difference in response rates between the two medications (RR, 0.93; 95% CI, 0.76 to 1.14). Treatment effects between the formulations of MPH showed a significant SMD in ADHD-RS favoring OROS-MPH (SMD, 0.32; 95% CI, 0.12 to 0.53). MPH-IR was not superior to atomoxetine (SMD, -0.04; 95% CI, -0.19 to 0.12). There was no significant difference in acceptability between atomoxetine and MPH (RR, 1.22; 95% CI, 0.87 to 1.71). Secondary: Not reported
Bloch et al.[129] (2009) ADHD medications	MA (11 trials) Children diagnosed with ADHD and Tourette's	N=77 Variable duration	Primary: ADHD severity (ADHD-RS, CADS-P, CADS-T, CTRS-R) and tic severity (YGTSS, STSSS, HMVTS, and GTSS) Secondary: Not reported	Primary: MPH, α-2 agonists, desipramine, and atomoxetine demonstrated efficacy in improving ADHD symptoms in children with co-morbid tics. α-2 agonists and atomoxetine significantly improved co-morbid tic symptoms. There was evidence that supratherapeutic doses of DXM worsened tics; however, there was no evidence that MPH worsened tic severity in the short term. Secondary: Not reported
Binge Eating Disorder				
McElroy et al.[130] (2015) LDX 30 mg/day vs LDX 50 mg/day	DB, PC, PG, RCT Adults 18 to 55 years of age with moderate to severe binge eating disorder, as indicated by at least	N=260 11 weeks	Primary: Number of binge eating days per week Secondary: Number of binge eating episodes per	Primary: The mean (SD) changes from baseline to week 11 or early termination in nontransformed binge eating days per week for the placebo and the 30, 50, and 70 mg treatment groups were −3.3 (2.04), −3.5 (1.95), −4.1 (1.52), and −4.1 (1.57), respectively. The primary efficacy end point was significantly decreased in the 50 and 70 mg treatment groups but not in the 30 mg treatment group compared with the placebo group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs LDX 70 mg/day vs placebo	three binge eating days per week for the two weeks before the baseline visit		week, one-week binge eating response status, four-week cessation from binge eating, CGI-I	Secondary: The LS mean change from baseline to week 11 of binge eating episodes per week was significantly decreased for the 50 and 70 mg treatment groups. At week 11 or early termination, the one-week response status was improved in the 50 and 70 mg treatment groups compared with the placebo group, and the four-week binge eating cessation response status was improved in the 50 and 70 mg treatment groups compared with the placebo group. Greater proportions of participants receiving lisdexamfetamine were rated improved (CGI-I rating, one or two) compared with those receiving placebo at week 11 or early termination.

Drug regimen abbreviations: AMP=mixed amphetamine salts, DEX=dextroamphetamine, DXM=dexmethylphenidate, ER=extended release, IR=immediate release, LDX=lisdexamfetamine, MPH=methylphenidate, OROS=osmotic-release oral system, SR=sustained release, XR=extended release
Study abbreviations: CI=confidence interval, DB=double blind, DR=dosing ranging, ES=extension study, FD=fixed dose, HR=hazard ratio, MA=meta-analysis, MC=multi-center, OL=open-label, OR=odds ratio, OS=observational study, PC=placebo-controlled, PG=parallel-group, PRO=prospective trial, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk, SA=single arm, SB=single blind, TB=triple blind, XO=crossover design
Other abbreviations: AAQoL=Adult ADHD quality of life scale, ADHD=attention deficit hyperactivity disorder, ADHD-RS=ADHD rating scale, AIM-A=ADHD impact module-adult, AISRS=Adult ADHD investigator system symptom report scale, ASRS=Adult self-rating scale, BFI=Brief Fatigue Inventory, BP=blood pressure, BRIEF=Behavior Rating Inventory of Executive Function, BRIEF-A=Behavior Rating Inventory of Executive Function-Adult Version, CAARS=Conner's adult ADHD rating scale, CAARS-Inv:SV=Conners' Adult ADHD Rating Scale–Investigator Rated: Screening Version, CAARS-Self:SV=Conners' Adult ADHD Rating Scale–Self Rated: Screening Version, CADS-P=Conners ADHD/DSM IV scale-parent version, CADS-T=Conners ADHD/DSM IV scale-teacher version, CANTAB-CRT=Cambridge Neuropsychological Test Automated Battery-Choice Reaction Time, CANTAB-SWM=Cambridge Neuropsychological Test Automated Battery-Working Memory and Strategy Performance, CASQ-P=Conner's abbreviated symptom questionnaire for parents, CASQ-T=Conner's abbreviated symptom questionnaire for teachers, CBC=Conner's behavior checklist, CGAS=Children's Global Assessment Scale, CGI=clinical global impression CGI-C=clinical global impression of change, CGI-I=clinical global impression of improvement, CGI-S=clinical global impression of severity, CHIP-CE=Child Health and Illness Profile-Child Edition, CPRS=Conners parent rating scale, CHQ=child health questionnaire, CHQ-PF50=Child Health Questionnaire-Parent Form, CPRS=Conners parent rating scale, CPRS-R=Conners parent rating scale—revised, CPRS-R:S=Conners parent rating scale: short form, CPRS-R:L=Conners' parent rating scale-revised: long form, CPT=Continuous performance test, CSHQ=Children's Sleep Habits Questionnaire, CTRS-R=Conners teacher rating scale–revised, CTRS-R: S=Conners teacher rating scale-revised: short form, DBP=diastolic blood pressure, DSST=Digit Symbol Substitution Task/Coding Test, EESC=Expression and Emotion Scale for Children, FBIM=Family Burden of Illness Module, HAMA=Hamilton Anxiety Rating Scale, GEC=global executive composite, GTSS=Global tic severity scale, $HAMD_{17}$=Hamilton 17-item Depression Rating scale, HMVTS=Hopkins motor/vocal tic scale, HR=heart rate, HSPP=Harter Self-Perception Profile, I/O=inattention/overactivity, JAMES=Joint Attention Measure from the EScs (Early and Social Communication Scale), LS=least square, MI=myocardial infarction, O/D=oppositional/defiance, ODD=oppositional defiant disorder, PDD=pervasive developmental disorders, PERMP=permanent product measure of performance, PGA=parent global assessment, PSQ=parental satisfaction questionnaire, Q-LES-Q=quality of life, enjoyment, and satisfaction questionnaire, SAICA=Social Adjustment Scale for Children and Adolescents, SBP=systolic blood pressure, SD=standard deviation, SDS=Sheehan disability scale, SF-36=36-item Short Form Health Survey, SERS=side effect ratings scale, SKAMP=Swanson, Kotkin, Agler, M-Flynn, and Pelham, SKAMP-A=SKAMP-Attention, SKAMP-D=SKAMP-Deportment, SMD=standard mean difference, SNAP=Swanson, Nolan and Pelham, SNAP-ODD=Swanson, Nolan and Pelham-oppositional defiant disorder, SNAP-P=Swanson, Nolan and Pelham-parent rating scale, SNAP-T=Swanson, Nolan and Pelham-teacher rating scale, SSERS=Stimulant Side Effects Rating Scale, STAI=State and trait anxiety inventory, STSSS=Shapiro Tourette syndrome severity scale, TOVA=test of variables of attention, WFIS=Weiss Functional Impairment Scale, WRAADDS=Wender-Reimherr Adult Attention-Deficit Disorder Scale, YGTSS=Yale global tic severity scale, YQOL-R=Youth quality of life-research version

Additional Evidence

Dose Simplification
Once-daily formulations increase patient compliance and eliminate the need for medication use during school. Prescribing immediate-release stimulants that require dosing during school hours can be problematic, especially with controlled drugs which have the potential for abuse. A few studies have compared immediate-release formulations with extended-release products. Lage et al. evaluated a pharmacy claims database to assess medication compliance among patients who took methylphenidate three times daily compared to those taking an extended-release product (Concerta®).[131] The investigators found better compliance in patients taking the extended-release product, less likelihood of switching medications, and a lower probability of discontinuing the medication. The use of the extended-release product was associated with a lower rate of emergency-room visits and fewer physician visits.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 19. Relative Cost of the Cerebral Stimulants/Agents Used for Attention-Deficit/Hyperactivity Disorder

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Central Alpha-Agonists				
Clonidine	sustained-release tablet	Kapvay®*	$$$$$	$
Amphetamine Derivatives				
Amphetamine sulfate	tablet	Evekeo®	$$$$$	N/A
Amphetamine aspartate, amphetamine sulfate, and dextroamphetamine	extended-release capsule, tablet	Adderall®*, Adderall XR®*	$$$$$	$$
Dextroamphetamine	sustained-release capsule, solution, tablet	Dexedrine®*, ProCentra®*, Zenzedi®*	$$$$$	$$$$

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Lisdexamfetamine	capsule	Vyvanse®	$$$$$	N/A
Methamphetamine	tablet	Desoxyn®*	$$$$$	$$$$
Respiratory and CNS Stimulants				
Dexmethylphenidate	extended-release capsule, tablet	Focalin®*, Focalin XR®*	$$$$$	$$$$$
Methylphenidate	chewable tablet, extended-release capsule, extended-release solution, extended-release tablet, sustained-release tablet, solution, tablet, transdermal patch	Aptensio XR®, Concerta®*, Daytrana®, Metadate CD®*, Metadate ER®*, Methylin®*, Ritalin®*, Ritalin LA®*, Quillivant XR®	$$-$$$$	$$$$
Central Nervous System Agents, Miscellaneous				
Atomoxetine	capsule	Strattera®	$$$$$	N/A
Guanfacine	extended-release tablet	Intuniv®*	$$$$$	$

*Generic is available in at least one dosage form or strength.
N/A=Not available.

X. Conclusions

The central nervous system agents that are included in this review are approved to treat attention deficit hyperactivity disorder (ADHD).[3-22] The cerebral stimulants are classified as Schedule II (amphetamines and methylphenidate derivatives) controlled substances. Atomoxetine, extended-release clonidine, and extended-release guanfacine are not cerebral stimulants; therefore, they are not classified as controlled substances. There is at least one short-acting, intermediate-acting, and long-acting central nervous system agent available in a generic formulation.

Guidelines recommend the use of an agent approved by the Food and Drug Administration (FDA) for the initial pharmacologic treatment of ADHD and they do not give preference to one agent over another.[25,26] The central nervous system agents have been shown to be effective for the treatment of ADHD in numerous clinical trials.[36-129] Although comparative trials have been conducted, it is difficult to interpret the results of these studies due to design flaws (small sample size, short duration, crossover design, variable outcomes, etc.).[37-39,52-57,59,66,71,102-108,112-114,122] Extended-release clonidine and extended-release guanfacine are approved for the treatment of ADHD as monotherapy and as adjunctive therapy to stimulants.[2,23,65,82,83]

There are several factors to take into consideration when selecting a pharmacologic agent for the treatment of children and adolescents with ADHD. This includes the presence of comorbid conditions, patient/family preference, storage/administration at school, history of substance abuse, drug diversion, pharmacokinetics, and adverse events.[2,25-27] The advantage of a once-daily formulation is that the medication does not need to be taken during school hours, as is the case with the immediate-release formulations. Administration of medications during school hours, especially Schedule II controlled substances, can be difficult since the medication must be administered by a licensed school nurse. Atomoxetine, extended-release clonidine, and extended-release guanfacine are not controlled substances, which may make it preferable to the stimulants in certain situations.

There is insufficient evidence to support that one brand cerebral stimulant/agent used for ADHD is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand cerebral stimulant/agent used for ADHD within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand cerebral stimulant/agent used for ADHD is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

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Alabama Medicaid Agency
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Pharmacotherapy Review of Wakefulness Promoting Agents
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I. Overview

Narcolepsy is a sleep disorder characterized by excessive daytime sleepiness and intermittent manifestations of rapid eye movement sleep during wakefulness.[1] Obstructive sleep apnea is the most common form of breathing-related sleep disorder, which is caused by obstruction of the airway.[2] Individuals with obstructive sleep apnea often suffer from excessive daytime sleepiness, as well as other serious health conditions (e.g., depression, hypertension, and cardiovascular/cerebrovascular disease).[3] Circadian rhythm sleep disorder consists of a persistent/recurrent pattern of sleep interruption. The shift work type occurs in individuals who work non-standard hours (e.g., night work, early morning work, and rotating schedules), and is characterized by excessive sleepiness and/or insomnia.[2,4]

Modafinil and armodafinil (the longer half-life enantiomer of modafinil) are wakefulness promoting agents approved to improve wakefulness in adult patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnea, and shift work sleep disorder.[5,6] The exact mechanism by which these two agents improve wakefulness is unknown; however, their actions are similar to other sympathomimetic agents. They have been shown to produce psychoactive and euphoric effects similar to stimulants, as well as alterations in mood, perception, thinking, and feelings.[5,6] As a result, these agents are classified as Schedule IV controlled substances.

Sodium oxybate is gamma-hydroxybutyric acid, a known drug of abuse.[7] It is classified as a miscellaneous central nervous system agent but included within this review as it is approved for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy. The exact mechanism by which sodium oxybate reduces cataplexy and excessive daytime sleepiness in patients with narcolepsy is unknown. It is classified as a Schedule III controlled substance; however, non-medical uses of sodium oxybate are classified under Schedule I.

The wakefulness promoting agents that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. In terms of duration of action, modafinil and armodafinil are both long-acting agents while sodium oxybate is a short-acting agent.[5-7] Modafinil is currently the only wakefulness promoting agent that is available generically. The agents in this class were last reviewed in May 2014.

Table 1. Wakefulness Promoting Agents Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Armodafinil	tablet	Nuvigil®	none
Modafinil	tablet	Provigil®*	Provigil®*†
Sodium oxybate	oral solution	Xyrem®	none

*Generic is available in at least one dosage form or strength.
†Generic product requires prior authorization.
PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the wakefulness promoting agents are summarized in Table 2.

Table 2. Treatment Guidelines Using the Wakefulness Promoting Agents

Clinical Guideline	Recommendation(s)
American Academy of Sleep Medicine: **Practice Parameters for the**	• Most of the agents used to treat excessive sleepiness have little effect on cataplexy or other rapid eye movement sleep associated symptoms. Most antidepressants and anticataplectics have little effect on alertness. However, some compounds act on both symptoms. Compounds should be selected depending on the diagnosis and the

Clinical Guideline	Recommendation(s)
Treatment of Narcolepsy and Other Hypersomnias of Central Origin (2007)[1]	targeted symptoms. Coadministration of two or more classes of compounds may be needed in some patients to adequately address their symptoms. • Modafinil is effective for treatment of daytime sleepiness due to narcolepsy. • Sodium oxybate is effective for treatment of cataplexy, daytime sleepiness, and disrupted sleep due to narcolepsy. Sodium oxybate may be effective for treatment of hypnagogic hallucinations and sleep paralysis. • Amphetamine, methamphetamine, dextroamphetamine, and methylphenidate are effective for treatment of daytime sleepiness due to narcolepsy. • Selegiline may be an effective treatment for cataplexy and daytime sleepiness. • Tricyclic antidepressants, selective serotonin reuptake inhibitors, and venlafaxine may be effective treatment for cataplexy. • Scheduled naps can be beneficial to combat sleepiness, but seldom suffice as primary therapy for narcolepsy.
European Federation of Neurological Sciences: **Guidelines on Management of Narcolepsy in Adults (2011)[8]**	<u>Excessive daytime sleepiness and irresistible episodes of sleep</u> • Modafinil should be prescribed when excessive daytime sleepiness is present. Modafinil should be dosed as 100 to 400 mg/day, given once in the morning or twice daily. • Sodium oxybate may be used when excessive daytime somnolence coexists with cataplexy and poor sleep. Depressed patients should not receive sodium oxybate. • Sodium oxybate should be initiated with 4.5 g/night, increasing by increments of 1.5 g at four-week intervals and should not be used with other sedatives, respiratory depressants or muscle relaxants. Monitor patients for possible development of sleep-disordered breathing. Adverse effects may limit the dose, and require slower titration. • The optimal response on excessive daytime sleepiness may take up to 12 weeks. • Supplementation with modafinil is generally more successful than sodium oxybate alone. • Methylphenidate may be considered if modafinil is insufficient and sodium oxybate is not recommended. • The short-acting effect of methylphenidate is of interest when modafinil needs to be supplemented at a specific time of the day, or in situations where maximum alertness is required. <u>Cataplexy</u> • First-line pharmacological treatment of cataplexy is sodium oxybate at a starting dose of 4.5 g/night divided into two equal doses of 2.25 g/night. The dose may be increased to a maximum of 9 g/night, divided into two equal doses of 4.5 g/night, by increments of 1.5 g at two-week intervals. • Adverse effects may limit the dose, and require slower titration and the optimal response on excessive daytime sleepiness may take up to 12 weeks. • Antidepressants are recommended as second-line pharmacological treatment. Tricyclic antidepressants, particularly clomipramine (10 to 75 mg), are potent anticataplectic drugs; however, anticholinergic adverse effects are common. • Selective serotonin reuptake inhibitors are slightly less active but have fewer adverse effects. • Venlafaxine is widely used but clinical evidence supporting its use is limited. • Reboxetine and atomoxetine, also lack published clinical evidence. • Given the efficacy of sodium oxybate and antidepressants, the place for other compounds is fairly limited. • There is no accepted behavioral treatment of cataplexy. <u>Poor sleep</u> • Sodium oxybate appears to be the most appropriate to treat poor sleep. • Benzodiazepine or non-benzodiazepine hypnotics may be effective in consolidating nocturnal sleep, but objective evidence is lacking over intermediate- or long-term

Clinical Guideline	Recommendation(s)
	follow-up. • The improvement in poor sleep reported by some patients once established on modafinil is noteworthy. <u>Obstructive sleep apnea/hypopnea syndrome, periodic limb movements in sleep, neuropsychiatric symptoms</u> • Obstructive sleep apnea/hypopnea syndrome should be similarly in narcoleptic patients and general population, although continuous positive airway pressure does not improve excessive daytime sleepiness in most narcolepsy subjects. • There is usually no need to treat periodic limb movements in narcoleptic patients. Antidepressants and psychotherapy should be used in depressed narcoleptic patients as in non-narcoleptic depressed patients.
American Academy of Sleep Medicine: **Clinical Guideline for the Evaluation, Management and Long-term Care of Obstructive Sleep Apnea in Adults (2009)**[3]	<u>Weight reduction</u> • Successful dietary weight loss may improve the apnea-hypopnea index in obese obstructive sleep apnea patients. • Dietary weight loss should be combined with a primary treatment for obstructive sleep apnea. • Bariatric surgery may be adjunctive in the treatment of obstructive sleep apnea in obese patients. <u>Pharmacologic agents</u> • Modafinil is recommended for the treatment of residual excessive daytime sleepiness in obstructive sleep apnea patients who have sleepiness despite effective positive airway pressure treatment and who are lacking any other identifiable cause for their sleepiness. • Selective serotonin reuptake inhibitors, protriptyline, methylxanthine derivatives (aminophylline and theophylline), and estrogen therapy are not recommended for treatment of obstructive sleep apnea. <u>Supplemental oxygen</u> • Oxygen supplementation is not recommended as a primary treatment for obstructive sleep apnea. <u>Medical therapies intended to improve nasal patency</u> • Short-acting nasal decongestants are not recommended for treatment of obstructive sleep apnea. • Topical nasal corticosteroids may improve the apnea-hypopnea index in patients with obstructive sleep apnea and concurrent rhinitis, and thus may be a useful adjunct to primary therapies for obstructive sleep apnea. <u>Positional therapies</u> • Positional therapy is an effective secondary therapy or can be a supplement to primary therapies for obstructive sleep apnea in patients who have a low apnea-hypopnea index in the non-supine vs that in the supine position. vs
American Academy of Sleep Medicine: **Practice Parameters for the Clinical Evaluation and Treatment of Circadian Rhythm Sleep Disorders (2007)**[4]	<u>Shift work disorder</u> • Planned napping before or during the night shift is indicated to improve alertness and performance among night shift workers. • Timed light exposure in the work environment and light restriction in the morning, when feasible, is indicated to decrease sleepiness and improve alertness during night shift work. • Administration of melatonin prior to daytime sleep is indicated to promote daytime sleep among night shift workers. • Hypnotic medications may be used to promote daytime sleep among night shift workers. Carryover of sedation to the nighttime shift with potential adverse consequences for nighttime performance and safety must be considered.

Clinical Guideline	Recommendation(s)
	• Modafinil is indicated to enhance alertness during the night shift for shift work disorder. • Caffeine is indicated to enhance alertness during the night shift for shift work disorder.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the wakefulness promoting agents are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Wakefulness Promoting Agents[5-7,9-10]

Generic Name(s)	Improve Wakefulness in Adult Patients with Excessive Sleepiness Associated with Narcolepsy	Improve Wakefulness in Adult Patients with Excessive Sleepiness Associated with Obstructive Sleep Apnea	Improve Wakefulness in Adult Patients with Excessive Sleepiness Associated with Shift Work Disorder	Cataplexy in Narcolepsy	Excessive Daytime Sleepiness in Narcolepsy
Armodafinil	✔	✔	✔		
Modafinil	✔	✔	✔		
Sodium oxybate				✔	✔

IV. Pharmacokinetics

The pharmacokinetic parameters of the wakefulness promoting agents are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Wakefulness Promoting Agents[10]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Armodafinil	Rapid	60	Liver (not reported)	Renal (not reported)	15
Modafinil	Rapid	60	Liver (90)	Renal (80) Feces (1)	15
Sodium oxybate	88	<1	Liver (not reported)	Renal (1 to 5)	<1

V. Drug Interactions

Major drug interactions with the wakefulness promoting agents are listed in Table 5.

Table 5. Major Drug Interactions with the Wakefulness Promoting Agents[10]

Generic Name(s)	Interaction	Mechanism
Modafinil	Tolvaptan	Concurrent use of modafinil and tolvaptan may result in decreased tolvaptan plasma concentrations.
Modafinil	Enzalutamide	Concurrent use of enzalutamide and modafinil may result in decreased enzalutamide plasma concentrations; decreased modafinil plasma concentrations.

Generic Name(s)	Interaction	Mechanism
Modafinil	Citalopram	Concurrent use of citalopram and modafinil may result in increased citalopram exposure and risk of QT interval prolongation.
Modafinil	Axitinib	Concurrent use of axitinib and modafinil may result in reduced axitinib exposure.
Modafinil	Ifosfamide	Concurrent use of ifosfamide and modafinil may result in increased neurotoxic and nephrotoxic effects.
Sodium oxybate	Barbiturates	Concurrent use of sodium oxybate and barbiturates may result in an increase in sleep duration and central nervous system depression.
Sodium oxybate	Benzodiazepines	Concurrent use of sodium oxybate and benzodiazepines may result in an increase in sleep duration and central nervous system depression.
Sodium oxybate	Central nervous system depressants	Concurrent use of sodium oxybate and central nervous system depressants may result in an increase in sleep duration and central nervous system depression.
Sodium oxybate	Opioid analgesics	Concurrent use of sodium oxybate and opioid analgesics may result in additive respiratory depression.
Sodium oxybate	Sedative hypnotics	Concurrent use of sodium oxybate and sedative hypnotics may result in increased central nervous system depression.
Sodium oxybate	Selected antiepileptics (topiramate, perampanel, difenoxin)	Concurrent use of sodium oxybate and selected antiepileptics may result in increased central nervous system depression.
Sodium oxybate	Selected antipsychotics (loxapine, thioridazine, chlorpromazine)	Concurrent use of sodium oxybate and selected antipsychotics may result in increased central nervous system depression.
Sodium oxybate	Skeletal muscle relaxants	Concurrent use of sodium oxybate and skeletal muscle relaxants may result in increased central nervous system depression.
Sodium oxybate	Buspirone	Concurrent use of sodium oxybate and buspirone may result in an increase in sleep duration and central nervous system depression.

VI. Adverse Drug Events

The most common adverse drug events reported with the wakefulness promoting agents are listed in Table 6. The boxed warning for sodium oxybate is listed in Table 7. Sodium oxybate is a known drug of abuse and has been associated with central nervous system-related adverse reactions, including confusion, respiratory depression, profound decreases in consciousness, and death. As such, sodium oxybate is classified as a Schedule III controlled substance by federal regulation and is available through a centralized pharmacy. Modafinil and armodafinil may produce psychoactive and euphoric effects similar to stimulants and are therefore classified as Schedule IV controlled substances by federal regulation.

Table 6. Adverse Drug Events (%) Reported with the Wakefulness Promoting Agents [5-7,9]

Adverse Events	Armodafinil	Modafinil	Sodium Oxybate
Cardiovascular			
Angina	-	-	-
Cardiac arrhythmia	-	-	-
Chest pain	-	3	-
Hypertension	-	3	✔
Hypotension	-	-	-
Myocardial infarction	-	-	-
Palpitations	2	2	-

Adverse Events	Armodafinil	Modafinil	Sodium Oxybate
Pulse increase/decrease	1	-	-
Raynaud's phenomenon	-	-	-
Sudden death	-	-	-
Systolic blood pressure increased	✔	-	-
Tachycardia	-	2	-
Vasodilation	-	2	-
Central Nervous System			
Abnormal dreams	-	-	-
Aggressive behavior	-	-	-
Agitation	1	1	-
Anxiety	4	5 to 21	1 to 2
Ataxia	-	-	-
Attention disturbance	1	-	0 to 4
Cerebral arteritis	-	-	-
Cerebral occlusion	-	-	-
Chills	-	-	-
Confusion	-	-	-
Depression	1 to 3	2	-
Disorientation	-	-	1 to 3
Dizziness	3 to 8	5	9 to 15
Drowsiness	-	-	-
Dyskinesia	-	1	-
Emotional instability	-	-	-
Fatigue/lethargy	2	-	-
Fever	1	-	-
Hallucinations	-	-	-
Headache	14 to 23	34	✔
Hyperkinesia	-	1	-
Hypertonia	-	1	-
Insomnia	4 to 6	3 to 21	-
Irritability	-	-	0 to 3
Jittery feeling	-	-	-
Labile affect	-	-	-
Mania	-	✔	-
Migraine	1	-	-
Nervousness	1	7	-
Neuroleptic malignant syndrome	-	-	-
Nightmare	-	-	-
Overstimulation	-	1	-
Paresthesia	1	2	1 to 3
Psychotic episodes	-	✔	-
Restlessness	-	-	-
Seizures	-	-	-
Sleep disorder	-	-	-
Sleep paralysis	-	-	1 to 3
Sleep walking	-	-	0 to 3
Somnolence	-	2	1 to 8
Suicidal ideation	-	-	-
Syncope	-	-	-
Tic	-	-	-
Tourette's exacerbation	-	-	-
Toxic psychosis	-	-	-
Tremor	1	1	0 to 5
Vertigo	-	1	-

Adverse Events	Armodafinil	Modafinil	Sodium Oxybate
Dermatological			
Alopecia	-	-	-
Application site reaction	-	-	-
Dermatitis	1	-	-
Diaphoresis	-	1	-
Erythema	-	-	-
Erythema multiforme	-	✔	-
Exfoliative dermatitis	-	-	-
Hair loss	-	-	-
Herpes simplex	-	1	-
Hyperhidrosis	1	-	1 to 3
Rash	1 to 4	<1	-
Stevens-Johnson syndrome	✔	✔	-
Toxic epidermal necrolysis	-	-	-
Urticaria	-	-	-
Gastrointestinal			
Abdominal pain	2	-	1 to 3
Anorexia	1	4	-
Appetite decreased	1	-	✔
Bruxism	-	-	-
Constipation	1	2	-
Diarrhea	3 to 5	6	3 to 4
Dry mouth	2 to 7	4	1 to 2
Dyspepsia	2	5	-
Flatulence	-	1	-
Mouth ulceration	-	1	-
Nausea	7 to 14	11	8 to 20
Stomach cramps	-	-	-
Thirst	-	1	-
Unpleasant taste	-	1	-
Vomiting	1	-	2 to 11
Weight increase	-	-	-
Weight loss	-	-	✔
Genitourinary			
Abnormal urine	-	1	-
Enuresis	-	-	3 to 7
Erectile disturbance	-	-	-
Hematuria	-	1	-
Libido decreased	-	-	-
Polyuria	1	-	-
Pyuria	-	1	-
Urinary incontinence	-	-	-
Hematologic			
Agranulocytosis	-	✔	-
Anemia	-	-	-
Eosinophilia	-	1	-
Leukopenia	-	-	-
Pancytopenia	✔	-	-
Thrombocytopenic purpura	-	-	-
Hepatic			
Hepatic coma	-	-	-
Liver function test abnormalities	✔	2	-
Musculoskeletal			
Arthralgia	-	-	✔

Adverse Events	Armodafinil	Modafinil	Sodium Oxybate
Back pain	-	6	-
Cataplexy	-	-	1 to 2
Hypoesthesia	-	-	-
Muscle spasms	-	-	<1 to 2
Pain in extremity	-	-	1 to 3
Weakness	-	-	-
Respiratory			
Bronchitis	-	-	-
Cough	-	-	-
Dyspnea	1	-	-
Epistaxis	-	1	-
Lung disorder	-	2	-
Nasal congestion	-	-	-
Pharyngitis	-	4	-
Pharyngolaryngeal pain	-	-	-
Rhinitis	-	7	-
Sinusitis	-	-	-
Special Senses			
Abnormal vision	-	1	-
Accommodation difficulties	-	1	-
Amblyopia	-	1	-
Blurred vision	-	1	✔
Dry eyes	-	-	-
Eye pain	-	1	-
Mydriasis	-	-	-
Tinnitus	-	-	-
Other			
Accidental injury	-	-	-
Anaphylaxis	✔	✔	-
Ear pain	-	-	-
Edema	-	1	0 to 3
Feeling drunk	-	-	0 to 3
Flu-like syndrome	1	4	-
Growth suppression	-	-	-
Hypersensitivity reactions	-	✔	-
Pain	1	-	<1 to 3
Thirst	1	-	-

✔ Percent not specified.
- Event not reported or incidence <1%.

Table 7. Boxed Warning for Sodium Oxybate[7]

WARNING
WARNING: CENTRAL NERVOUS SYSTEM DEPRESSION and MISUSE AND ABUSE Xyrem® (sodium oxybate) is a CNS depressant. In clinical trials at recommended doses obtundation and clinically significant respiratory depression occurred in Xyrem®-treated patients. Almost all of the patients who received Xyrem® during clinical trials in narcolepsy were receiving central nervous system stimulants. Xyrem® (sodium oxybate) is the sodium salt of gamma hydroxybutyrate (GHB). Abuse of GHB, either alone or in combination with other CNS depressants, is associated with CNS adverse reactions, including seizure, respiratory depression, decreases in the level of consciousness, coma, and death. Because of the risks of CNS depression, abuse, and misuse, Xyrem® is available only through a restricted

WARNING
distribution program called the Xyrem Success Program®, using a centralized pharmacy. Prescribers and patients must enroll in the program. For further information go to www.XYREM.com or call 1-866-XYREM88® (1-866-997-3688).

VII. Dosing and Administration

The usual dosing regimens for the wakefulness promoting agents are listed in Table 8.

Table 8. Usual Dosing Regimens for the Wakefulness Promoting Agents[5-7,9]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Armodafinil	Improve wakefulness in adult patients with excessive sleepiness associated with narcolepsy: Table: initial, 150 mg to 250 mg once daily in the morning Improve wakefulness in adult patients with excessive sleepiness associated with obstructive sleep apnea: Tablet: initial, 150 mg to 250 mg once daily in the morning Improve wakefulness in adult patients with excessive sleepiness associated with shift work disorder: Tablet: initial, 150 mg daily given one hour prior to start of work shift	Safety and efficacy in children have not been established.	Tablet: 50 mg 150 mg 200 mg 250 mg
Modafinil	Improve wakefulness in adult patients with excessive sleepiness associated with narcolepsy: Tablet: initial, 200 mg once daily in the morning Improve wakefulness in adult patients with excessive sleepiness associated with obstructive sleep apnea: Tablet: initial, 200 mg once daily in the morning Improve wakefulness in adult patients with excessive sleepiness associated with shift work disorder: Tablet: initial, 200 mg as a single dose one hour prior to start of work shift	Safety and efficacy in children have not been established.	Tablet: 100 mg 200 mg
Sodium oxybate	Cataplexy in narcolepsy and excessive daytime sleepiness in narcolepsy: Oral solution: initial, 4.5 g per night in two divided doses; first dose to be given at bedtime after the patient is in bed and second dose to be given 2.5 to four hours later; dose may be increased or adjusted in two-week intervals; maximum, 9 g per day	Safety and efficacy in children have not been established.	Oral solution: 500 mg/mL

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the wakefulness promoting agents are summarized in Table 9.

Table 9. Comparative Clinical Trials with the Wakefulness Promoting Agents

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Narcolepsy				
Harsh et al.[11] (2006) Armodafinil 150 to 250 mg once daily vs placebo	DB, MC, PC, RCT Patients 18 to 65 years of age diagnosed with narcolepsy	N=196 12 weeks	Primary: MWT 0900-1500 sleep latency, CGI-C Secondary: MWT 1500-1900 sleep latency, CGI-C, CDR, ESS, BFI	Primary: Mean MWT 0900–1500 sleep latency increased 1.3, 2.6, and 1.9 minutes from baseline in the 150 mg, 250 mg, and armodafinil combined groups, respectively, and decreased 1.9 minutes from baseline in the placebo group (P<0.01 for all comparisons). Secondary: Mean MWT 1500–1900 sleep latency increased 1.5, 1.6, and 1.6 minutes in the 150 mg, 250 mg, and armodafinil combined groups, respectively, and decreased 1.2 minutes from baseline in the placebo group. The differences for the armodafinil combined group vs placebo and the 150 mg group vs the placebo group were significant (P<0.05 for both comparisons). The proportion of patients with at least minimal improvement in their CGI-C rating was significantly higher for the armodafinil 150 mg, 250 mg, and combined groups compared to the placebo group (P<0.0001 for all comparisons). The proportion of patients rated as minimally, much, and very much improved on the CGI-C from baseline to final visit was 21, 33, and 16%, respectively, for armodafinil 150 mg; 20, 35, and 18%, respectively, for armodafinil 250 mg; 20, 34, and 17%, respectively, for the armodafinil combined group; and 17, 12, and 3%, respectively, for placebo. Power of attention was significantly improved in the armodafinil 150 mg/day and armodafinil combined groups compared to placebo at the final visit (P<0.05). There were not significant effects on mean continuity of attention between the treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Armodafinil demonstrated significantly greater improvements in quality of episodic secondary memory compared to placebo at the final visit (P<0.05). Armodafinil 250 mg and the combined group demonstrated significantly greater improvement in speed of memory compared to placebo at the final visit (P<0.05). Differences in the change from baseline on the ESS were statistically significant in favor of each armodafinil group compared to placebo at weeks eight (P<0.01 for all comparisons) and 12 (P<0.01) and at the final visit (150 mg/day, -4.1; P=0.0044, 250 mg/day, -3.8; P=0.0015, and combined group, -3.9; P=0.0006). At the final visit, 21% of patients in the armodafinil 150 mg/day group (P=0.0312) and 28% of patients in the armodafinil 250 mg/day group (P=0.0023) had an ESS score <10, compared to only 7% of patients in the placebo group. Improvements in global fatigue were significantly greater with armodafinil compared to placebo at the final visit (150 mg/day, -1.5; P=0.0007; 250 mg/day, -1.3; P=0.0018; combined group, -1.4; P=0.0002; placebo, -0.3). Headache, nausea, dizziness, and decreased appetite were the most commonly reported adverse events with armodafinil.
U.S. Modafinil in Narcolepsy Group[12] (1998) Modafinil 200 to 400 mg daily vs	DB, MC, PC, RCT Adults 18 to 68 years of age diagnosed with narcolepsy	N=283 9 weeks	Primary: ESS Secondary: MSLT, MWT, CGI-C	Primary: Both modafinil treatment groups reduced mean ESS scores and subjective sleepiness at each time point (weeks three, six, and nine) compared to the placebo group (P<0.001). The two modafinil groups did not differ from each other. Secondary: Mean sleep latency for MSLT significantly increased in both modafinil groups compared to the placebo group (P<0.001). Modafinil groups did not differ from each other.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				Mean sleep latencies for MWT significantly increased in each of the modafinil groups compared to the placebo group (P<0.001). The two modafinil groups did not differ from each other. There were significantly more patients with improved CGI-C scores in each of the modafinil groups compared to the placebo group (P<0.005), but the number of patients did not differ between modafinil groups.
U.S. Modafinil in Narcolepsy Group[13] (2000) Modafinil 200 to 400 mg daily vs placebo	DB, MC, PC, RCT Adults 17 to 67 years of age diagnosed with narcolepsy	N=271 9 weeks	Primary: MWT, CGI-C Secondary: MSLT, ESS	Primary: MWT improved for both modafinil groups vs the placebo group (P<0.001) at each follow-up visit (weeks three, six, nine). The percent of patients with improvement in CGI-C scores at week nine were as follows: modafinil 200 mg, 58%; modafinil 400 mg, 61%; and placebo, 38% (P<0.03). Secondary: MSLT increased by 5.1 minutes with modafinil 400 mg vs 3.5 minutes with placebo (P<0.001). The impact of the 200 mg modafinil dose was not significant. Mean ESS scores were reduced by both treatment groups (P<0.001) vs the placebo group.
Broughton et al.[14] (1997) Modafinil 200 to 400 mg daily vs placebo	MC, PC, RCT, XO Patients 27 to 59 years of age diagnosed with narcolepsy	N=75 6 weeks	Primary: MWT results, patient assessed sleepiness Secondary: ESS	Primary: MWT (sleep latency) increased by 40% with modafinil 200 mg (P<0.002) and by 54% with modafinil 400 mg (P<0.001) compared to placebo. There was not a significant difference between modafinil groups. Both modafinil groups significantly decreased the patient assessed mean number of involuntary sleep and somnolence episodes by 24% in the 200 mg group and 26% in the 400 mg group as compared to the placebo group (P<0.013 and P<0.007). Secondary: ESS was significantly decreased in modafinil 200 mg (P<0.018) and modafinil 400 mg (P<0.0009) groups compared to the placebo group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Billiard et al.[15] (1994) Modafinil 100 mg in the morning and 200 mg at noon (or vice versa) vs placebo	DB, MC, PC, RCT, XO Patients 27 to 54 years of age diagnosed with narcolepsy	N=50 12 weeks	Primary: Results of sleep logs, CGI Secondary: MWT	Primary: In the patient sleep logs, the number of episodes of sleepiness and duration of daytime total sleep time were significantly reduced in the modafinil groups compared to the placebo group (P=0.05, P=0.0002). The CGI scores were not statistically significantly different between the modafinil group and the placebo group (P=0.19). Secondary: MWT scores were significantly improved in the modafinil group compared to the placebo group (P<0.05).
Boivin et al.[16] (1993) Modafinil 200 mg in morning and 100 mg at noon vs placebo	DB, PC, RCT, XO Patients 31 to 61 years of age with a history of EDS, cataplexy, at least two sleep onset REM periods and MSLT less than five minutes	N=10 12 weeks	Primary: Subjectively assessed sleepiness, FCRTT, PLM, nocturnal sleep organization Secondary: Not reported	Primary: Subjective sleepiness was significantly reduced in the modafinil group compared to the placebo group (P<0.05) based on home questionnaires. Modafinil significantly reduced the number of gaps and % of error at the FCRTT (P<0.05), but did not significantly reduce the mean reaction time over placebo (P=0.08). Modafinil did not statistically significantly decrease PLMs over placebo (P=0.06). Modafinil did not display negative effects on any of the nocturnal sleep parameters measured (P value not significant). Secondary: Not reported
Thorpy et al.[17] (2003) Modafinil 200 to 400 mg/day	OL, RCT Adults 17 to 65 years of age diagnosed with narcolepsy who had been receiving MPH for EDS for a	N=40 5 weeks	Primary: ESS, tolerability Secondary: Not reported	Primary: Mean ESS scores were <12 for all groups at the end of the study: 11.3 in the no-washout group, 8.2 for in the washout group, and 10.1 in the taper-down/titrate-up group. Headache was the most frequently reported adverse event during therapy, experienced by 42% of patients in the no-washout group, 36% of patients in the washout group, and 21% of patients in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	month			taper/titrate group. Secondary: Not reported
U.S. Xyrem Multicenter Study Group[18] (2004) <u>Phase One (Two weeks)</u> Continue sodium oxybate at the dose previously prescribed. <u>Phase Two (Two weeks)</u> Continue sodium oxybate treatment at previously prescribed dose vs conversion to placebo	DB treatment withdrawal study design (alternative to conventional DB, PC, RCT) Patients ≥16 years of age with narcolepsy or symptoms of narcolepsy who were previously stabilized on sodium oxybate 3 to 9 g/day	N=55 4 weeks	Primary: Cataplexy attacks, treatment-emergent adverse events Secondary: Not reported	Primary: During the two-week DB phase, the abrupt cessation of sodium oxybate therapy in the placebo study patients resulted in a significant increase in the number of cataplexy attacks (median, 21; P<0.001) compared to patients who remained on sodium oxybate (median, 0). Cataplexy attacks returned gradually with placebo study patients reporting a median of 4.2 and 11.7 cataplexy attacks during the first and second weeks, respectively. There were no symptoms of withdrawal reported by the study investigators. Secondary: Not reported
Xyrem International Study Group[19] (2005) Sodium oxybate 4.5 to 9 g/day administered at bedtime	DB, MC, PC, RCT Patients ≥16 years of age with narcolepsy or symptoms of narcolepsy	N=228 8 weeks	Primary: ESS, MWT, CGI-C Secondary: Not reported	Primary: Study patients displayed dose related decreases in median ESS scores and frequency of weekly inadvertent naps, which were significant at the 6 and 9 g doses (P<0.001 for each). Study patients treated with 9 g of sodium oxybate nightly displayed a significant median increase of >10 minutes in the MWT (P<0.001). Improvements in EDS were incremental in those study patients who

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				received concomitant stimulants alone. Significant improvements in the CGI-C were observed for each group treated with sodium oxybate (P≤0.001). The most common adverse events were mild to moderate and included nausea, dizziness, and enuresis, which seemed to be dose related. Other adverse events less common included feeling drunk, contusion, back pain, muscle cramp, somnolence, disturbance in attention, dysarthria, tremor, disorientation, sleepwalking, dyspnea, and snoring. Secondary: Not reported
Xyrem International Study Group[20] (2005) Sodium oxybate 4.5 to 9 g/day administered at bedtime vs placebo	DB, MC, PC, RCT Patients ≥16 years of age with narcolepsy or symptoms of narcolepsy	N=228 8 weeks	Primary: Narcolepsy symptoms, medication use, adverse events Secondary: Not reported	Primary: Compared to placebo, nightly doses of 4.5, 6, and 9 g of sodium oxybate for eight weeks resulted in significant decreases in weekly cataplexy attacks of 57.0 (P=0.003), 65.0 (P=0.002), and 84.7% (P<0.001), respectively. The decrease in cataplexy at the 4.5 g dose was significant compared to placebo at eight weeks of treatment (P=0.003). The reduction in the number of weekly cataplexy attacks was dependent on the length of time study patients received treatment and the amount of medication received. The weekly increase in sodium oxybate dose was associated with fewer adverse events than previously reported in double-blind sodium oxybate studies using fixed doses. The most common adverse events included nausea and dizziness, which demonstrated a clear dose–response relationship. Although greater than 5% of study patients reported emesis, this adverse event was not significantly different than placebo-treated patients. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Black et al.[21] (2010) Sodium oxybate 4.5 to 9 g/day administered at bedtime vs placebo	DB, PC, PG, RCT Patients ≥16 years of age with narcolepsy or symptoms of narcolepsy	N=228 8 weeks	Primary: Sleep architecture, narcolepsy symptoms and adverse events Secondary: Not reported	Primary: Following four (P<0.001) and eight weeks (P<0.001) of sodium oxybate treatment, study patients demonstrated significant dose-related increases in the duration of stage three and four sleep, reaching a median increase of 52.5 minutes in patients receiving 9 g nightly. Compared to placebo-treated patients, delta power was significantly increased in all treatment dose groups. Stage one sleep and the frequency of nocturnal awakenings were each significantly decreased at the 6 and 9 g/night doses. The changes in nocturnal sleep coincided with significant decreases in the severity and frequency of narcolepsy symptoms. The most common adverse events included nausea, headache, dizziness, nasopharyngitis, and enuresis with a statistical significant difference in nausea and dizziness compared to placebo. Adverse events were mild to moderate in severity and appeared to be dose-related as documented by study investigators. Secondary: Not reported
Weaver et al.[22] (2006) Sodium oxybate 4.5 to 9 g/day in two divided doses taken at bedtime and again 2.5 to 4 hours later vs placebo	DB, MC, RCT Patients 16 to 75 years of age with narcolepsy who were experiencing cataplexy and EDS with recurrent episodes for ≥3 months	N=285 4 weeks	Primary: FOSQ Secondary: Not reported	Primary: The nightly administration of sodium oxybate showed statistically significant dose-related improvements in functional status and quality of life as evidenced by the total FOSQ (P<0.001), as well as in the activity level (P<0.001), vigilance (P<0.001), general productivity (P=0.002), and social outcomes (P<0.001) subscales. Effect sizes escalated from small effects for the 6 g per day dose of sodium oxybate to large effects for the 9 g/day dose. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Wang et al.[23] (2009) Sodium oxybate	RETRO Patients receiving sodium oxybate	N=~26,000 68 months	Primary: Occurrence of abuse/misuse of sodium oxybate Secondary: Not reported	Primary: During the study period, 3,781 adverse event reports were reported to the manufacturer worldwide. Overall, there were no new significant safety findings from the postmarketing adverse event profile compared to what was reported in clinical trials described in the product prescribing information. Of those 26,000 patients, 0.2% reported ≥1 of the events studied. These included 10 cases (0.039%) meeting DSM-IV abuse criteria, four cases (0.016%) meeting DSM-IV dependence criteria, eight cases (0.031%, including three of the previous four) with withdrawal symptoms reported after discontinuation of sodium oxybate, two confirmed cases (0.008%) of sodium oxybate–facilitated sexual assault, eight cases (0.031%) of overdose with suicidal intent, 21 deaths (0.08%) in patients receiving sodium oxybate treatment with one death known to be related to sodium oxybate, and three cases (0.01%) of traffic accidents involving drivers taking sodium oxybate. During the study period, approximately 600,000 bottles of sodium oxybate were distributed, and five incidents (0.0009%) of diversion were reported. Secondary: Not reported
Mamelak et al.[24] (2015) Sodium oxybate 3 to 9 g/night (titrated to clinical effect)	MC, OL Patients ≥16 years of age with a history of narcolepsy with cataplexy who were sodium oxybate-naïve or had participated in one of three randomized clinical trials of sodium oxybate and had not been titrated	N=202 12 weeks	Primary: Adverse events Secondary: NSAQ	Primary: In total, 56% of patients reported adverse events. Nine patients discontinued due to a variety of adverse events that included psychosis, migraine headache, dizziness, nausea, anxiety, fatigue, insomnia, abdominal pain, shortness of breath, and depression. Five patients had serious adverse events, and two of these were serious adverse events were considered treatment related: headache in a patient taking 7.5 g/night who continued with study participation, and psychosis in a patient taking 9 g/night who discontinued treatment. The most common adverse events were nausea (10%), headache (7%), and dizziness (5%). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	to adequate clinical effect			Based on the response criterion of "much improved" or "somewhat improved" relative to baseline for overall symptoms on the NSAQ, 92% of all patients were rated as treatment responders at week six, and 90% were responders at week 12. The response rate among patients across treatment doses was similar at the two time points. At week six, 54% of all patients reported being "much improved," and 60% at week 12.
Black et al.[25] (2006) Sodium oxybate 6 to 9 g/day vs modafinil 200 to 600 mg/day vs sodium oxybate 6 to 9 g/day and modafinil 200 to 600 mg/day vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with narcolepsy taking 200 to 600 mg of modafinil daily for the treatment of EDS	N=270 8 weeks	Primary: MWT Secondary: ESS, CGI-C	Primary: Following the switch from modafinil to placebo, the mean average daytime sleep latency on the MWT decreased from 9.74 minutes at baseline to 6.87 minutes after eight weeks (P<0.001). In the sodium oxybate group, there was no decrease in sleep latency, suggesting that this medication was as efficacious in treating EDS as previously administered modafinil. In the sodium oxybate plus modafinil group, there was an increase in daytime sleep latency from 10.43 to 13.15 minutes (P<0.001), suggesting that this combination of drugs produced an additive effect. Secondary: The sodium oxybate group showed a decrease in median average EES scores, from 15 to 12 (P<0.001). The sodium oxybate plus modafinil group showed a decreased in median average EES scores from 15 to 11 (P<0.001). Treatment with sodium oxybate, alone (P=0.002) and together with modafinil (P=0.023), showed significant overall clinical improvements as compared to the placebo-treated study patients. The placebo and the modafinil-treated study patients demonstrated no significant change in symptoms.
Black et al.[26] (2009) Sodium oxybate	DB, PC, RCT Patients ≥18 years of age with	N=278 8 weeks	Primary: Sleep architecture, MWT	Primary: Following eight weeks of treatment, there was no significant change in total sleep time for any group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
6 g/day vs modafinil 200 to 600 mg/day vs sodium oxybate 6 g/day and modafinil 200 to 600 mg/day vs placebo	narcolepsy taking modafinil 200 to 600 mg/day for the treatment of EDS		Secondary: Not reported	Significant changes in total non-REM sleep among patients receiving sodium oxybate and sodium oxybate plus modafinil included a median increase in Stage three and four sleep (43.5 and 24.25 minutes, respectively; P<0.001 for each) and delta power (P<0.001 for each) and significant decrease in the number of nocturnal awakenings in sodium oxybate (P=0.008) and sodium plus modafinil (P=0.014) treated study patients. No significant changes in PSG parameters were noted in patients treated with placebo or modafinil alone. Patients who had been randomized to placebo demonstrated a significant decrease in MWT sleep latency at eight weeks (P<0.001) once they had been switched to placebo following stable chronic modafinil treatment. A slight worsening of EDS indicated by increased ESS scores, was noted in placebo-treated patients (P=0.011) after stopping baseline modafinil, and ESS scores continued unchanged in the group that was randomized to continue modafinil treatment. Sodium oxybate-treated patients and sodium oxybate plus modafinil-treated patients experienced significant improvements in ESS scores (P<0.001 for each). There was no change in ESS scores in the group maintained on modafinil alone. Secondary: Not reported
Obstructive Sleep Apnea				
Hirshkowitz et al.[27] (2007) Armodafinil 150 mg/day vs	DB, MC, PC, RCT Patients 18 to 65 years of age with a diagnosis of OSA/hypopnea syndrome who complained of	N=263 12 weeks	Primary: MWT, CGI-C Secondary: CDR, ESS, BFI	Primary: Armodafinil significantly improved wakefulness compared to placebo. The mean MWT sleep latency increased from baseline by 2.3 minutes in the armodafinil group and decreased by 1.3 minutes in the placebo group (P=0.0003). Armodafinil significantly improved MWT sleep latency compared to placebo at each visit (P<0.01 for all).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo	residual excessive sleepiness during CPAP therapy			The proportion of patients with at least ‘‘minimal improvement’’ on the CGI-C scale was greater for armodafinil than placebo (71 vs 53%; P=0.0069). Secondary: As assessed on the CDR, armodafinil significantly improved the quality of episodic secondary memory compared to placebo. The quality of episodic secondary memory increased by 7.6 points from baseline to the final visit for patients in the armodafinil group and decreased by 7.0 points for those in the placebo group (P=0.0102). The mean change from baseline in ESS total score was significantly greater for patients receiving armodafinil than for those receiving placebo (P<0.01 for all). As assessed on the BFI, armodafinil significantly reduced global fatigue and worst fatigue in the past 24 hours at weeks four and 12 and at the final visit compared to placebo (P<0.05 for all).
Roth et al.[28] (2006) Armodafinil 150 to 250 mg/day vs placebo	DB, MC, PC, RCT Patients 18 to 65 years of age with a diagnosis of moderate OSA/ hypopnea syndrome and residual excessive sleepiness despite effective, regular, and stable use of CPAP treatment	N=395 12 weeks	Primary: MWT, CGI-C Secondary: ESS, CDR, BFI	Primary: The mean changes in MWT sleep latency across the first four tests were significantly greater in the armodafinil 150 mg/day, 250 mg/day, and combined groups compared to the placebo group at the final visit (P<0.001 for all). There was no difference between the two modafinil doses. The proportions of patients who had at least minimal improvement on the CGI-C were significantly greater in the armodafinil 150 mg/day, 250 mg/day, and combined groups compared to the placebo group (P<0.001 for all). There was no difference between the two modafinil doses. Secondary: The mean change in ESS total score was significantly greater in the armodafinil combined group compared to the placebo group at the final visit (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Mean changes in global fatigue scores were significantly greater in the armodafinil combined group compared to the placebo group at all visits (P<0.05 for all). The mean change in score for worst fatigue during the past 24 hours was statistically greater in the armodafinil combined group compared to placebo at week eight (P<0.05). Mean changes in quality of episodic secondary memory score were significantly greater with armodafinil 150 and 250 mg/day compared to placebo at week four (both, P<0.05) and with armodafinil 250 mg/day vs placebo at week eight (P<0.01). No significant differences in speed of memory or power of attention were found between the armodafinil combined and placebo groups across the first four or last three sessions at any assessment. At weekeight8, mean changes in continuity of attention across the first four sessions were significantly greater in the armodafinil 150 mg/day, 250 mg/day, and combined groups compared to the placebo group (P<0.05 for all). The most frequently reported adverse event was headache, occurring in 17.6% of patients in the armodafinil combined group and 8.5% of patients in the placebo group (P<0.05). The severity of adverse events was generally mild or moderate in patients receiving armodafinil (58.4%) or placebo (46.9%).
Krystal et al.[29] (2010) Armodafinil 200 mg/day vs placebo	DB, PC, PG, RCT Patients 18 to 65 years of age diagnosed with obstructive sleep apnea	N=249 18 months	Primary: CGI-C as related to sleepiness, mean change from baseline in MWT to mean sleep latency at final visit Secondary:	Primary: The proportion of patients with least minimal improvement on CGI-C was significantly greater in the armodafinil group compared to the placebo group (69 vs 53%; P=0.012). Mean MWT sleep latency was increased following armodafinil (2.6 minutes) compared to placebo (1.1 minutes), but was not statistically significant (P=0.30). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			ESS	Mean ESS scores were significantly reduced in study patients treated with armodafinil compared to patients treated with placebo (-6.3 vs -4.8; P=0.003). The most common adverse effects included headache, dry mouth and insomnia. Most adverse events were considered mild or moderate by the study investigator.
Black et al.[30] (2005) Modafinil 200 to 400 mg/day vs placebo	DB, MC, PC, RCT Adults 18 to 70 years of age with OSA/ hypopnea syndrome and having residual excessive sleepiness during CPAP therapy	N=305 12 weeks	Primary: MWT, ESS Secondary: CGI-C, FOSQ	Primary: Modafinil significantly improved mean sleep latency on the MWT compared to placebo (P<0.001). Modafinil significantly decreased the ESS scores compared to placebo (P<0.001). There were no significant differences in MWT or ESS scores seen between the two modafinil treatment groups (P>0.15 for each). Secondary: At the end of the study, modafinil had significant improvements in CGI-C compared to placebo (P<0.001). Modafinil improved mean FOSQ scores compared to placebo (P<0.02) for vigilance, general productivity, and activity level.
Weaver et al.[31] (2009) Modafinil 200 to 400 mg/day vs placebo	2 DB, MC, PC, RCT (Pooled analysis) Patients 24 to 76 years of age diagnosed with OSA and residual excessive sleepiness associated with CPAP	N=480 4 to 12 weeks	Primary: FOSQ Secondary: Not reported	Primary: After treatment with modafinil, there were greater improvements from baseline in the total FOSQ score (P<0.0001) as well as activity level (P=0.002), productivity level (P=0.007), intimacy and sexual relationships (P=0.01) and vigilance (P<0.001) compared to treatment with placebo. A greater proportion of patients who received modafinil were considered responders compared to patients who received placebo (45 vs 25%; P<0.001). Analysis based on the individual FOSQ questions demonstrated that 18 of the 30 questions increased at least one point for significantly more patients who received modafinil (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Williams et al.[32] (2010) Modafinil 200 mg/day vs placebo	DB, RCT, XO Men diagnosed with OSA who were modafinil-naïve	N=21 2 days	Primary: Driving simulation, subjective sleepiness Secondary: Not reported	Primary: During CPAP withdrawal, severe sleep-disordered breathing was evident and administration of modafinil improved simulated driving performance (steering variability; P<0.0001, mean reaction time; P<0.0002, lapses on a current task; P<0.01), psychomotor vigilance task (mean one/reaction time and lapses, both P<0.0002), and subjective sleepiness (P<0.01). Secondary: Not reported
Shift Work Sleep Disorder				
Czeisler et al.[33] (2009) Armodafinil 150 mg daily administered 30 to 60 minutes before the start of work shift vs placebo	DB, MC, PC, RCT Patients 18 to 65 years of age who exhibited signs and symptoms of SWD of moderate or greater severity, as documented by a CGI-S rating of four or higher for sleepiness on work nights, including the commute to and from work	N=254 12 weeks	Primary: MSLT, CGI-C Secondary: KSS, CDR	Primary: Armodafinil improved mean nighttime sleep latency (2 to 8 AM) by 3.1 to 5.3 minutes compared to an increase of 0.4 to 2.8 minutes at in patients receiving placebo at the final visit (P<0.001). Of the patients who received armodafinil, 79% were rated as improved in the CGI-C ratings compared to 59% of the patients who received placebo at the final visit (P=0.001). Secondary: Patient-reported levels of sleepiness during the night shift on the KSS were reduced with armodafinil compared to placebo at all visits. Armodafinil improved most items assessed in the electronic diaries, including the maximum level of sleepiness during the night shift and commute home, and mean number of mistakes, accidents, or near misses compared to placebo. Armodafinil significantly improved the mean score for the quality of episodic secondary memory factor compared to placebo at each visit (P<0.001 at weeks four and eight; P=0.002 at week 12; P<0.001 at final visit) and during the first four tests on the final night shift (P=0.002 at 12:30 AM; P<0.001 at 2:30 AM; P=0.02 at 4:30 AM;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				P=0.006 at 6:30 AM). Armodafinil significantly improved speed of memory from baseline compared to placebo at week eight (armodafinil, -240.9 milliseconds; placebo, -6.5 milliseconds; P=0.02) and week 12 (armodafinil, -307.7 milliseconds; placebo, -115.2 milliseconds; P=0.01). However, this was not significant at the final visit (armodafinil, -257.2 milliseconds; placebo. -140.4 milliseconds; P=0.09). Armodafinil significantly improved mean power of attention at each study visit (P=0.005 at week four; P=0.006 at week eight; P=0.005 at week 12; P=0.001 at final visit) and during the first four tests on the final night shift compared to placebo (P=0.002 at 12:30 AM; P=0.006 at 2:30 AM; P=0.004 at 4:30 AM; P=0.03 at 6:30 AM). Continuity of attention improved at the final visit in patients who received armodafinil compared to those who received placebo (P<0.001). Adverse events included headache, nausea, nasopharyngitis and anxiety. Most adverse events were considered mild or moderate by the investigator.
Tembe et al.[34] (2011) Armodafinil 150 mg administered one hour prior to night shift vs modafinil 200 mg administered one hour prior to night shift	DB, MC, RCT Patients 18 to 60 years of age suffering from excessive sleepiness associated with SWD	N=211 12 weeks	Primary: Proportion of patients showing ≥2 grades of improvement (responder) based on SSS in both groups Secondary: Improvement in mean SSS grades, compliance, patients' as well as physicians' global	Primary: Responder rates with armodafinil (72.12%) and modafinil (74.29%) were comparable (P=0.76). Secondary: Armodafinil and modafinil significantly improved mean sleepiness grades as compared to baseline (P<0.0001). At the end of therapy, compliance in both modafinil group (99.31%) and armodafinil group (99.13%) was found to be comparable (P=0.63). Both physicians' and patients' assessment of efficacy was comparable among the treatment groups. Adverse events were similar with modafinil (40.57%) and armodafinil

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			assessment for efficacy and safety	(42.87%; P=0.78). The most commonly treatment-emergent adverse events reported were mild to moderate in severity and included headache, nausea, and dry mouth.
Erman et al. (abstract)[35] (2012) Armodafinil 150 mg administered one hour prior to night shift vs placebo	DB, MC, PC, PG, RCT Patients 18 to 65 years of age suffering from excessive sleepiness associated with SWD	N=383 6 weeks	Primary: SDS-M and FOSQ-10 Secondary: Not reported	Primary: Patients treated with armodafinil experienced significantly greater improvements in SDS-M composite scores at final visit compared to patients treated with placebo (-6.8 vs -4.5, respectively; P=0.0027). Patients in the armodafinil treatment group demonstrated a greater improvement in total FOSQ-10 score from baseline to six weeks compared to placebo (3.6 vs 2.7; P=0.0351); however, there was no difference between treatments at the final visit (3.4 vs 2.7; P=0.0775). Secondary: Not reported
Erman et al.[36] (2011) Armodafinil 150 mg administered one hour prior to night shift vs placebo	DB, MC, PC, RCT Patients 18 to 65 years of age suffering from excessive sleepiness associated with SWD	N=383 6 weeks	Primary: CGI-C Secondary: GAF and KSS	Primary: Significantly more patients treated with armodafinil experienced an improvement in CGI-C compared to placebo at three weeks (78 vs 51%; P<0.0001) and at six weeks (80 vs 56%; P<0.0001). Similarly, more patients treated with armodafinil experienced an improvement in late-in-shift CGI-C at the final visit compared to placebo (77 vs 57%; P<0.0001). At the final visit, most patients in the armodafinil group were categorized as 'much improved' (33%) or 'very much improved' (24%) on the late-in-shift CGI-C rating scale. For patients treated with placebo, 38% had 'no change' in their condition compared to only 19% of patients in the armodafinil group. Secondary: The mean (±SD) improvement from baseline in GAF score at the final visit was significantly greater in the armodafinil group compared to the placebo group (9.4 vs 5.0; P<0.0001). Improvements in GAF scores were also significantly greater for armodafinil-treated patients at three weeks (6.9 vs 3.7; P<0.0001) and six weeks (9.8 vs 4.9; P<0.0001) compared to patients treated with placebo. A higher proportion of patients treated with armodafinil had GAF scores greater than 70

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				("normal function") at each visit, with almost twice as many patients receiving armodafinil reaching GAF scores greater than 70 at final visit compared to placebo (51 vs 28%; P value not reported). The improvements in KSS scores from baseline to the final visit were significantly greater for armodafinil-treated patients compared to patients receiving placebo (-2.8 vs -1.8; P<0.0001). The KSS scores were also significantly improved in the armodafinil group compared to the placebo group at three weeks (-2.6 vs -1.6; P<0.0001) and six weeks (-2.9 vs -1.8; P<0.0001).
Czeisler et al.[37] (2005) Modafinil 200 mg daily administered 30 to 60 minutes before the start of work shift vs placebo	DB, MC, PC, RCT Adults 18 to 60 years of age diagnosed with SWD and worked each month at least five night shifts for ≤12 hours, with ≥6 hours or worked between 10 PM and 8 AM and at least three shifts occurring consecutively	N=204 3 months	Primary: MSLT, CGI-C, Psychomotor Vigilance Test Secondary: Not reported	Primary: The modafinil group produced a significant increase in overall mean MSLT from 2.1 minutes at baseline to 3.8 minutes at endpoint compared to the placebo change of 2.04 to 2.37 minutes (P=0.002). The modafinil group significantly improved the CGI-C test scores with 74% of the patients rated as at least minimally improved compared to 36% in the placebo group (P<0.001). The modafinil group produced a significant decrease in mean number of lapses of attention during the Psychomotor Vigilance Test from baseline vs the placebo group (P=0.005). Secondary: Not reported
Miscellaneous				
Black et al.[38] (2010) Armodafinil 100 to 250 mg/day (OSA) or 100 to 250 mg/night 30 minutes to one hour before night shift but no later than 23:00 (SWD)	DB, MC, OL Men and women 18 to 65 years of age with a diagnosis of OSA, SWD, or narcolepsy	N=743 ≥12 months	Primary: Tolerability and efficacy (CGI-C, ESS, BFI) Secondary: Not reported	Primary: Discontinuations due to adverse events occurred in 13% of study patients during the initial study period. Most adverse events were mild to moderate in severity and included headache (25%), nasopharyngitis (17%), and insomnia (14%). Small increases were observed in BP (3.6/2.3 mm Hg), HR (6.7 beats per minute) across all study patient groups with most of the changes occurring by month three.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Greater improvement, compared to baseline, on the CGI-C was reported in the three study groups (75 to 92%) at the final visit with the SWD group reporting the greatest improvement. Study patients reported significant improvement at the final visit by 65% with treated OSA (95% CI, 60.2 to 68.9), 88% with SWD (95% CI, 81.3 to 93.9), and 62% with narcolepsy (95% CI, 54.2 to 69.8). Armodafinil improved wakefulness, measured by the ESS, in the treated OSA and narcolepsy groups, at all follow-up visits compared to baseline. The level of fatigue and its impact on daily activities was consistently reduced from baseline, at all visits, in each of the study groups, measured by BFI scores. Secondary: Not reported
Schwartz et al.[39] (2010) Armodafinil 100 to 250 mg/day (OSA and narcolepsy) or 100 to 250 mg/day 30 minutes to one hour before the start of night shift but no later than 23:00 (SWD)	MC, OL Patients 18 to 65 years of age who had a complaint of excessive sleepiness associated with OSA, SWD, or narcolepsy	N=328 12 months	Primary: CGI, ESS, adverse events Secondary: Not reported	Primary: At the final visit, 80% (95% CI, 74.1 to 86.7) of patients with OSA and 84% (95% CI, 72.7 to 94.8) of patients with narcolepsy were rated with the CGI-I scale as at least minimally improved with regard to overall clinical condition. Armodafinil improved EES scores in study patients treated with OSA (-7.3; 95% CI, -8.39 to -6.30) and narcolepsy (-4.7; 95% CI, -7.41 to -1.93). A total of 98% (95% CI, 95.2 to 100.0) of patients with SWD were rated as improved with regard to sleepiness during night shifts, including the commute to and from work. Across the diagnosis groups, the most commonly occurring adverse event was headache (14 to 24%). The adverse event was mild to moderate in severity as noted by the study investigators. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Jean-Pierre et al.[40] (2010) Modafinil 200 mg/day vs placebo	DB, MC, PC, RCT Patients ≥18 years of age diagnosed with cancer with a survival expectancy >6 months	N=877 4.5 years	Primary: BFI question 3, ESS, POMS-DD Secondary: Not reported	Primary: Patients with severe fatigue at baseline benefited from modafinil (P=0.033) whereas patients with mild (P=0.09) to moderate (P=0.41) fatigue did not benefit from modafinil as compared to placebo. Daytime sleepiness improved significantly in the modafinil group (P=0.002). Modafinil had no statistically significant effect on depression (P>0.05). Secondary: Not reported
Orlikowski et al.[41] (2009) Modafinil 300 mg/day vs placebo	DB, MC, PC, RCT Patients ≥18 years of age diagnosed with myotonic muscular dystrophy type one experiencing hypersomnia	N=28 2.5 years	Primary: MWT Secondary: MSLT, ESS, global assessment (patient and physician), HAMD, SF-36	Primary: At four weeks, the mean MWT score was 16.4 minutes in the modafinil group and 15.8 minutes in the placebo group (P=0.71). Secondary: There were no significant differences between the treatment groups in MSLT latency, ESS or treatment efficacy scores. There were no significant differences between the groups in disturbances of personality and mood or quality-of-life. A total of eight patients reported at least one adverse event, including digestive, neurologic and skin symptoms. The adverse events were considered mild or moderate by the study investigator.

Study abbreviations: DB=double blind, CI=confidence interval, MC=multi-center, OL=open-label, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial, RETRO=retrospective, SD=standard deviation, XO=crossover design

Other abbreviations: BFI=Brief Fatigue Inventory, CDR=Cognitive Drug Research, CGI-C=clinical global impression of change, CGI-S=clinical global impression of severity, CPAP=continuous positive airway pressure, DSM-IV=Diagnostic and Statistical Manual of Mental Disorders Fourth Edition, EDS=excessive daytime sleepiness, ESS=Epworth sleep scale, FCRTT=four-choice reaction time test, FOSQ=Functional outcomes of sleep questionnaire, GAF=Global Assessment of Functioning, $HAMD_{17}$=Hamilton 17-item Depression Rating scale, KSS=Karolinska Sleepiness Scale, MPH=methylphenidate, MSLT=multiple sleep latency test, MWT=maintenance of wakefulness test, NSAQ=Narcolepsy Symptom Assessment Questionnaire, OSA=obstructive sleep apnea, PLM=periodic leg movements, POMS-DD=depression-dejection subscale of profile of mood states, PSG=Polysomnogram, REM=rapid eye movement, SDS-M=modified Sheehan Disability Scale, SF-36=36-item Short Form Health Survey, SSS=Stanford sleepiness score, SWD=shift work disorder

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 10. Relative Cost of the Wakefulness Promoting Agents

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Armodafinil	tablet	Nuvigil®	$$$$$	N/A
Modafinil	tablet	Provigil®*	$$$$$	$$$$$
Sodium oxybate	oral solution	Xyrem®	$$$$$	N/A

*Generic is available in at least one dosage form or strength.
N/A=Not available

X. Conclusions

The central nervous system agents that are included in this review are approved to improve wakefulness in patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnea, and shift work sleep disorder.[5-7,9-10] Armodafinil and modafinil are Schedule IV controlled substances. Sodium oxybate is a central nervous system depressant and is classified as a Schedule III controlled substance. Armodafinil and modafinil are long-acting agents while sodium oxybate is a short-acting agent. Modafinil is currently the only generically available wakefulness promoting agent.[5-7]

The American Academy of Sleep Medicine guidelines for the treatment of narcolepsy state that amphetamines, methylphenidate, modafinil, and sodium oxybate are all effective for the treatment of narcolepsy.[1] Modafinil is also recommended as one of several initial treatment options for individuals with excessive sleepiness due to obstructive sleep apnea and shift work sleep disorder.[3,4] Armodafinil is not specifically addressed in the available

guidelines. Armodafinil, modafinil, and sodium oxybate have been shown to be more effective than placebo in patients with narcolepsy, obstructive sleep apnea, and shift work sleep disorder[11-21,25-33,37]

There is insufficient evidence to support that one brand wakefulness promoting agent is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand wakefulness promoting agents within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand wakefulness promoting agent is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Anxiolytics, Sedatives, and Hypnotics – Barbiturates
AHFS Class 282404
May 11, 2016

I. Overview

The barbiturates are approved for the treatment of insomnia and for the induction of sedation. Some of the agents are also approved for use as an adjunct to anesthesia, as well as for the treatment of seizure disorders. The barbiturates affect the gamma-aminobutyric acid system and cause reversible depression of all excitable tissues, especially the central nervous system. They depress the sensory cortex, decrease motor activity, and alter cerebellar function. Depression of the central nervous system may range from sedation to general anesthesia.[1-7]

The use of barbiturates is associated with abuse and psychological/physical dependence.[1-7] Individuals who have psychological dependence may increase the dosage or decrease the dosing interval. This behavior may result in a fatal overdose. Tolerance to the sedative-hypnotic effects occurs rapidly, and these agents lose their effectiveness for sleep induction/maintenance after two weeks.[1-8] Complex behaviors such as "sleep driving", as well as other behaviors, have been reported in patients who are not fully awake after taking a sedative-hypnotic.[1,2,4] Despite their extensive use in the past, the use of barbiturates has largely been replaced by benzodiazepines.

The barbiturates that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Phenobarbital is available in a generic formulation. This class was last reviewed in May 2014.

Table 1. Barbiturates Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Amobarbital	injection	Amytal Sodium®	none
Butabarbital	tablet	Butisol Sodium®	none
Phenobarbital	elixir, injection, tablet	N/A	phenobarbital
Secobarbital	capsule	Seconal Sodium®	none

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the barbiturates are summarized in Table 2.

Table 2. Treatment Guidelines Using the Barbiturates

Clinical Guideline	Recommendation(s)

American Academy of Sleep Medicine: **Clinical Guideline for the Evaluation and Management of Chronic Insomnia in Adults (2008)**[9]	• The primary treatment goals are to improve sleep quality/quantity and to improve insomnia related daytime impairments.
	• Short-term hypnotic treatment should be supplemented with behavioral and cognitive therapies when possible.
	• When pharmacotherapy is utilized, the choice of a specific pharmacological agent should be directed by: symptom pattern, treatment goals, past treatment responses, patient preference, availability of other treatments, comorbid conditions, contraindications, concurrent medication interactions, and side effects.
	• For patients with primary insomnia, when pharmacologic treatment is utilized alone or in combination therapy, the recommended general sequence of medication trials is:
	  o Short-intermediate acting benzodiazepine receptor agonists or ramelteon.
	  o Alternate short-intermediate acting benzodiazepine receptor agonists or ramelteon if the initial agent has been unsuccessful.
	  o Sedating antidepressants, especially when used in conjunction with

Clinical Guideline	Recommendation(s)
	treating comorbid depression/anxiety. Examples of these include trazodone, amitriptyline, doxepin, and mirtazapine. o Combined benzodiazepine receptor agonists or ramelteon and sedating antidepressant. o Other sedating agents. Examples include anti-epilepsy medications (gabapentin, tiagabine) and atypical antipsychotics (quetiapine and olanzapine). These medications may only be suitable for patients with comorbid insomnia who may benefit from the primary action of these drugs as well as from the sedating effect. • Over-the-counter antihistamine or antihistamine/analgesic type drugs (over-the-counter "sleep aids"), as well as herbal and nutritional substances (e.g., valerian and melatonin), are not recommended in the treatment of chronic insomnia due to the relative lack of efficacy and safety data. • Older approved drugs for insomnia including barbiturates, barbiturate-type drugs and chloral hydrate are not recommended for the treatment of insomnia. • Pharmacological treatment should be accompanied by patient education regarding treatment goals, safety concerns, potential side effects and drug interactions, other treatment modalities (cognitive and behavioral treatments), potential for dosage escalation, and rebound insomnia. • Patients should be followed on a regular basis, every few weeks in the initial period of treatment when possible, to assess for effectiveness, possible side effects, and the need for ongoing medication. • Efforts should be made to employ the lowest effective maintenance dosage of medication and to taper medication when conditions allow. Medication tapering and discontinuation are facilitated by cognitive behavioral therapy for insomnia. • Chronic hypnotic medication may be indicated for long-term use in those with severe or refractory insomnia or chronic comorbid illness. Whenever possible, patients should receive an adequate trial of cognitive behavioral treatment during long-term pharmacotherapy. • Long-term prescribing should be accompanied by consistent follow-up, ongoing assessment of effectiveness, monitoring for adverse effects, and evaluation for new onset or exacerbation of existing comorbid disorders. • Long-term administration may be nightly, intermittent (e.g., three nights per week), or as needed.
National Institutes of Health: **Manifestations and Management of Chronic Insomnia in Adults (2005)**[10]	<u>Behavioral and cognitive therapies</u> • Behavioral methods include relaxation training, stimulus control, and sleep restriction. • Cognitive therapy methods have been added to behavioral methods and include cognitive restructuring, in which anxiety-producing beliefs and erroneous beliefs about sleep and sleep loss are specifically targeted. • The combination of cognitive methods and behavioral methods has been found to be as effective as prescription medications for short-term treatment of chronic insomnia. The beneficial effects of cognitive-behavioral therapy may last well beyond the termination of active treatment. <u>Benzodiazepine receptor agonists</u> • Benzodiazepine receptor agonists include benzodiazepines (e.g., flurazepam, temazepam, and triazolam) as well as nonbenzodiazepine-structured anxiolytic agents acting at benzodiazepine receptors (e.g., eszopiclone, zaleplon, and zolpidem). • Benzodiazepine receptor agonists have been shown to be effective in the short-term management of insomnia. • The frequency and severity of the adverse effects are much lower for the newer benzodiazepine receptor agonists, most likely because these agents have shorter half-lives.

Clinical Guideline	Recommendation(s)
	• In the short term, abuse of the benzodiazepine receptor agonists is not a major problem, but problems associated with their long-term use require further study. • Barbiturates (e.g., phenobarbital) have been used in the treatment of insomnia, however, short-term and long-term studies are lacking; such drugs bear significant risks and are not recommended in the treatment of chronic insomnia. <u>Other prescription medications</u> • Other sedating medications have been used in the treatment of insomnia. These include barbiturates and antipsychotics. • Studies demonstrating the usefulness of these medications for either short- or long-term management of insomnia are lacking. • All of these agents have significant risks. Thus, their use in the treatment of chronic insomnia cannot be recommended. <u>Antidepressants</u> • Antidepressants (especially trazodone) are often prescribed for insomnia, although they are not Food and Drug Administered (FDA)-approved for this purpose. • In short-term use, trazodone and doxepin have been shown to have some beneficial effects, but there are no studies on long-term use. • Data on other antidepressants (e.g., amitriptyline and mirtazapine) in individuals with chronic insomnia are lacking. • These guidelines were published prior to the FDA approval of ramelteon. <u>Nonprescription medications</u> • Antihistamines are the most commonly used over-the-counter treatments for chronic insomnia, but there is no systematic evidence for efficacy and there are significant concerns about risks of these medications. • Adverse effects include residual daytime sedation, diminished cognitive function, and delirium, the latter being of particular concern in the elderly. Other adverse effects include dry mouth, blurred vision, urinary retention, constipation, and risk of increased intraocular pressure in individuals with narrow angle glaucoma.
International League Against Epilepsy: **Updated International League Against Epilepsy Evidence Review of Antiepileptic Drug Efficacy and Effectiveness as Initial Monotherapy for Epileptic Seizures and Syndromes (2013)**[11]	<u>Adults with partial onset seizures</u> • Carbamazepine, levetiracetam, phenytoin, and zonisamide are established treatments as initial monotherapy for adults with newly diagnosed or untreated partial-onset seizures. Valproic acid is probably effective and gabapentin, lamotrigine, oxcarbazepine, phenobarbital, topiramate and vigabatrin are possibly effective for partial onset seizures. Clonazepam and primidone are potentially efficacious/effective. <u>Children with partial-onset seizures</u> • Oxcarbazepine is established as initial monotherapy for children with newly diagnosed or untreated partial-onset seizures. Carbamazepine, phenobarbital, phenytoin, topiramate, valproic acid and vigabatrin may be effective and clobazam, clonazepam, lamotrigine and zonisamide are potentially efficacious/ effective. <u>Elderly adults with partial-onset seizures</u> • Gabapentin and lamotrigine are effective as initial monotherapy for elderly adults with newly diagnosed or untreated partial-onset seizures. Carbamazepine may be effective and topiramate and valproic acid are potentially efficacious/effective. <u>Adults with generalized-onset tonic-clonic seizures</u> • Carbamazepine, lamotrigine, oxcarbazepine, phenobarbital, phenytoin, topiramate and valproic acid are possibly effective as initial monotherapy for adults with newly diagnosed or untreated generalized-onset tonic-clonic seizures. Gabapentin,

Clinical Guideline	Recommendation(s)
	levetiracetam and vigabatrin are potentially efficacious/effective. Carbamazepine and phenytoin may precipitate or aggravate generalized-onset tonic-clonic seizures. <u>Children with generalized-onset tonic-clonic seizures</u> • Carbamazepine, phenobarbital, phenytoin, topiramate and valproic acid are possibly effective for children with newly diagnosed or untreated generalized onset tonic-clonic seizures. Oxcarbazepine is potentially efficacious/effective. Carbamazepine and phenytoin may precipitate or aggravate generalized-onset tonic-clonic seizures. <u>Children with absence seizures</u> • Ethosuximide and valproic acid are established treatments for children with newly diagnosed or untreated absence seizures. Lamotrigine is possibly efficacious/ effective as initial monotherapy. Gabapentin is inefficacious/ineffective for children with absence seizures. • Based on scattered reports, the following antiepileptic drugs may precipitate or aggravate absence seizures: carbamazepine, oxcarbazepine, phenobarbital, phenytoin, tiagabine and vigabatrin. No conclusion can be made about levetiracetam efficacy/effectiveness for absence seizures since the failed class III placebo-controlled trial was uninformative. <u>Children with benign childhood epilepsy with centrotemporal spikes</u> • Carbamazepine and valproic acid are possibly effective as initial monotherapy for children with benign childhood epilepsy with centrotemporal spikes. Gabapentin, levetiracetam, oxcarbazepine, and sulthiame* are potentially efficacious/effective. <u>Juvenile myoclonic epilepsy</u> • Topiramate and valproic acid are potentially efficacious/effective for patients with newly diagnosed juvenile myoclonic epilepsy. Carbamazepine, gabapentin, oxcarbazepine, phenytoin, tiagabine and vigabatrin may precipitate or aggravate absence seizures, myoclonic seizures, and in some cases generalized tonic-clonic seizures. There has been a report that lamotrigine may exacerbate seizures in juvenile myoclonic epilepsy.
National Institute for Clinical Excellence: **The Epilepsies: The Diagnosis and Management of the Epilepsies in Adults and Children in Primary and Secondary Care (2012)**[12] **Reaffirmed 2014**	<u>Treatment of atonic or tonic seizures</u> • First-line treatment in children, young people, and adults with tonic or atonic seizure: sodium valproate. • Offer lamotrigine as adjunctive treatment if sodium valproate is ineffective or not tolerated. • Discuss with a tertiary epilepsy specialist if adjunctive treatment is ineffective or not tolerated. Other antiepileptics that may be considered by the tertiary epilepsy specialist are rufinamide and topiramate. • Do not offer carbamazepine, gabapentin, oxcarbazepine, pregabalin, tiagabine or vigabatrin. <u>Treatment of generalized tonic-clonic seizures</u> • First-line treatment in children, young people, and adults with newly diagnosed focal seizures: sodium valproate. • Offer lamotrigine if sodium valproate is unsuitable. • Consider carbamazepine and oxcarbazepine. • Offer clobazam, lamotrigine, levetiracetam, sodium valproate, or topiramate as adjunctive treatment to all patients if first-line treatments are ineffective or not tolerated. • If there are absence or myoclonic seizures, or if juvenile myoclonic epilepsy is suspected, do not offer carbamazepine, gabapentin, oxcarbazepine, phenytoin,

Clinical Guideline	Recommendation(s)
	pregabalin, tiagabine, or vigabatrin. <u>Treatment of infantile spasms</u> • Discuss with, or refer to, a tertiary pediatric epilepsy specialist when an infant presents with infantile spasms. • Offer a steroid or vigabatrin as first-line treatment to infants with infantile spasms that are not due to tuberous sclerosis. • Offer vigabatrin as first-line treatment to infant with infantile spasms due to tuberous sclerosis. If vigabatrin is ineffective, offer a steroid. <u>Treatment of Lennox-Gastaut Syndrome</u> • Discuss with, or refer to, a tertiary pediatric epilepsy specialist when a child presents with suspected Lennox-Gastaut syndrome. • Offer sodium valproate as first-line treatment to children with Lennox-Gastaut syndrome. • Offer lamotrigine as adjunctive treatment if first-line treatments are ineffective or not tolerated. • Discuss with a tertiary epilepsy specialist if adjunctive treatment is ineffective or not tolerated. Other antiepileptics that may be considered by the tertiary epilepsy specialist are rufinamide and topiramate. • Do not offer carbamazepine, gabapentin, oxcarbazepine, pregabalin, tiagabine or vigabatrin. • Only offer felbamate in centers providing tertiary epilepsy specialist care and when treatment with all of the antiepileptics listed above have proved ineffective or not tolerated. <u>Treatment of myoclonic seizures</u> • First-line treatment in children, young people, and adults with myoclonic seizures: valproate, unless unsuitable. • Consider levetiracetam or topiramate if sodium valproate is unsuitable or not tolerated. • Offer levetiracetam, sodium valproate, or topiramate as adjunctive treatment to all patients if first-line treatments are ineffective or not tolerated. • If adjunctive treatment is ineffective or not tolerated, discuss with, or refer to, a tertiary epilepsy specialist or consider clobazam, clonazepam, piracetam*, or zonisamide. • Do not offer carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin. <u>Treatment of absence seizures</u> • First-line treatment in children, young people, and adults with absence seizures: ethosuximide or sodium valproate. If there is a high risk of generalized tonic-clonic seizures, offer sodium valproate first, unless it is unsuitable. • Offer lamotrigine if ethosuximide and sodium valproate are unsuitable, ineffective, or not tolerated. • If two first-line antiepileptics are ineffective, consider a combination of two of these three antiepileptics as adjunctive treatment: ethosuximide, lamotrigine, or sodium valproate. • If adjunctive treatment is ineffective or not tolerated, discuss with, or refer to, a tertiary epilepsy specialist and consider clobazam, clonazepam, levetiracetam, topiramate or zonisamide. • Do not offer carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin. <u>Treatment of focal seizures</u>

Clinical Guideline	Recommendation(s)
	• First-line treatment in children, young people, and adults with newly diagnosed focal seizures: carbamazepine or lamotrigine. • Offer levetiracetam, oxcarbazepine, or sodium valproate if first-line treatments are unsuitable or not tolerated. If the first antiepileptic tried is ineffective, offer an alternative from the five antiepileptics noted above. • Consider adjunctive treatment if a second well-tolerated antiepileptic is ineffective. • For refractory focal seizures, offer carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate, or topiramate as adjunctive treatment to all patients with focal seizures if first-line treatments are ineffective or not tolerated. • For refractory focal seizures, if adjunctive treatment is ineffective or not tolerated, discuss with, or refer to, a tertiary epilepsy specialist. Other antiepileptics that may be considered by a specialist are eslicarbazepine acetate*, lacosamide, phenobarbital, phenytoin, pregabalin, tiagabine, vigabatrin and zonisamide. <u>Treatment of Dravet syndrome</u> • Discuss with, or refer to, a tertiary pediatric epilepsy specialist when a child presents with suspected Dravet syndrome. • Consider sodium valproate or topiramate as first-line treatment in children with Dravet syndrome. • Discuss with a tertiary epilepsy specialist if first-line treatments are ineffective or not tolerated, and consider clobazam or stiripentol as adjunctive treatment. • Do not offer carbamazepine, gabapentin, lamotrigine, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin. <u>Treatment of benign epilepsy with centrotemporal spikes, Panayiotopoulos syndrome, or late-onset childhood occipital epilepsy (Gastaut type)</u> • Discuss with the child or young person, and their family and/or caretakers, whether antiepileptic drug treatment is indicated. • Offer carbamazepine or lamotrigine as first-line treatment to children and young people. • Offer levetiracetam, oxcarbazepine, or sodium valproate if first-line treatments are unsuitable or not tolerated. If the first antiepileptic drug tried is ineffective, offer an alternative from the five antiepileptics noted above. • Consider adjunctive treatment if a second well-tolerated antiepileptic drug is ineffective. • Offer carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate, or topiramate as adjunctive treatment if first-line treatments are ineffective or not tolerated. • If adjunctive treatment is ineffective or not tolerated, discuss with, or refer to, a tertiary epilepsy specialist. Other antiepileptic drugs that may be considered are eslicarbazepine acetate*, lacosamide, phenobarbital, phenytoin, pregabalin, tiagabine, vigabatrin and zonisamide. <u>Treatment of idiopathic generalized epilepsy</u> • First-line treatment in children, young people, and adults with idiopathic generalized epilepsy: sodium valproate. • Offer lamotrigine if sodium valproate is unsuitable or not tolerated. • Consider topiramate. • Offer lamotrigine, levetiracetam, sodium valproate, or topiramate as adjunctive treatment if first-line treatments are ineffective or not tolerated. • If adjunctive treatment is ineffective or not tolerated, discuss with, or refer to, a tertiary epilepsy specialist and consider clobazam, clonazepam or zonisamide. • Do not offer carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin,

Clinical Guideline	Recommendation(s)
	tiagabine or vigabatrin. <u>Treatment of juvenile myoclonic epilepsy</u> • First-line treatment in children, young people, and adults with juvenile myoclonic epilepsy: sodium valproate. • Consider lamotrigine, levetiracetam, or topiramate if sodium valproate is unsuitable or not tolerated. • Offer lamotrigine, levetiracetam, sodium valproate, or topiramate as adjunctive treatment if first-line treatments are ineffective or not tolerated. • If adjunctive treatment is ineffective or not tolerated, discuss with, or refer to, a tertiary epilepsy specialist and consider clobazam, clonazepam, or zonisamide. • Do not offer carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin. <u>Treatment of epilepsy with generalized tonic-clonic seizures only</u> • First-line treatment in children, young people, and adults with epilepsy with generalized tonic-clonic seizures only: lamotrigine, sodium valproate. • Consider carbamazepine or oxcarbazepine. • Offer clobazam, lamotrigine, levetiracetam, sodium valproate, or topiramate as adjunctive treatment if first-line treatments are ineffective or not tolerated. <u>Treatment of childhood absence epilepsy, juvenile absence epilepsy, or other absence epilepsy syndromes</u> • First-line treatment in children, young people, and adults: ethosuximide, sodium valproate. • Offer lamotrigine if first-line treatments are unsuitable, ineffective, or not tolerated. • If two first-line antiepileptic drugs are ineffective, consider a combination of two of these three antiepileptic drugs adjunctive treatment: ethosuximide, lamotrigine, or sodium valproate. • If adjunctive treatment is ineffective or not tolerated, discuss with, or refer to, a tertiary epilepsy specialist and consider clobazam, clonazepam, levetiracetam, topiramate, or zonisamide. • Do not offer carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin.
American Academy of Neurology: **Evidence-Based Guideline Update: Medical Treatment of Infantile Spasms: Report of the Guideline Development Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society (2012)**[13] **Reaffirmed 2015**	• To date, there is insufficient evidence to support the use of agents other than adrenocorticotropic hormone, and vigabatrin. • Low-dose adrenocorticotropic hormone should be considered as an alternative to high-dose adrenocorticotropic hormone for treatment of infantile spasms. • Adrenocorticotropic hormone or vigabatrin may be offered for short-term treatment of infantile spasms. Evidence suggests that adrenocorticotropic hormone may be offered over vigabatrin. • There is insufficient evidence to recommend the use of dexamethasone, prednisolone and methylprednisolone as being as effective as adrenocorticotropic hormone for short-term treatment of infantile spasms. • The data is insufficient to recommend other therapies (valproic acid, vitamin B6, nitrazepam, levetiracetam, zonisamide, topiramate, the ketogenic diet, or novel/combination therapies) for the treatment of infantile spasms. • Hormonal therapy (adrenocorticotropic hormone or prednisolone) may be considered for use in preference to vigabatrin in infants with cryptogenic infantile spasms, to possibly improve developmental outcome. • A shorter lag time to treatment of infantile spasms with either hormonal therapy or vigabatrin may be considered to improve long-term cognitive outcomes.
Infantile Spasms	• To improve outcomes in infantile spasms, the goals include early recognition and

Clinical Guideline	Recommendation(s)
Working Group: **Infantile Spasms: A U.S. Consensus Report (2010)**[14]	diagnosis, short-term treatment with a first-line therapy, timely electroencephalography evaluation to assess treatment effectiveness and prompt treatment modification if indicated. • Effective treatment should produce both cessation of spasms and resolution of hypsarrhythmia on electroencephalography. • The dose of the chosen first-line agent should be adjusted to achieve the maximum effective dose in as short amount of time as clinically indicated. • There is insufficient evidence to recommend the best approach in events of relapse. Possible treatment options include using the previously effective agent and dose, using the previously effective agent at the maximum dose or using a new agent. • Adrenocorticotropic hormone is considered first-line therapy for infantile spasms. There is insufficient evidence to recommend the optimal dose and duration of treatment, although short duration is preferable to avoid adverse events. Treatment with the maximum dose of adrenocorticotropic hormone should be continued for two weeks followed by taper and evaluation of treatment response. • Vigabatrin is considered first-line therapy for infantile spasms, especially in patients with comorbid tuberous sclerosis complex. Vigabatrin should be initiated at 50 mg/kg/day and increased up to 100 to 150 mg/kg/day if indicated. Efficacy should be assessed within two weeks following dose titration. Responders to treatment may continue therapy for six to nine months, with continued ophthalmic evaluation. • No recommendations can be given with regard to oral corticosteroids in the treatment of infantile spasms. • Ketogenic diet may be considered as second-line therapy when first-line therapies fail or are inappropriate. • Patients with refractory spasms, concomitant partial seizures or focal abnormalities on the electroencephalography may be evaluated for surgery.
European Federation of Neurological Societies: **Guideline on the Management of Status Epilepticus (2010)**[15]	<u>Initial pharmacological treatment for generalized convulsive status epilepticus and non-convulsive status epilepticus</u> • The preferred treatment is intravenous administration of lorazepam 0.1 mg/kg; however, depending on the patients' general medical condition, treatment can be started at a lower dose of 4 mg, to be repeated if seizures continue for >10 minutes after first injection. • If lorazepam is not available, diazepam 10 mg (route of administration not specified) directly followed by phenytoin (15 to 18 mg/kg) or equivalent fosphenytoin. • General management of refractory status epilepticus includes treatment in an intensive care unit. <u>Pharmacological treatment for refractory generalized convulsive status epilepticus and subtle status epilepticus</u> • Immediate infusions of anesthetic doses of midazolam, propofol or barbiturates are recommended due to the progressive risk of brain and systemic damage. • If midazolam is given, seizure suppression is recommended. This goal should be maintained for at least 24 hours. Simultaneous initiation of the chronic medication the patient with be treated with in the future should be initiated. • For elderly patients in whom intubation and artificial ventilation would not be justified, further non-anesthetizing anticonvulsants may be tried. <u>Pharmacological treatment for refractory non-convulsive status epilepticus</u> • Due to poor evidence and lack of any head-to-head trials, no recommendations can be made regarding which of the non-anaesthetizing anticonvulsants should be the drug of choice. • Recommendations include phenobarbital, valproic acid and levetiracetam.

Clinical Guideline	Recommendation(s)
	• If treatment regimen includes the administration of anesthetics, use the same protocol as refractory generalized convulsive status epilepticus.
Journal of Child Neurology: **Treatment of Pediatric Epilepsy: Expert Opinion (2005)**[16]	• Rectal diazepam is the treatment of choice for acute treatment of a prolonged febrile seizure or cluster of seizures. • Intravenous phenobarbital is the treatment of choice and intravenous lorazepam or fosphenytoin are also first line options for the initial therapy of neonatal status epilepticus. • Lorazepam is the treatment of choice and intravenous diazepam is also a first line option for the initial therapy of all types of pediatric status epilepticus. • Rectal diazepam or fosphenytoin are the first-line options for generalized tonic-clonic status epilepticus. • Benzodiazepines were not identified as being first-line or treatment of choice for the following: complex partial status epilepticus, absence status epilepticus, symptomatic myoclonic and generalized tonic-clonic seizures, complex partial seizures, infantile spasms, Lennox-Gastaut syndrome, benign childhood epilepsy with centro-temporal spikes, childhood absence epilepsy, juvenile absence epilepsy, and juvenile myoclonic epilepsy.
American Academy of Neurology/ American Epilepsy Society: **Efficacy and Tolerability of the New Antiepileptic Drugs I: Treatment of New Onset Epilepsy (2004)**[17]	• At this time, there are no studies that assessed the efficacy and tolerability of the new antiepileptic drugs (gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate and zonisamide) in adults with newly diagnosed (exclusively) idiopathic or symptomatic generalized epilepsy. • Lamotrigine can be included in the treatment options for children with newly diagnosed absence seizures. At this time, there is insufficient evidence to recommend use of gabapentin, levetiracetam, oxcarbazepine, tiagabine, topiramate and zonisamide in children with newly diagnosed (exclusively) idiopathic or symptomatic generalized epilepsy. • Patients with newly diagnosed partial or mixed seizure disorders who require treatment can be initiated on carbamazepine, gabapentin, lamotrigine, oxcarbazepine, phenobarbital, phenytoin, topiramate or valproic acid. The choice of drug will depend on individual patient characteristics. At this time, there is insufficient evidence to determine effectiveness in newly diagnosed patients for levetiracetam, tiagabine and zonisamide.
American Academy of Neurology/ American Epilepsy Society: **Efficacy and Tolerability of the New Antiepileptic Drugs II: Treatment of Refractory Epilepsy (2004)**[18]	• Topiramate may be used for the treatment of refractory generalized tonic-clonic seizures in adults and children. At this time, there is insufficient evidence to recommend use of gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine or zonisamide for refractory generalized tonic-clonic seizures in adults and children. • Lamotrigine and topiramate may be used to treat drop attacks associated with Lennox Gastaut syndrome in adults and children. • Lamotrigine, oxcarbazepine and topiramate can be used as monotherapy in adults with refractory partial epilepsy. At this time, there is insufficient evidence to recommend use of gabapentin, levetiracetam, tiagabine or zonisamide in monotherapy for refractory partial epilepsy. • Gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate and zonisamide are appropriate treatment options as adjunctive therapy for refractory partial epilepsy in adults. • Gabapentin, lamotrigine, oxcarbazepine and topiramate may be used as adjunctive treatment of refractory partial seizures in children. At this time, there is insufficient evidence to recommend levetiracetam, tiagabine or zonisamide as adjunctive treatment of refractory partial seizures in children.

*Agent not available in the United States.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the barbiturates are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Barbiturates[1-7]

Indication	Amobarbital	Butabarbital	Phenobarbital	Secobarbital
Anesthesia				
Preanesthetic	✔	✔	✔ *	✔
Anticonvulsant				
Anticonvulsant in the emergency control of certain acute convulsive episodes			✔ *	
Long-term anticonvulsant for the treatment of generalized tonic-clonic and cortical focal seizures			✔ *	
Treatment of generalized and partial seizures			✔ *	
Sedative-Hypnotic				
Short-term treatment of insomnia	✔	✔	✔ *	✔
Sedation	✔	✔	✔ *†	

*Parenteral formulation.
†Oral formulation.

IV. Pharmacokinetics

The pharmacokinetic parameters of the barbiturates are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Barbiturates[2]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life
Amobarbital	Not reported	Not reported	Liver	Renal Feces (4 to 5)	8 to 42 hours
Butabarbital	Not reported	Not reported	Liver	Renal	34 to 100 hours
Phenobarbital	80 to 100	20 to 60	Liver	Renal (21)	1.5 to 4.9 days
Secobarbital	90	52 to 57	Liver	Renal	19 to 34 hours

V. Drug Interactions

Major drug interactions with the barbiturates are listed in Table 5.

Table 5. Major Drug Interactions with the Barbiturates[2]

Generic Name(s)	Interaction	Mechanism
Barbiturates (amobarbital, butabarbital, phenobarbital, secobarbital)	Anticoagulants	Barbiturates reduce the effects of anticoagulants through increased metabolic clearance of anticoagulants, probably caused by induction of hepatic microsomal enzymes.
Barbiturates (amobarbital, butabarbital,	Benzodiazepines	Concurrent use of barbiturates and benzodiazepines may result in additive respiratory depression.

Generic Name(s)	Interaction	Mechanism
phenobarbital, secobarbital)		
Barbiturates (amobarbital, butabarbital, phenobarbital, secobarbital)	Centrally acting muscle relaxants	Concurrent use of barbiturates and centrally acting muscle relaxants may result in additive respiratory depression.
Barbiturates (amobarbital, butabarbital, phenobarbital, secobarbital)	Sodium oxybate	Concurrent use of sodium oxybate and barbiturates may result in an increase in sleep duration and central nervous system depression.
Barbiturates (phenobarbital)	Hepatitis C virus protease inhibitors	Plasma concentrations and pharmacologic effects of hepatitis C virus protease inhibitors may be decreased by phenobarbital. Induction of CYP3A4 by phenobarbital may increase the metabolic elimination of hepatitis C virus protease inhibitors.
Barbiturates (phenobarbital)	Lurasidone	Plasma concentrations and pharmacologic effects of lurasidone may be decreased by phenobarbital. Induction of CYP3A4 by phenobarbital may increase the metabolic elimination of lurasidone.
Barbiturates (phenobarbital)	Praziquantel	Praziquantel plasma concentrations may be decreased by phenobarbital. The antiparasitic effect of praziquantel may be decreased. Induction of cytochrome P450 3A4 isoenzymes by phenobarbital may increase the metabolic elimination of praziquantel.
Barbiturates (phenobarbital)	Ranolazine	Pharmacologic effects and plasma concentrations of ranolazine may be decreased by phenobarbital. Induction of cytochrome P450 3A4 isoenzymes by phenobarbital may increase the metabolic elimination of ranolazine.
Barbiturates (phenobarbital)	Rilpivirine	Plasma concentrations and pharmacologic effects of rilpivirine may be reduced by phenobarbital possibly resulting in loss of virologic response or resistance. Induction of cytochrome P450 3A4 isoenzymes by phenobarbital may increase the metabolic elimination of rilpivirine.
Barbiturates (phenobarbital)	Voriconazole	Plasma concentrations and pharmacologic effects of Voriconazole may be decreased by phenobarbital. Induction of cytochrome P450 3A4 isoenzymes by phenobarbital may increase the metabolic elimination of voriconazole.
Barbiturates (amobarbital, butabarbital, phenobarbital, secobarbital)	Clozapine	Clozapine plasma concentrations may be reduced, possibly through induction of hepatic metabolism of clozapine, decreasing the pharmacologic effects.
Barbiturates (amobarbital, butabarbital, phenobarbital, secobarbital)	Methoxyflurane	Barbiturates appear to stimulate degradation of methoxyflurane, perhaps to nephrotoxic metabolites. Enhanced renal toxicity may occur.
Barbiturates (amobarbital, butabarbital, phenobarbital, secobarbital)	Tacrolimus	Plasma concentrations and pharmacologic effects of tacrolimus may be decreased, due to increased hepatic metabolism of tacrolimus via CYP3A4.
Barbiturates (amobarbital, butabarbital, phenobarbital, secobarbital)	Ulipristal	Plasma concentrations and pharmacologic effects of ulipristal may be decreased by barbiturates. Coadministration of butabarbital with ulipristal may reduce the efficacy of ulipristal.
Barbiturates (phenobarbital)	Epothilones	The pharmacologic effects of epothilones may be decreased by strong CYP3A4 inducers, such as phenobarbital. Induction of cytochrome P450 3A4 isoenzymes by phenobarbital may increase the metabolic elimination of epothilones.
Barbiturates	Human	Plasma concentrations and pharmacologic effects of

Generic Name(s)	Interaction	Mechanism
(phenobarbital)	immunodeficiency virus protease inhibitors	human immunodeficiency virus protease inhibitors may be decreased by phenobarbital. Induction of CYP3A4 isoenzymes by barbiturates may increase the metabolic elimination of human immunodeficiency virus protease inhibitors.
Barbiturates (phenobarbital)	Mammalian target of rapamycin inhibitors	Induction of CYP34A isoenzymes by phenobarbital may increase the metabolic elimination and decrease pharmacological of mammalian target of rapamycin inhibitors.
Barbiturates (phenobarbital)	Non-nucleoside reverse transcriptase inhibitors	Induction of CYP34A isoenzymes by phenobarbital may increase the metabolic elimination and decrease pharmacological of non-nucleoside reverse transcriptase inhibitors.
Barbiturates (phenobarbital)	Tyrosine kinase receptor inhibitors	Induction of CYP34A isoenzymes by phenobarbital may increase the metabolic elimination of tyrosine kinase receptor inhibitors. Concomitant use is not recommended.
Barbiturates (amobarbital, butabarbital, phenobarbital, secobarbital)	Vasopressin receptor antagonists	Plasma concentrations and pharmacologic effects of vasopressin receptor antagonists may be decreased by barbiturates. Induction of CYP3A4 isoenzymes by barbiturates may increase the metabolic elimination of vasopressin receptor antagonists.
Barbiturates (phenobarbital)	Deferasirox	Plasma concentrations and pharmacologic effects of deferasirox may be decreased by phenobarbital. Induction of UDP-glucuronosyltransferase by phenobarbital may increase the metabolic elimination of deferasirox.
Barbiturates (phenobarbital)	Dronedarone	Plasma concentrations and pharmacologic effects of dronedarone may be decreased by phenobarbital. Induction of cytochrome P450 3A4 isoenzymes by phenobarbital may increase the metabolic elimination of dronedarone.
Barbiturates (phenobarbital)	Maraviroc	Induction of CYP3A4 isoenzymes by long-acting barbiturates may increase the metabolic elimination of maraviroc and decrease its pharmacologic effects.
Barbiturates (phenobarbital)	Mifepristone	Plasma concentrations and pharmacologic effects of mifepristone may be decreased by phenobarbital. Induction of CYP3A4 isoenzymes by barbiturates may increase the metabolic elimination of mifepristone.
Barbiturates (phenobarbital)	Roflumilast	Plasma concentrations and pharmacologic effects of roflumilast may be decreased by phenobarbital. Induction of CYP3A4 isoenzymes by barbiturates may increase the metabolic elimination of roflumilast.
Barbiturates (phenobarbital)	Ticagrelor	Plasma concentrations and pharmacologic effects of ticagrelor may be decreased by phenobarbital. Induction of CYP3A4 isoenzymes by barbiturates may increase the metabolic elimination of ticagrelor.
Barbiturates (phenobarbital)	Vandetanib	Plasma concentrations and pharmacologic effects of vandetanib may be decreased by phenobarbital. Induction of CYP3A4 isoenzymes by barbiturates may increase the metabolic elimination of vandetanib.

VI. Adverse Drug Events

The most common adverse drug events reported with the barbiturates are listed in Table 6.

Table 6. Adverse Drug Events (%) Reported with the Barbiturates[1-7]

Adverse Events	Amobarbital	Butabarbital	Phenobarbital	Secobarbital
Cardiovascular				
Bradycardia	✔	✔	✔	-
Hypotension	✔	✔	✔	✔
Syncope	✔	✔	✔	-
Central Nervous System				
Abnormal thinking	✔	✔	-	-
Agitation	✔	✔	✔	-
Anxiety	✔	✔	✔	-
Ataxia	✔	✔	✔	-
Confusion	✔	✔	✔	✔
Central nervous system depression	✔	-	✔	✔
Central nervous system excitation	-	-	✔	-
Complex sleep-related activities	-	<1	-	✔
Depression	-	✔	-	✔
Dizziness	✔	✔	✔	✔
Drowsiness	-	-	✔	✔
Excitement	-	-	-	✔
Faint feeling	-	-	-	✔
Fever	✔	✔	-	✔
Hallucinations	✔	✔	✔	✔
Hangover effect	-	-	✔	✔
Headache	✔	✔	✔	✔
Hyperkinesia	✔	✔	✔	-
Impaired judgment	-	-	✔	-
Insomnia	✔	✔	✔	✔
Lethargy	-	-	✔	-
Lightheadedness	-	-	-	✔
Nervousness	✔	✔	✔	✔
Nightmares	✔	✔	✔	✔
Psychiatric disturbances	✔	✔	-	-
Somnolence	✔	1 to 3	✔	-
Dermatological				
Exfoliative dermatitis	-	✔	✔	✔
Injection site reaction	✔	-	-	-
Rash	-	✔	✔	✔
Stevens-Johnson syndrome	-	✔	✔	✔
Urticaria	-	-	-	✔
Gastrointestinal				
Constipation	✔	✔	✔	✔
Nausea	✔	✔	✔	✔
Vomiting	✔	✔	✔	✔
Hematologic				
Agranulocytosis	-	✔	✔	✔
Megaloblastic anemia	✔	✔	✔	✔
Thrombocytopenia	-	✔	✔	✔
Thrombophlebitis	-	✔	✔	✔
Respiratory				
Apnea	✔	✔	✔	✔
Atelectasis	✔	-	-	-

Adverse Events	Amobarbital	Butabarbital	Phenobarbital	Secobarbital
Hypoventilation	✔	✔	✔	-
Laryngospasm	-	-	✔	✔
Respiratory depression	-	✔	✔	✔
Other				
Anaphylaxis	-	✔	-	✔
Angioedema	✔	✔	-	✔
Dependence	-	✔	-	-
Gangrene	-	-	✔	-
Hypersensitivity reaction	✔	✔	-	-
Liver damage	✔	✔	-	-
Oliguria	-	-	✔	-
Pain at injection site	-	-	✔	✔

✔ Percent not specified.
- Event not reported or incidence <1%.

VII. Dosing and Administration

The usual dosing regimens for the barbiturates are listed in Table 7.

Table 7. Usual Dosing Regimens for the Barbiturates[1-7]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Amobarbital	Preanesthetic: Injection: 65 to 500 mg administered intramuscularly or intravenously two to three times daily Hypnotic (short-term treatment of insomnia): Injection: 65 to 200 mg administered intramuscularly or intravenously at bedtime Sedative (sedation): Injection: 30 to 50 mg administered intramuscularly or intravenously two to three times daily	Preanesthetic: Injection: 65 to 500 mg administered intravenously Hypnotic (short-term treatment of insomnia): Injection: six to 12 years of age, 65 to 500 mg administered intravenously Sedative (sedation): Injection: six years of age and older, 30 to 50 mg administered intramuscularly or intravenously two to three times daily	Injection: 500 mg
Butabarbital	Preanesthetic: Tablet: 50 to 100 mg administered 60 to 90 minutes before surgery Hypnotic (short-term treatment of insomnia): Tablet: 50 to 100 mg at bedtime Sedative (sedation): Tablet: 15 to 30 mg administered three to four times daily	Preanesthetic: Tablet: 2 to 6 mg/kg administered 60 to 90 minutes before surgery; maximum, 100 mg	Tablet: 30 mg
Phenobarbital	Acute convulsions: Injection: 20 to 320 mg intramuscularly or intravenously, repeated in six hours as necessary, maximum 600 mg/24 hours Anticonvulsant:	Anticonvulsant: Elixir: 3 to 6 mg/kg/day Injection: 4 to 6 mg/kg/day for seven to 10 days to blood level of 10 to 15	Elixir: 20 mg/5 mL Injection: 65 mg/mL

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Elixir: 60 to 200 mg/day Tablet: 50 to 100 mg two or three times daily Hypnotic (short-term treatment of insomnia): Elixir: 100 to 200 mg/day at bedtime, up to maximum 400 mg in 24 hours Injection, tablet: 100 to 320 mg at bedtime, up to maximum 600 mg in 24 hours for injection and 400 mg in 24 hours for tablet Preanesthetic: Injection: 100 to 200 mg intramuscularly 60 to 90 minutes before surgery Sedative (sedation): Elixir, tablet: 30 to120 mg/day in two to three divided doses, up to maximum 400 mg in 24 hours Injection: 30 to 120 mg/day in two to three divided doses intramuscularly or intravenously	µg/mL or 10 to 15 mg/kg/day intramuscularly or intravenously Tablet: 15 to 50 mg two or three times daily Preanesthetic: Injection: 1 to 3 mg/kg intramuscularly or intravenously 60 to 90 minutes prior to procedure Sedative (sedation): Tablet: 6 mg/kg/day in three divided doses Status epilepticus: Injection: 15 to 20 mg/kg intravenously over 10 to 15 minutes	Tablet: 15 mg 16.2 mg 30 mg 32.4 mg 60 mg 64.8 mg 97.2 mg 100 mg
Secobarbital	Hypnotic (short-term treatment of insomnia): Capsule: 100 mg at bedtime Preanesthetic: Capsule: 200 to 300 mg one to two hours before surgery	Preanesthetic: Capsule: 2 to 6 mg/kg one to two hours before surgery, maximum dose of 100 mg	Capsule: 100 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the barbiturates are summarized in Table 8. Although the barbiturates have been available for decades, there are few clinical trials available that directly compare the various agents.

Table 8. Comparative Clinical Trials with the Barbiturates

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Alcohol Detoxification				
Mariani et al.[19] (2006) Phenobarbital 60 mg QID for one day, 60 mg TID for one day, 60 mg BID for one day then 60 mg QD for one day vs gabapentin 2,400 mg on day one (titrated), 600 mg TID for one day, 600 mg BID for one day, then 600 mg QD for one day	OL, RCT Patients 18 to 60 years of age who were admitted for inpatient alcohol detoxification	N=27 4 days	Primary: Treatment failure and severity of withdrawal symptoms Secondary: Not reported	Primary: There was no significant difference in the number of patients completing treatment among the phenobarbital treatment group compared to the gabapentin group (62 vs 71%; P<0.70). Rescue medication was required in 38% of the phenobarbital group and this proportion did not differ significantly from the gabapentin group (57%; P<0.45). The results of each withdrawal-symptom rating scale and the number of hours of sleep per night did not differ significantly between treatment groups. No withdrawal seizures or symptoms of alcohol withdrawal delirium were demonstrated in either treatment group. Secondary: Not reported
Insomnia				
Okawa et al.[20] (1978) Secobarbital 100 mg vs	DB, RCT, XO (two trials) Patients 18 to 60 years of age with a history of insomnia and two of the following: onset of	N=76 2 nights	Primary: Patient preference questionnaire, success (defined as sleep onset in 30 minutes or less and sleep duration of six hours or more),	Primary: One trial compared triazolam to placebo and involved 19 patients. Sixteen patients preferred triazolam over placebo and three expressed no preference (P<0.001). Triazolam demonstrated greater efficacy over placebo in overall sleep (P<0.001), onset (P<0.001), duration (P<0.002) and number of awakenings (P<0.002). Triazolam was determined to be significantly more successful in 15 of 19 patients (P<0.004). No difference in next-morning alertness was noted between the two study groups. Seven

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
triazolam 0.5 mg vs placebo	sleep longer than 30 minutes, duration of sleep six hours or less, or experiencing three or more awakenings		adverse effects Secondary: Not reported	patients receiving active treatment experienced mild-to-moderate adverse effects, with dizziness, drowsiness and headache as the most frequently reported. In comparison, three of the patients in the placebo group experienced mild-to-moderate side effects. The second trial was a combined study of 57 patients comparing triazolam and secobarbital. The results of the patient preference questionnaire were analyzed and showed a significant preference for triazolam (41 patients) over secobarbital (10 patients), with six having no preference for either agent (P<0.001). Significant improvement was seen with triazolam compared to secobarbital (P<0.001) in sleep onset, duration of sleep and number of awakenings. Feelings of alertness the next morning did not differ between treatment groups. Success was established in 73% of triazolam treated patients whereas only 30% of the secobarbital treated patients were determined successful (P<0.001). Thirteen patients in the secobarbital group reported adverse effects ranging from drowsiness and restlessness to dry mouth. More patients on triazolam reported side effects. Secondary: Not reported
Seizures				
Arya et al.[21] (2013) Antiepileptic drugs as monotherapy and adjunctive therapy	SR RCTs, SRs and MAs for pediatric population with partial onset or focal seizures classified based on monotherapy and add-on therapy criteria modified from updated International League Against Epilepsy guidelines and American	46 trials Variable duration	Primary: Complete seizure freedom during the observed unit time using 50% responder rate (the proportion of patients experiencing a reduction of ≥50% in seizure frequency during the treatment phase compared to the baseline phase), retention of	Primary: The only antiepileptic drug with Class I evidence for efficacy as initial monotherapy for partial-onset seizures in children is oxcarbazepine. Carbamazepine, clobazam, lamotrigine, phenobarbital, phenytoin, topiramate, valproate, vigabatrin and zonisamide have Class III evidence of efficacy for monotherapy of partial-onset seizures in children. Gabapentin, lamotrigine, levetiracetam, oxcarbazepine and topiramate have Class I evidence of efficacy for treatment of partial-onset seizures in children. The efficacy of phenobarbital monotherapy in children with partial-onset seizures was from open-label trials and as a result, the status of phenobarbital as monotherapy remains undefined. There is no systematic evidence for the efficacy or tolerability of phenobarbital as adjunctive

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	Academy of Neurology/ American Epilepsy Society report		patients on study medication Secondary: Not reported	therapy in children with refractory partial-onset seizures. Secondary: Not reported
Nolan SJ et al.[22] (2013) Phenobarbitone vs phenytoin	SR Adults and children with partial onset seizures or generalized tonic-clonic seizures with or without other generalized seizure types	N=599 (4 trials) Variable duration	Primary: Time to treatment withdrawal (a HR>1 indicates a clinical advantage for phenytoin) Secondary: Time to 12-month seizure-free period (remission), six-month remission and first seizure post randomization; for all outcomes, a HR>1 indicates a clinical advantage for phenytoin	Primary: Phenobarbitone was more likely to be withdrawn than phenytoin based on the overall pooled HR that was calculated using fixed effects and adjusted for seizure type (HR, 1.62; 95% CI, 1.23 to 2.14; P=0.0007). Substantial heterogeneity was present between the trials and when this was accounted for with random effects, the test for interaction between treatment effect and epilepsy type was not significant (Chi^2=1.92; P=0.17). Secondary: The pooled HR for time to 12-month remission was 0.90 (95% CI, 0.69 to 1.18). The pooled HR for time to six-month remission was 0.92 (95% CI, 0.73 to 1.16). The pooled HR for time to first seizure was 0.85 (95% CI, 0.68 to 1.05).
Malamiri et al.[23] (2012) Phenobarbital 20 mg/kg (loading dose) followed by 5 mg/kg divided in two doses and given 12 hours and 24 hours after the loading dose (maintenance dose)	RCT Children two years of age and older (range three to 16 years) with convulsive status epilepticus and acute prolonged seizures who had experienced convulsions while attending	N=60 24 hours	Primary: Termination of all convulsive activity within 20 minutes of starting anticonvulsant infusion, without respiratory depression or hypotension and without another convulsion within one hour	Primary: Twenty-seven out of thirty patients (90%) in the valproate group had their seizures controlled in less than 20 minutes after beginning infusion. Twenty-three out of thirty patients (77%) in the phenobarbital group had their seizures controlled in less than 20 minutes after beginning infusion. There was no statistically significant difference found between the two groups (Fischer Exact Test; P=0.189). Secondary: Termination of seizures within 20 minutes and no seizure recurrence within 24 hours after termination of seizure was 77% in the valproate group (23 out of 30 participants). Termination of seizures within 20 minutes and no seizure recurrence within 24 hours after termination of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs sodium valproate 20 mg/kg diluted in 20 mL saline (loading dose) followed by continuous infusion of 1 mg/kg per hour, given 60 minutes after the bolus dose (maintenance dose)	emergency rooms and whose seizures were not controlled by a bolus of intravenous diazepam 0.2 mg/kg within five minutes		Secondary: Freedom from seizures for 24 hours after seizure termination, adverse effects	seizure was 37% in the phenobarbital group (11 out of 30 participants); (Fisher Exact Test; P=0.004). The overall occurrence of clinical adverse effects was 74% in the phenobarbital group and 24% in the valproate group (Fisher Exact Test; P<0.001). Seven patients in the valproate group had adverse effects: three reported lethargy, three reported vomiting, and one developed significant hypotension requiring vasopressor infusion. Seventeen patients in the phenobarbital group had adverse effects: 17 reported lethargy, four had vomiting, and one developed respiratory depression requiring bag and mask ventilation.
Painter et al.[24] (1999) Phenobarbital 25 µg/mL vs phenytoin 3 µg/mL	RCT, SB Neonates with seizures	N=59 5 years	Primary: Complete seizure control determined by electro-encephalography Secondary: Not reported	Primary: Phenobarbital controlled seizures completely in 43% of patients, while phenytoin controlled seizures in 45% of patients (P=1.00). Secondary: Not reported
Smith et al.[25] (2003) Phenobarbital vs carbamazepine	MA Children or adults with partial-onset seizures or generalized-onset tonic-clonic seizures	N=684 (4 trials) Variable duration	Primary: Time to withdrawal, time to 12-month remission, time to first seizure Secondary: Not reported	Primary: Time to withdrawal was significantly improved with carbamazepine over phenobarbital (HR, 1.63; 95% CI, 1.23 to 2.15). There was no significant difference between treatment groups for the time to 12-month remission and time to first seizure (HR, 0.87; 95% CI, 0.65 to 1.17 and HR, 0.85; 95% CI, 0.68 to 1.05 respectively). Further analysis of each type of seizure indicated that phenobarbital provided statistical benefit over carbamazepine for time to first partial-onset seizure, whereas carbamazepine demonstrated benefit over phenobarbital in patients for time to first generalized-onset tonic-clonic seizures.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Nolan et al.[26] (2015) Phenobarbital vs carbamazepine	MA Children or adults with newly onset partial or generalized epilepsy	N=836 (6 trials) Variable duration	Primary: Time to withdrawal Secondary: Time to 12-month remission, time to first seizure	Primary: Time to withdrawal was significantly improved with carbamazepine over phenobarbital (HR, 1.49; 95% CI, 1.15 to 1.94). Secondary: There was no significant difference between treatment groups for the time to 12-month remission and time to first seizure (HR, 0.93; 95% CI, 0.72 to 1.19 and HR, 0.86; 95% CI, 0.71 to 1.04 respectively).
Treiman et al.[27] (1998) Phenobarbital 15 mg/kg vs diazepam 0.15 mg/kg, followed by phenytoin 18 mg/kg vs lorazepam 0.1 mg/kg vs phenytoin 18 mg/kg	DB, MC, RCT Adults with overt or subtle generalized convulsive status epilepticus	N=518 5 years	Primary: Success (defined as cessation of all motor and electrical seizure activity within 20 minutes of start of drug infusion and no recurrence of seizure activity within the next 40 minutes), side effects, outcomes 30 days posttreatment Secondary: Not reported	Primary: For treatment success in overt status epilepticus, a significant difference overall in the frequency of success was found, reported as: lorazepam, 64.9%; phenobarbital, 58.2%; diazepam/phenytoin, 55.8%; and phenytoin, 43.6% (P<0.02 between all groups). For subtle status epilepticus, no significant differences were seen between treatment groups (P<0.18). Lorazepam showed significantly higher frequency of treatment success compared to phenytoin in a pairwise comparison of patients with overt status epilepticus (P<0.002). Pairwise comparisons among other individual treatments showed no significant differences. There were no significant differences among any of the treatment groups with respect to adverse effects or 30-day posttreatment outcomes. Secondary: Not reported
Yasiry et al.[28] (2014) Phenobarbital	MA Patients with status epilepticus who	N=Not reported (22 trials)	Primary: Cessation of seizure activity	Primary: Efficacy of levetiracetam was 68.5% (95% CI, 56.2 to 78.7), phenobarbital 73.6% (95% CI, 58.3 to 84.8), phenytoin 50.2% (95% CI, 34.2 to 66.1) and valproate 75.7% (95% CI, 63.7 to 84.8). Lacosamide studies were

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs lacosamide vs levetiracetam vs phenytoin vs valproate	have been resistant to initial therapy with benzodiazepines	Variable duration	Secondary: Not reported	excluded from the meta-analysis due to insufficient data. Secondary: Not reported
Miscellaneous				
Gerhardt et al.[29] (2011) Secobarbital 100 mg for one to two doses post-discharge vs placebo	DB, PC, RCT Patients 18 to 65 years of age who presented to the emergency department with a migraine (with or without aura); patients underwent standard treatment in the emergency department (intravenous fluids, antiemetics, ketorolac, and opiate rescue therapy as required)	N=50 1 day	Primary: Change in perceived headache pain using a 100 mm visual analog scale Secondary: Difference in self-reported headache resolution rate	Primary: The average change in reported headache pain for the placebo group was an increase of 3 mm (95% CI, −13 to 19 mm) at 24 hours after emergency department discharge. In the secobarbital group, the average change in reported headache pain was a decrease of 25 mm (95% CI, −13 to −38; P=0.01 vs placebo). Secondary: A total of 94% of patients receiving secobarbital self-reported partial or complete headache resolution (95 CI, 81 to 100) compared to 50% of patients receiving placebo (95% CI, 24 to 76; P=0.012). This translated to a number needed to treat of 2.3 patients treated with secobarbital to affect one additional partial or complete headache resolution.

Drug regimen abbreviations: BID=twice daily, QD=once daily, QID=four times daily, TID=three times daily

Study abbreviations: DB=double-blind, MA=meta-analysis, MC=multicenter, OL=open-label, PC=placebo-controlled, RCT=randomized controlled trial, SB=single-blind, SR=systematic review, XO=crossover
Other abbreviations: CI=confidence interval, HR=hazard ratio

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 9. Relative Cost of the Barbiturates

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Amobarbital	injection	Amytal sodium®	$$$$$	N/A
Butabarbital	tablet	Butisol sodium®	$$$-$$$$$	N/A
Phenobarbital	elixir, injection, tablet	N/A	N/A	$$
Secobarbital	capsule	Seconal sodium®	$$$$	N/A

*Generic is available in at least one dosage form or strength.
N/A=Not available

X. Conclusions

The barbiturates are approved for the treatment of insomnia and for the induction of sedation. Some of the agents are also approved for use as an adjunct to anesthesia, as well as for the treatment of seizure disorders. Phenobarbital is available in a generic formulation.[1-7]

Currently, there are no clinical guidelines that recommend the use of a barbiturate as first-line therapy for any condition in an outpatient setting.[9-18] There are few clinical trials available that directly compare the various agents. Studies suggest that the barbiturates are not as effective as other sedative-hypnotic agents.[19-29]

The use of barbiturates is associated with abuse and psychological/physical dependence. Individuals who have psychological dependence may increase the dosage or decrease the dosing interval. This behavior may result in a fatal overdose. Tolerance to the sedative-hypnotic effects occurs rapidly, and these agents lose their effectiveness

for sleep induction/maintenance after two weeks.[1-8] The use of barbiturates has been largely replaced by benzodiazepines.

There is insufficient evidence to support that one brand barbiturate is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand barbiturates within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand barbiturate is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Anxiolytics, Sedatives, and Hypnotics – Benzodiazepines
AHFS Class 282408
May 11, 2016

I. Overview

The benzodiazepines are approved for the treatment of anxiety disorders and insomnia.[1-13] Anxiety disorders include generalized anxiety disorder, panic disorder, posttraumatic stress disorder, and social phobia.[14] The agents approved for the treatment of anxiety include alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, lorazepam, and oxazepam.

The benzodiazepines that are approved solely for the treatment of insomnia include estazolam, flurazepam, temazepam, and triazolam. The key diagnostic feature of primary insomnia is difficulty initiating or maintaining sleep for at least three months, which causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.[14] Insomnia may be considered either an acute or chronic disorder (especially if associated with underlying illnesses).

Some of the benzodiazepines are also approved for the treatment of seizure disorders (monotherapy, adjunctive therapy, Lennox-Gastaut syndrome, and status epilepticus) and for the management of acute alcohol withdrawal. Clobazam is indicated only for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in patients two years of age or older.[5] Midazolam is a unique product compared to the other benzodiazepines; it is used for the induction/maintenance of general anesthesia and as a sedative (e.g., preoperative, prior to diagnostic/radiologic procedures, and intensive care unit sedation).[1-13]

Benzodiazepines potentiate the effects of gamma-aminobutyric acid and other inhibitory neurotransmitters.[1-13] Within the body there are three major benzodiazepine receptor subtypes. Benzodiazepine receptor subtype-1 is located throughout the central nervous system and is thought to mediate the anxiolytic, sedative and anticonvulsant properties of the benzodiazepines. Benzodiazepine receptor subtype-2 is located in the cortex, hippocampus, striatum, and spinal cord and is believed to mediate muscle relaxation, central nervous system depression, as well as psychomotor impairment. Depression of the central nervous system may range from mild impairment of task performance to hypnosis.[1,2] Benzodiazepine receptor subtype-3 is located throughout the body and glial cells, and is believed to contribute to tolerance and withdrawal when activated.[1,2] The benzodiazepines are mechanistically similar; however, they differ with regards to their pharmacokinetic properties. This includes onset, duration of action, and metabolism. Benzodiazepines with an active parent compound and rapid onset of action may produce euphoria and are more likely to be abused.[15-16]

The benzodiazepines that are included in this review are listed in Table 1. Prior to January 1, 2014 benzodiazepines were an excludable/optional drug class in accordance with the Omnibus Budget Reconciliation Act of 1990 (OBRA 90). This review encompasses all dosage forms and strengths, regardless of coverage status. All of the benzodiazepines are available in a generic formulation, with the exception of clobazam. This class was last reviewed in May 2014.

Table 1. Benzodiazepines Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Alprazolam	extended-release tablet, oral concentrate, orally disintegrating tablet, tablet	Xanax®*, Xanax XR®*	alprazolam
Chlordiazepoxide	capsule	N/A	chlordiazepoxide
Clobazam	oral suspension, tablet	Onfi®	none
Clonazepam	orally disintegrating tablet, tablet	Klonopin®*	clonazepam
Clorazepate	tablet	Tranxene T-Tab®*	clorazepate
Diazepam	injection, oral concentrate,	Diastat®*, Diastat	Diastat®*†, Diastat

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
	oral solution, rectal gel, tablet	AcuDial®*	AcuDial®*†, diazepam (excluding rectal gel)
Estazolam	tablet	N/A	estazolam
Flurazepam	capsule	N/A	flurazepam
Lorazepam	injection, oral concentrate, tablet	Ativan®*	lorazepam
Midazolam	injection, oral syrup	N/A	midazolam
Oxazepam	capsule	N/A	oxazepam
Temazepam	capsule	Restoril®*	temazepam
Triazolam	tablet	Halcion®*	triazolam

*Generic is available in at least one dosage form or strength.
†Generic product requires prior authorization.
PDL=Preferred Drug List
N/A=Not available

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the benzodiazepines are summarized in Table 2.

Table 2. Treatment Guidelines Using the Benzodiazepines

Clinical Guideline	Recommendation(s)

National Institute for Clinical Excellence: **Generalized Anxiety Disorder and Panic Disorder in Adults: management (2011)**[17]	<u>Stepped care for people with generalized anxiety disorder (GAD)</u>
	• If a person with GAD chooses drug treatment, offer a selective serotonin reuptake inhibitor (SSRI), specifically sertraline.
	• If sertraline is ineffective, offer an alternative SSRI or a serotonin–noradrenaline reuptake inhibitor (SNRI), taking into account the following factors:
	  o Tendency to produce a withdrawal syndrome (especially with paroxetine and venlafaxine).
	  o The side-effect profile and the potential for drug interactions.
	  o The risk of suicide and likelihood of toxicity in overdose (especially with venlafaxine).
	  o The person's prior experience of treatment with individual drugs (particularly adherence, effectiveness, side effects, experience of withdrawal syndrome and the person's preference).
	• If the person cannot tolerate SSRIs or SNRIs, consider offering pregabalin.
	• Do not offer a benzodiazepine for the treatment of GAD in primary or secondary care except as a short-term measure during crises.
	• Do not offer an antipsychotic for the treatment of GAD in primary care.
	
	<u>Panic disorder general considerations</u>
	• Benzodiazepines are associated with a less effective outcome in the long term and should not be prescribed for panic disorder.
	• Sedating antihistamines or antipsychotics should not be prescribed for panic disorder.
	• Interventions with evidence for the longest duration of effect are listed in descending order, where preference of the patient should be taken into account:
	  o Psychological therapy (i.e., cognitive behavioral therapy, structured problem solving, psychoeducation).
	  o Pharmacological therapy (antidepressant therapy).
	  o Self-help interventions (i.e., bibliotherapy, support groups, exercise, cognitive behavioral therapy via a computer interface).
	• Antidepressants should be the only pharmacologic intervention used in the longer term.
	• Two types of medication are considered in the guideline for the treatment of panic disorder, tricyclic antidepressants (TCAs) and SSRIs.

Clinical Guideline	Recommendation(s)
	• Unless otherwise indicated, an SSRI (e.g., paroxetine, fluvoxamine, citalopram) licensed for panic disorder should be offered. If an SSRI is not suitable or there is no improvement after a 12-week course and if further medication is appropriate, imipramine or clomipramine may be considered. • If the patient is showing improvement, the medication should be continued for at least six months after optimal dose is reached, after which the dose may be tapered slowly over an extended period of time to minimize the risk of discontinuation/withdrawal symptoms.
American Psychiatric Association: **Practice Guideline for the Treatment of Patients with Panic Disorder, Second Edition (2009)**[18]	• SSRIs, SNRIs, TCAs, and benzodiazepines have demonstrated efficacy in numerous controlled trials and are recommended for treatment of panic disorder. • Because SSRIs, SNRIs, TCAs, and benzodiazepines appear roughly comparable in their efficacy for panic disorder, selecting a medication involves considerations of side effects, pharmacological properties, potential drug interactions, prior treatment history, and comorbid medical and psychiatric conditions. • The relatively favorable safety and side effect profile of SSRIs and SNRIs makes them the best initial choice for many patients with panic disorder. • There is no evidence of differential efficacy between the SSRIs, although differences in the side-effect profile (e.g., potential for weight gain, discontinuation-related symptoms), half-life, propensity for drug interactions, and availability of generic formulations may be clinically relevant. They are safer than TCAs and monoamine oxidase inhibitors. They are rarely lethal in overdose and have few serious effects on cardiovascular function. • Venlafaxine extended release has been shown to be effective for panic disorder. It is generally well tolerated and has a side effect profile similar to the SSRIs. No systematic data are currently available supporting the use of duloxetine, in panic disorder, although its mechanism of action suggests it might be an effective agent. • Although TCAs are effective, the side effects and greater toxicity in overdose limit their acceptability to patients and clinical utility. Given the equivalency of TCAs in treating depression, there is little reason to expect other TCAs to work less well for panic disorder. TCAs that are more noradrenergic (e.g., desipramine, maprotiline) may be less effective than agents that are more serotonergic. • SSRIs, SNRIs, and TCAs are all preferable to benzodiazepines as monotherapies for patients with comorbid depression or substance use disorders. Benzodiazepines may be especially useful adjunctively with antidepressants to treat residual anxiety symptoms. • Benzodiazepines may be preferred for patients with very distressing or impairing symptoms in whom rapid symptom control is critical. The benefit of more rapid response to benzodiazepines must be balanced against the possibilities of troublesome side effects and physiological dependence that may lead to difficulty discontinuing the medication. • MAOIs appear effective for panic disorder but, because of their safety profile, they are generally reserved for patients who have failed to respond to several first-line treatments. • Neither trazodone nor nefazodone can be recommended as a first-line treatment for panic disorder. There is minimal support for the use of trazodone in panic disorder and it appears less effective than imipramine and alprazolam. There are a few small, uncontrolled studies showing benefits of nefazodone in some patients with panic disorder; however, its use has been limited by concerns about liver toxicity. • Bupropion was effective in one small trial and ineffective in another. It cannot be recommended as a first line treatment for panic disorder. • Other medications with less empirical data may be considered as monotherapies

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	or adjunctive treatments for panic disorder when patients have failed to respond to several standard treatments or based on other individual circumstances.
American Academy of Child and Adolescent Psychiatry: **Practice Parameter for the Assessment and Treatment of Children and Adolescents With Obsessive-Compulsive Disorder (2012)**[19]	• The psychiatric assessment of children and adolescents should routinely screen for the presence of obsessions and/or compulsions or repetitive behaviors. • If screening suggests obsessive-compulsive symptoms, clinicians should fully evaluate the child using the DSM-IV-TR criteria and scalar assessment. • A complete psychiatric evaluation should be performed, including information from all available sources and compromising standard elements of history and a mental state examination, with attention to the presence of commonly occurring comorbid psychiatric disorders. • It is possible that three out of four children with obsessive-compulsive disorder (OCD) meet criteria for at least one comorbid diagnosis, and these children have lower response rates to CBT than children without comorbid diagnoses. • Identification of MDD and bipolar disorder is very important before initiating treatment with a SSRI. • Comorbid eating disorders are infrequent in younger children; however, comorbid eating disorders become more prevalent in adolescents. • A full medical, developmental, family and school history should be included with the psychiatric history and examination. • CBT is the first-line treatment for mild to moderate OCD in children, whenever possible. • For moderate to severe OCD, medication is indicated in addition to CBT. • Serotonin reuptake inhibitors (SRIs) are the first-line medications recommended for OCD in children, including clomipramine (a TCA) and certain SSRIs (fluoxetine, fluvoxamine, paroxetine and sertraline). • There is no SRI that is proven to be more efficacious over another. • The modality of assigned treatment should be guided by empirical evidence on the moderators and predictors of treatment response. • Multimodal treatment with CBT and medication is recommended if CBT fails to achieve a clinical response after several months or in more severe cases. • Medication augmentation strategies are reserved for treatment-resistant cases in which impairments are deemed moderate in at least one important domain of function despite adequate monotherapy. • Adding clomipramine to an SSRI is a useful medication augmentation strategy. • Augmenting with an atypical neuroleptic is also a strategy employed by experts (e.g. haloperidol and risperidone combined) based on studies in adults with OCD; however, controlled data for the use of atypical antipsychotics in children with OCD does not exist. • A minimum of two adequate SSRI trials or an SSRI and clomipramine trial is recommended before atypical augmentation. • Empirically validated medication and psychosocial treatments for comorbid disorders should be considered.
American Psychiatric Association: **Practice Guideline for the Treatment of Patients with Obsessive-Compulsive Disorder (2007)**[20]	<u>General considerations</u> • OCD is a chronic illness which typically waxes and wanes. • Patients who have symptoms interfering with daily functioning should be treated. • Clinical remission and recovery may not always occur and will not occur rapidly. • Goals of treatment include improving symptoms, patient functioning, and quality of life. <u>Initial treatment options</u> • The choice of treatment depends on the patient's ability to comply with therapy, whether psychotherapy, pharmacotherapy, or both. • First-line treatments include cognitive-behavioral therapy, SRIs, or a combination of the two. The choice depends on past treatment history, comorbid psychiatric conditions, severity of symptoms, and functional limitations.

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	• Cognitive-behavioral therapy or SRI therapy may be used alone or in combination, and combination therapy may be considered in patients who do not respond fully to monotherapy, those with severe symptoms, those with comorbid psychiatric illnesses for which an SRI is indicated, or in patients who wish to limit SRI exposure. • All SRIs appear to be equally effective, though patients may respond to agents differently. • Prescribers should consider the safety, side effects, FDA warnings, drug interactions, past response to treatment, and comorbid medical conditions when choosing a medication for treatment. • Most patients do not experience a significant improvement until four to six weeks after treatment initiation, and some may ultimately respond after as many as 10 to 12 weeks. • Patients not responding after 10 to 12 weeks may respond to a higher dose of the same medication. <u>Changing treatments and pursuing sequential treatment trials</u> • Augmentation strategies may be preferred to switching strategies in patients who have a partial response to the initial treatment. • Augmentation of SRIs with trials of different antipsychotic medications or with cognitive-behavioral therapy or augmentation of cognitive-behavioral therapy with an SRI. • Patients who do not respond to their first SRI may have their medication switched to a different SRI. A switch to venlafaxine is less likely to produce an adequate response. • For patients who have not benefitted from their first SSRI trial, a switch to mirtazapine can be considered. • After first- and second-line treatments and well-supported augmentation strategies have been exhausted, less well-supported treatment strategies may be considered. These include augmenting SRIs with clomipramine, buspirone, pindolol, riluzole, or once- weekly oral morphine sulfate. • Evidence for beneficial effects of benzodiazepines as monotherapy for OCD is limited to case reports with clonazepam and alprazolam. Modest doses of benzodiazepines may relieve anxiety and distress in OCD without directly diminishing the frequency or duration of obsessions or compulsions. Given their limited evidence for efficacy, benzodiazepines cannot be recommended as monotherapy for OCD, except in those rare individuals who are unable or unwilling to take standard anti-OCD medications.
American Academy of Child and Adolescent Psychiatry: **Practice Parameter for the Assessment and Treatment of Children and Adolescents With Posttraumatic Stress Disorder (2010)**[21]	• The psychiatric evaluation of children and adolescents should routinely include questions about traumatic experiences and posttraumatic stress disorder (PTSD) symptoms. • If the evaluation indicates symptoms of PTSD, the clinician should formally determine if PTSD is present, the severity of PTSD symptoms and the degree of functional impairment. Caregivers should be included in the formal evaluation. • A differential diagnosis should be conducted in order to rule out diagnoses with symptoms that can mimic PTSD symptoms. • The treatment plan should be comprehensive in approach and should consider the severity of symptoms and impairment, as well as comorbid psychiatric conditions. • Trauma-focused psychotherapies should be considered first-line in children and adolescents with PTSD, including psychoanalytic, attachment and cognitive behavioral treatment models. • SSRIs can be considered for treatment of children and adolescents with PTSD. • The effect of SSRIs in children with PTSD may be more consistent with a placebo effect.

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	• Other medications such as clonidine and propranolol may be useful in decreasing symptoms of hyperarousal, and anticonvulsants may beneficial in treating PTSD symptoms other than avoidance. • Benzodiazepines have not been found to be beneficial in treating PTSD symptoms. • School-based accommodations are recommended for children with PTSD, especially in children with school-based trauma, such as bullying. • The use of restrictive, "rebirthing," binding or other coercive therapies are not recommended. • Screening for PTSD in the school or community should be conducted after traumatic events that affect significant numbers of children.
American Psychiatric Association: **Guideline Watch: Practice Guideline for the Treatment of Patients with Acute Stress Disorder and Posttraumatic Stress Disorder (2009)**[22]	• Meta-analyses and several randomized controlled trials published since 2004 support the greater efficacy of SSRIs and SNRIs over placebo for non-combat-related PTSD. • The evidence base for pharmacological intervention in combat-related PTSD has not been significantly augmented by recent studies. Studies suggest that SSRIs may not be recommended with the previous level of confidence for the treatment of PTSD in this particular population. Further research is needed to answer why these populations have been shown to have differential responses to SSRI treatment. • As described in the 2004 guideline, no significant differences among antidepressants, including the SSRIs, were found in the few head-to-head studies then available. Since that time, studies have been published comparing nefazodone and sertraline, venlafaxine and sertraline, the SNRI reboxetine and fluvoxamine, and fluoxetine, moclobemide, and tianeptine. These studies have generally demonstrated the greater efficacy of antidepressants to placebo but have done little to clarify the relative utility of these different antidepressants. • There is a relatively robust evidence basis for pharmacological treatment with antidepressant medications (particularly SSRIs and SNRIs for noncombat PTSD) as compared to other classes of medications. • Comparison of other treatments with the SSRIs and SNRIs is complicated by methodological differences in the available studies. SSRIs and SNRIs have mostly been studied in rigorous trials compared to placebo; other agents have been studied against "treatment as usual" or as augmentation agents in patients with refractory illness.
American Psychiatric Association: **Practice Guideline for the Treatment of Patients with Acute Stress Disorder and Posttraumatic Stress Disorder (2004)**[23]	• Goals of treatment for patients with PTSD and acute stress disorder (ASD) include lessening the severity of symptoms and preventing trauma-related comorbid conditions. • Clinical trial data and randomized studies are limited and difficult to perform. • Treatment includes pharmacotherapy, psychotherapy and supportive measures. • SSRIs are first-line therapy for PTSD and ASD and if found effective, treatment should be continued in order to continue to see benefit. • Second-line treatment agents include TCAs (specifically amitriptyline and imipramine, but not desipramine) and MAOIs. • Benzodiazepines should not be used as monotherapy, but may be effective as sedatives and anxiolytics. • Atypical antipsychotics may be necessary for patients experiencing psychotic symptoms. • Anticonvulsants (divalproex, carbamazepine, topiramate and lamotrigine) have produced mixed results for treating PTSD and ASD but may prove to be beneficial. • Limited data exists for the use of adrenergic inhibitors and their use is not part of the guideline at this time. • An adequate trial of therapy requires a minimum of three months of treatment. If treatment is effective, it should be continued for up to 12 months or longer.

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American Academy of Sleep Medicine: **Clinical Guideline for the Evaluation and Management of Chronic Insomnia in Adults (2008)**[24]	• The primary treatment goals are to improve sleep quality/quantity and to improve insomnia related daytime impairments.
	• Short-term hypnotic treatment should be supplemented with behavioral and cognitive therapies when possible.
	• When pharmacotherapy is utilized, the choice of a specific pharmacological agent should be directed by: symptom pattern, treatment goals, past treatment responses, patient preference, availability of other treatments, comorbid conditions, contraindications, concurrent medication interactions, and side effects.
	• For patients with primary insomnia, when pharmacologic treatment is utilized alone or in combination therapy, the recommended general sequence of medication trials is:
	  o Short-intermediate acting benzodiazepine receptor agonists or ramelteon.
	  o Alternate short-intermediate acting benzodiazepine receptor agonists or ramelteon if the initial agent has been unsuccessful.
	  o Sedating antidepressants, especially when used in conjunction with treating comorbid depression/anxiety. Examples of these include trazodone, amitriptyline, doxepin, and mirtazapine.
	  o Combined benzodiazepine receptor agonists or ramelteon and sedating antidepressant.
	  o Other sedating agents. Examples include anti-epilepsy medications (gabapentin, tiagabine) and atypical antipsychotics (quetiapine and olanzapine). These medications may only be suitable for patients with comorbid insomnia who may benefit from the primary action of these drugs as well as from the sedating effect.
	• Over-the-counter antihistamine or antihistamine/analgesic type drugs (over-the-counter "sleep aids"), as well as herbal and nutritional substances (e.g., valerian and melatonin), are not recommended in the treatment of chronic insomnia due to the relative lack of efficacy and safety data.
	• Older approved drugs for insomnia including barbiturates, barbiturate-type drugs and chloral hydrate are not recommended for the treatment of insomnia.
	• Pharmacological treatment should be accompanied by patient education regarding treatment goals, safety concerns, potential side effects and drug interactions, other treatment modalities (cognitive and behavioral treatments), potential for dosage escalation, and rebound insomnia.
	• Patients should be followed on a regular basis, every few weeks in the initial period of treatment when possible, to assess for effectiveness, possible side effects, and the need for ongoing medication.
	• Efforts should be made to employ the lowest effective maintenance dosage of medication and to taper medication when conditions allow. Medication tapering and discontinuation are facilitated by cognitive behavioral therapy for insomnia.
	• Chronic hypnotic medication may be indicated for long-term use in those with severe or refractory insomnia or chronic comorbid illness. Whenever possible, patients should receive an adequate trial of cognitive behavioral treatment during long-term pharmacotherapy.
	• Long-term prescribing should be accompanied by consistent follow-up, ongoing assessment of effectiveness, monitoring for adverse effects, and evaluation for new onset or exacerbation of existing comorbid disorders.
	• Long-term administration may be nightly, intermittent (e.g., three nights per week), or as needed.

National Institutes of Health: **Manifestations and Management of**	<u>Behavioral and cognitive therapies</u> • Behavioral methods include relaxation training, stimulus control, and sleep restriction. • Cognitive therapy methods have been added to behavioral methods and include

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Chronic Insomnia in Adults (2005)[25]	cognitive restructuring, in which anxiety-producing beliefs and erroneous beliefs about sleep and sleep loss are specifically targeted. • The combination of cognitive methods and behavioral methods has been found to be as effective as prescription medications for short-term treatment of chronic insomnia. The beneficial effects of cognitive-behavioral therapy may last well beyond the termination of active treatment. <u>Benzodiazepine receptor agonists</u> • Benzodiazepine receptor agonists include benzodiazepines (e.g., flurazepam, temazepam, and triazolam) as well as nonbenzodiazepine-structured anxiolytic agents acting at benzodiazepine receptors (e.g., eszopiclone, zaleplon, and zolpidem). • Benzodiazepine receptor agonists have been shown to be effective in the short-term management of insomnia. • The frequency and severity of the adverse effects are much lower for the newer benzodiazepine receptor agonists, most likely because these agents have shorter half-lives. • In the short term, abuse of the benzodiazepine receptor agonists is not a major problem, but problems associated with their long-term use require further study. • Barbiturates (e.g., phenobarbital) have been used in the treatment of insomnia, however, short-term and long-term studies are lacking; such drugs bear significant risks and are not recommended in the treatment of chronic insomnia. <u>Other prescription medications</u> • Other sedating medications have been used in the treatment of insomnia. These include barbiturates and antipsychotics. • Studies demonstrating the usefulness of these medications for either short- or long-term management of insomnia are lacking. • All of these agents have significant risks. Thus, their use in the treatment of chronic insomnia cannot be recommended. <u>Antidepressants</u> • Antidepressants (especially trazodone) are often prescribed for insomnia, although they are not FDA-approved for this purpose. • In short-term use, trazodone and doxepin have been shown to have some beneficial effects, but there are no studies on long-term use. • Data on other antidepressants (e.g., amitriptyline and mirtazapine) in individuals with chronic insomnia are lacking. • These guidelines were published prior to the FDA approval of ramelteon. <u>Nonprescription medications</u> • Antihistamines are the most commonly used over-the-counter treatments for chronic insomnia, but there is no systematic evidence for efficacy and there are significant concerns about risks of these medications. • Adverse effects include residual daytime sedation, diminished cognitive function, and delirium, the latter being of particular concern in the elderly. Other adverse effects include dry mouth, blurred vision, urinary retention, constipation, and risk of increased intraocular pressure in individuals with narrow angle glaucoma.
International League Against Epilepsy: **Updated International League Against Epilepsy Evidence Review of Antiepileptic Drug**	<u>Adults with partial onset seizures</u> • Carbamazepine, levetiracetam, phenytoin, and zonisamide are established treatments as initial monotherapy for adults with newly diagnosed or untreated partial-onset seizures. Valproic acid is probably effective and gabapentin, lamotrigine, oxcarbazepine, phenobarbital, topiramate and vigabatrin are possibly effective for partial onset seizures. Clonazepam and primidone are potentially efficacious/effective.

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Efficacy and Effectiveness as Initial Monotherapy for Epileptic Seizures and Syndromes (2013)[26]	<u>Children with partial-onset seizures</u> • Oxcarbazepine is established as initial monotherapy for children with newly diagnosed or untreated partial-onset seizures. Carbamazepine, phenobarbital, phenytoin, topiramate, valproic acid and vigabatrin may be effective and clobazam, clonazepam, lamotrigine and zonisamide are potentially efficacious/ effective. <u>Elderly adults with partial-onset seizures</u> • Gabapentin and lamotrigine are effective as initial monotherapy for elderly adults with newly diagnosed or untreated partial-onset seizures. Carbamazepine may be effective and topiramate and valproic acid are potentially efficacious/effective. <u>Adults with generalized-onset tonic-clonic seizures</u> • Carbamazepine, lamotrigine, oxcarbazepine, phenobarbital, phenytoin, topiramate and valproic acid are possibly effective as initial monotherapy for adults with newly diagnosed or untreated generalized-onset tonic-clonic seizures. Gabapentin, levetiracetam and vigabatrin are potentially efficacious/effective. Carbamazepine and phenytoin may precipitate or aggravate generalized-onset tonic-clonic seizures. <u>Children with generalized-onset tonic-clonic seizures</u> • Carbamazepine, phenobarbital, phenytoin, topiramate and valproic acid are possibly effective for children with newly diagnosed or untreated generalized onset tonic-clonic seizures. Oxcarbazepine is potentially efficacious/effective. Carbamazepine and phenytoin may precipitate or aggravate generalized-onset tonic-clonic seizures. <u>Children with absence seizures</u> • Ethosuximide and valproic acid are established treatments for children with newly diagnosed or untreated absence seizures. Lamotrigine is possibly efficacious/effective as initial monotherapy. Gabapentin is inefficacious/ineffective for children with absence seizures. • Based on scattered reports, the following antiepileptic drugs may precipitate or aggravate absence seizures: carbamazepine, oxcarbazepine, phenobarbital, phenytoin, tiagabine and vigabatrin. No conclusion can be made about levetiracetam efficacy/effectiveness for absence seizures since the failed class III placebo-controlled trial was uninformative. <u>Children with benign childhood epilepsy with centrotemporal spikes</u> • Carbamazepine and valproic acid are possibly effective as initial monotherapy for children with benign childhood epilepsy with centrotemporal spikes. Gabapentin, levetiracetam, oxcarbazepine, and sulthiame* are potentially efficacious/effective. <u>Juvenile myoclonic epilepsy</u> • Topiramate and valproic acid are potentially efficacious/effective for patients with newly diagnosed juvenile myoclonic epilepsy. Carbamazepine, gabapentin, oxcarbazepine, phenytoin, tiagabine and vigabatrin may precipitate or aggravate absence seizures, myoclonic seizures, and in some cases generalized tonic-clonic seizures. There has been a report that lamotrigine may exacerbate seizures in juvenile myoclonic epilepsy.
National Institute for Clinical Excellence: **The Epilepsies: The Diagnosis and**	<u>Treatment of atonic or tonic seizures</u> • First-line treatment in children, young people, and adults with tonic or atonic seizure: sodium valproate.

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Management of the Epilepsies in Adults and Children in Primary and Secondary Care (2012)[27] **Reaffirmed 2014**	• Offer lamotrigine as adjunctive treatment if sodium valproate is ineffective or not tolerated. • Discuss with a tertiary epilepsy specialist if adjunctive treatment is ineffective or not tolerated. Other antiepileptics that may be considered by the tertiary epilepsy specialist are rufinamide and topiramate. • Do not offer carbamazepine, gabapentin, oxcarbazepine, pregabalin, tiagabine or vigabatrin. <u>Treatment of generalized tonic-clonic seizures</u> • First-line treatment in children, young people, and adults with newly diagnosed focal seizures: sodium valproate. • Offer lamotrigine if sodium valproate is unsuitable. • Consider carbamazepine and oxcarbazepine. • Offer clobazam, lamotrigine, levetiracetam, sodium valproate, or topiramate as adjunctive treatment to all patients if first-line treatments are ineffective or not tolerated. • If there are absence or myoclonic seizures, or if juvenile myoclonic epilepsy is suspected, do not offer carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine, or vigabatrin. <u>Treatment of infantile spasms</u> • Discuss with, or refer to, a tertiary pediatric epilepsy specialist when an infant presents with infantile spasms. • Offer a steroid or vigabatrin as first-line treatment to infants with infantile spasms that are not due to tuberous sclerosis. • Offer vigabatrin as first-line treatment to infant with infantile spasms due to tuberous sclerosis. If vigabatrin is ineffective, offer a steroid. <u>Treatment of Lennox-Gastaut Syndrome</u> • Discuss with, or refer to, a tertiary pediatric epilepsy specialist when a child presents with suspected Lennox-Gastaut syndrome. • Offer sodium valproate as first-line treatment to children with Lennox-Gastaut syndrome. • Offer lamotrigine as adjunctive treatment if first-line treatments are ineffective or not tolerated. • Discuss with a tertiary epilepsy specialist if adjunctive treatment is ineffective or not tolerated. Other antiepileptics that may be considered by the tertiary epilepsy specialist are rufinamide and topiramate. • Do not offer carbamazepine, gabapentin, oxcarbazepine, pregabalin, tiagabine or vigabatrin. • Only offer felbamate in centers providing tertiary epilepsy specialist care and when treatment with all of the antiepileptics listed above have proved ineffective or not tolerated. <u>Treatment of myoclonic seizures</u> • First-line treatment in children, young people, and adults with myoclonic seizures: valproate, unless unsuitable. • Consider levetiracetam or topiramate if sodium valproate is unsuitable or not tolerated. • Offer levetiracetam, sodium valproate, or topiramate as adjunctive treatment to all patients if first-line treatments are ineffective or not tolerated. • If adjunctive treatment is ineffective or not tolerated, discuss with, or refer to, a tertiary epilepsy specialist or consider clobazam, clonazepam, piracetam*, or zonisamide. • Do not offer carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin,

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	tiagabine or vigabatrin. <u>Treatment of absence seizures</u> • First-line treatment in children, young people, and adults with absence seizures: ethosuximide or sodium valproate. If there is a high risk of generalized tonic-clonic seizures, offer sodium valproate first, unless it is unsuitable. • Offer lamotrigine if ethosuximide and sodium valproate are unsuitable, ineffective, or not tolerated. • If two first-line antiepileptics are ineffective, consider a combination of two of these three antiepileptics as adjunctive treatment: ethosuximide, lamotrigine, or sodium valproate. • If adjunctive treatment is ineffective or not tolerated, discuss with, or refer to, a tertiary epilepsy specialist and consider clobazam, clonazepam, levetiracetam, topiramate or zonisamide. • Do not offer carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin. <u>Treatment of focal seizures</u> • First-line treatment in children, young people, and adults with newly diagnosed focal seizures: carbamazepine or lamotrigine. • Offer levetiracetam, oxcarbazepine, or sodium valproate if first-line treatments are unsuitable or not tolerated. If the first antiepileptic tried is ineffective, offer an alternative from the five antiepileptics noted above. • Consider adjunctive treatment if a second well-tolerated antiepileptic is ineffective. • For refractory focal seizures, offer carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate, or topiramate as adjunctive treatment to all patients with focal seizures if first-line treatments are ineffective or not tolerated. • For refractory focal seizures, if adjunctive treatment is ineffective or not tolerated, discuss with, or refer to, a tertiary epilepsy specialist. Other antiepileptics that may be considered by a specialist are eslicarbazepine acetate*, lacosamide, phenobarbital, phenytoin, pregabalin, tiagabine, vigabatrin and zonisamide. <u>Treatment of Dravet syndrome</u> • Discuss with, or refer to, a tertiary pediatric epilepsy specialist when a child presents with suspected Dravet syndrome. • Consider sodium valproate or topiramate as first-line treatment in children with Dravet syndrome. • Discuss with a tertiary epilepsy specialist if first-line treatments are ineffective or not tolerated, and consider clobazam or stiripentol as adjunctive treatment. • Do not offer carbamazepine, gabapentin, lamotrigine, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin. <u>Treatment of benign epilepsy with centrotemporal spikes, Panayiotopoulos syndrome, or late-onset childhood occipital epilepsy (Gastaut type)</u> • Discuss with the child or young person, and their family and/or caretakers, whether antiepileptic drug treatment is indicated. • Offer carbamazepine or lamotrigine as first-line treatment to children and young people. • Offer levetiracetam, oxcarbazepine, or sodium valproate if first-line treatments are unsuitable or not tolerated. If the first antiepileptic drug tried is ineffective, offer an alternative from the five antiepileptics noted above. • Consider adjunctive treatment if a second well-tolerated antiepileptic drug is

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	ineffective. • Offer carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate, or topiramate as adjunctive treatment if first-line treatments are ineffective or not tolerated. • If adjunctive treatment is ineffective or not tolerated, discuss with, or refer to, a tertiary epilepsy specialist. Other antiepileptic drugs that may be considered are eslicarbazepine acetate*, lacosamide, phenobarbital, phenytoin, pregabalin, tiagabine, vigabatrin and zonisamide. <u>Treatment of idiopathic generalized epilepsy</u> • First-line treatment in children, young people, and adults with idiopathic generalized epilepsy: sodium valproate. • Offer lamotrigine if sodium valproate is unsuitable or not tolerated. • Consider topiramate. • Offer lamotrigine, levetiracetam, sodium valproate, or topiramate as adjunctive treatment if first-line treatments are ineffective or not tolerated. • If adjunctive treatment is ineffective or not tolerated, discuss with, or refer to, a tertiary epilepsy specialist and consider clobazam, clonazepam or zonisamide. • Do not offer carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin. <u>Treatment of juvenile myoclonic epilepsy</u> • First-line treatment in children, young people, and adults with juvenile myoclonic epilepsy: sodium valproate. • Consider lamotrigine, levetiracetam, or topiramate if sodium valproate is unsuitable or not tolerated. • Offer lamotrigine, levetiracetam, sodium valproate, or topiramate as adjunctive treatment if first-line treatments are ineffective or not tolerated. • If adjunctive treatment is ineffective or not tolerated, discuss with, or refer to, a tertiary epilepsy specialist and consider clobazam, clonazepam, or zonisamide. • Do not offer carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin. <u>Treatment of epilepsy with generalized tonic-clonic seizures only</u> • First-line treatment in children, young people, and adults with epilepsy with generalized tonic-clonic seizures only: lamotrigine, sodium valproate. • Consider carbamazepine or oxcarbazepine. • Offer clobazam, lamotrigine, levetiracetam, sodium valproate, or topiramate as adjunctive treatment if first-line treatments are ineffective or not tolerated. <u>Treatment of childhood absence epilepsy, juvenile absence epilepsy, or other absence epilepsy syndromes</u> • First-line treatment in children, young people, and adults: ethosuximide, sodium valproate. • Offer lamotrigine if first-line treatments are unsuitable, ineffective, or not tolerated. • If two first-line antiepileptic drugs are ineffective, consider a combination of two of these three antiepileptic drugs adjunctive treatment: ethosuximide, lamotrigine, or sodium valproate. • If adjunctive treatment is ineffective or not tolerated, discuss with, or refer to, a tertiary epilepsy specialist and consider clobazam, clonazepam, levetiracetam, topiramate, or zonisamide. • Do not offer carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin.
American Academy of	• To date, there is insufficient evidence to support the use of agents other than

Clinical Guideline	Recommendation(s)
Neurology: **Evidence-Based Guideline Update: Medical Treatment of Infantile Spasms: Report of the Guideline Development Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society (2012)**[28] **Reaffirmed 2015**	adrenocorticotropic hormone, and vigabatrin. • Low-dose adrenocorticotropic hormone should be considered as an alternative to high-dose adrenocorticotropic hormone for treatment of infantile spasms. • Adrenocorticotropic hormone or vigabatrin may be offered for short-term treatment of infantile spasms. Evidence suggests that adrenocorticotropic hormone may be offered over vigabatrin. • There is insufficient evidence to recommend the use of dexamethasone, prednisolone and methylprednisolone as being as effective as adrenocorticotropic hormone for short-term treatment of infantile spasms. • The data is insufficient to recommend other therapies (valproic acid, vitamin B6, nitrazepam, levetiracetam, zonisamide, topiramate, the ketogenic diet, or novel/combination therapies) for the treatment of infantile spasms. • Hormonal therapy (adrenocorticotropic hormone or prednisolone) may be considered for use in preference to vigabatrin in infants with cryptogenic infantile spasms, to possibly improve developmental outcome. • A shorter lag time to treatment of infantile spasms with either hormonal therapy or vigabatrin may be considered to improve long-term cognitive outcomes.
Infantile Spasms Working Group: **Infantile Spasms: A U.S. Consensus Report (2010)**[29]	• To improve outcomes in infantile spasms, the goals include early recognition and diagnosis, short-term treatment with a first-line therapy, timely electroencephalography evaluation to assess treatment effectiveness and prompt treatment modification if indicated. • Effective treatment should produce both cessation of spasms and resolution of hypsarrhythmia on electroencephalography. • The dose of the chosen first-line agent should be adjusted to achieve the maximum effective dose in as short amount of time as clinically indicated. • There is insufficient evidence to recommend the best approach in events of relapse. Possible treatment options include using the previously effective agent and dose, using the previously effective agent at the maximum dose or using a new agent. • Adrenocorticotropic hormone is considered first-line therapy for infantile spasms. There is insufficient evidence to recommend the optimal dose and duration of treatment, although short duration is preferable to avoid adverse events. Treatment with the maximum dose of adrenocorticotropic hormone should be continued for two weeks followed by taper and evaluation of treatment response. • Vigabatrin is considered first-line therapy for infantile spasms, especially in patients with comorbid tuberous sclerosis complex. Vigabatrin should be initiated at 50 mg/kg/day and increased up to 100 to 150 mg/kg/day if indicated. Efficacy should be assessed within two weeks following dose titration. Responders to treatment may continue therapy for six to nine months, with continued ophthalmic evaluation. • No recommendations can be given with regard to oral corticosteroids in the treatment of infantile spasms. • Ketogenic diet may be considered as second-line therapy when first-line therapies fail or are inappropriate. • Patients with refractory spasms, concomitant partial seizures or focal abnormalities on the electroencephalography may be evaluated for surgery.
European Federation of Neurological Societies: **Guideline on the Management of Status Epilepticus (2010)**[30]	<u>Initial pharmacological treatment for generalized convulsive status epilepticus and non-convulsive status epilepticus</u> • The preferred treatment is intravenous administration of lorazepam 0.1 mg/kg; however, depending on the patients' general medical condition, treatment can be started at a lower dose of 4 mg, to be repeated if seizures continue for >10 minutes after first injection. • If lorazepam is not available, diazepam 10 mg (route of administration not specified) directly followed by phenytoin (15 to 18 mg/kg) or equivalent

Clinical Guideline	Recommendation(s)
	fosphenytoin. • General management of refractory status epilepticus includes treatment in an intensive care unit. <u>Pharmacological treatment for refractory generalized convulsive status epilepticus and subtle status epilepticus</u> • Immediate infusions of anesthetic doses of midazolam, propofol or barbiturates are recommended due to the progressive risk of brain and systemic damage. • If midazolam is given, seizure suppression is recommended. This goal should be maintained for at least 24 hours. Simultaneous initiation of the chronic medication the patient with be treated with in the future should be initiated. • For elderly patients in whom intubation and artificial ventilation would not be justified, further non-anesthetizing anticonvulsants may be tried. <u>Pharmacological treatment for refractory non-convulsive status epilepticus</u> • Due to poor evidence and lack of any head-to-head trials, no recommendations can be made regarding which of the non-anaesthetizing anticonvulsants should be the drug of choice. • Recommendations include phenobarbital, valproic acid and levetiracetam. • If treatment regimen includes the administration of anesthetics, use the same protocol as refractory generalized convulsive status epilepticus.
Journal of Child Neurology: **Treatment of Pediatric Epilepsy: Expert Opinion (2005)**[31]	• Rectal diazepam is the treatment of choice for acute treatment of a prolonged febrile seizure or cluster of seizures. • Intravenous phenobarbital is the treatment of choice and intravenous lorazepam or fosphenytoin are also first line options for the initial therapy of neonatal status epilepticus. • Lorazepam is the treatment of choice and intravenous diazepam is also a first line option for the initial therapy of all types of pediatric status epilepticus. • Rectal diazepam or fosphenytoin are the first-line options for generalized tonic-clonic status epilepticus. • Benzodiazepines were not identified as being first-line or treatment of choice for the following: complex partial status epilepticus, absence status epilepticus, symptomatic myoclonic and generalized tonic-clonic seizures, complex partial seizures, infantile spasms, Lennox-Gastaut syndrome, benign childhood epilepsy with centro-temporal spikes, childhood absence epilepsy, juvenile absence epilepsy, and juvenile myoclonic epilepsy.
American Academy of Neurology/ American Epilepsy Society: **Efficacy and Tolerability of the New Antiepileptic Drugs I: Treatment of New Onset Epilepsy (2004)**[32]	• At this time, there are no studies that assessed the efficacy and tolerability of the new antiepileptic drugs (gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate and zonisamide) in adults with newly diagnosed (exclusively) idiopathic or symptomatic generalized epilepsy. • Lamotrigine can be included in the treatment options for children with newly diagnosed absence seizures. At this time, there is insufficient evidence to recommend use of gabapentin, levetiracetam, oxcarbazepine, tiagabine, topiramate and zonisamide in children with newly diagnosed (exclusively) idiopathic or symptomatic generalized epilepsy. • Patients with newly diagnosed partial or mixed seizure disorders who require treatment can be initiated on carbamazepine, gabapentin, lamotrigine, oxcarbazepine, phenobarbital, phenytoin, topiramate or valproic acid. The choice of drug will depend on individual patient characteristics. At this time, there is insufficient evidence to determine effectiveness in newly diagnosed patients for levetiracetam, tiagabine and zonisamide.
American Academy of Neurology/ American Epilepsy Society: **Efficacy and**	• Topiramate may be used for the treatment of refractory generalized tonic-clonic seizures in adults and children. At this time, there is insufficient evidence to recommend use of gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine or zonisamide for refractory generalized tonic-clonic seizures in adults

Clinical Guideline	Recommendation(s)
Tolerability of the New Antiepileptic Drugs II: Treatment of Refractory Epilepsy (2004)[33]	and children. • Lamotrigine and topiramate may be used to treat drop attacks associated with Lennox Gastaut syndrome in adults and children. • Lamotrigine, oxcarbazepine and topiramate can be used as monotherapy in adults with refractory partial epilepsy. At this time, there is insufficient evidence to recommend use of gabapentin, levetiracetam, tiagabine or zonisamide in monotherapy for refractory partial epilepsy. • Gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate and zonisamide are appropriate treatment options as adjunctive therapy for refractory partial epilepsy in adults. • Gabapentin, lamotrigine, oxcarbazepine and topiramate may be used as adjunctive treatment of refractory partial seizures in children. At this time, there is insufficient evidence to recommend levetiracetam, tiagabine or zonisamide as adjunctive treatment of refractory partial seizures in children.
National Institute for Health and Clinical Excellence: **Alcohol-Use Disorders: Diagnosis, Assessment and Management of Harmful Drinking and Alcohol Dependence (2011)**[34] **Reaffirmed 2015**	Treatment for acute alcohol withdrawal • Offer pharmacotherapy to treat the symptoms of acute alcohol withdrawal. • Consider offering a benzodiazepine or carbamazepine. • Clomethiazole may be offered as an alternative to a benzodiazepine or carbamazepine. Management of delirium tremens • Lorazepam is considered a first-line treatment option. • If symptoms persist or oral medication is declined, give parenteral lorazepam, haloperidol or olanzapine. Management of alcohol withdrawal seizures • In people with alcohol withdrawal seizures, consider offering a quick-acting benzodiazepine (e.g., lorazepam) to reduce the likelihood of further seizures. • Do not offer phenytoin to treat alcohol withdrawal seizures.
American Psychiatric Association: **Treatment of Patients with Substance Use Disorders, Second Edition (2007)**[35]	Alcohol use disorders: treatment principles and alternatives • The treatment of patients in moderate to severe withdrawal includes efforts to reduce central nervous system irritability and restore physiological homeostasis. • Management of alcohol withdrawal generally requires the use of thiamine and fluids, benzodiazepines, and occasionally other medications such as anticonvulsants, clonidine, or antipsychotic agents. • Once clinical stability is achieved, the tapering of benzodiazepines and other medications should be carried out as necessary. • Naltrexone may attenuate some of the reinforcing effects of alcohol; however, long-term data regarding efficacy are limited. • Acamprosate may also be an effective adjunctive medication in motivated patients who are receiving psychosocial treatment. • Disulfiram is an effective adjunct to a comprehensive treatment program for reliable, motivated patients whose drinking may be triggered by events that suddenly increase alcohol craving.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the benzodiazepines are noted in Tables 3 to 4. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Benzodiazepines (Drugs A to E)[1-13]

Indication	Alprazolam	Chlordiazepoxide	Clobazam	Clonazepam	Clorazepate	Diazepam	Estazolam
Anxiety Disorders							
Management of anxiety disorders	✔ *†	✔			✔	✔ *‡	
Short-term relief of symptoms of anxiety	✔ *	✔			✔	✔ *‡	
Treatment of panic disorder, with or without agoraphobia	✔ *†§			✔			
Premedication for relief of anxiety and tension in patients who are to undergo surgical procedures						✔ ‡	
Premedication for the relief of anxiety and tension prior to cardioversion and to diminish the patient's recall of the procedure						✔ ‡	
Preoperative apprehension/anxiety		✔					
Sedative-Hypnotic							
Short-term management of insomnia							✔
Seizure Disorders							
Adjunct in partial seizures					✔		
Adjunct in status epilepticus and severe recurrent seizures						✔ ‡	
Adjunctive in convulsive disorders						✔ *	
Adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in patients two years of age or older			✔				
Management of patients with absence seizures who failed succinimides				✔			
Management of selected, refractory, patients with epilepsy, on stable regimens of antiepileptic drugs, who require intermittent use of diazepam to control bouts of increased seizure activity						✔ ‖	
Monotherapy or adjunctive treatment of Lennox-Gastaut syndrome, akinetic and				✔			

Indication	Alprazolam	Chlordiazepoxide	Clobazam	Clonazepam	Clorazepate	Diazepam	Estazolam
myoclonic seizures							
Miscellaneous							
Acute alcohol withdrawal		✔			✔	✔ *‡	
Adjunct for the relief of skeletal muscle spasm due to reflex spasm to local pathology, spasticity caused by upper motor neuron disorders, athetosis, and stiff-man syndrome						✔ *‡	

*Immediate-release formulation (tablet, concentrate and/or solution).
†Orally disintegrating tablet formulation.
‡Injection formulation.
§Extended-release formulation.
‖Rectal formulation.

Table 4. FDA-Approved Indications for the Benzodiazepines (Drugs F to T)[1-13]

Indication	Flurazepam	Lorazepam	Midazolam	Oxazepam	Temazepam	Triazolam
Anesthesia						
Induction of anesthesia, before administration of other anesthetic agents			✔ *			
Preanesthetic medication, producing sedation, relief of anxiety, and a decreased ability to recall events related to the day of surgery		✔ *				
Preoperative sedation/anxiolysis/amnesia			✔ *			
Sedation/anxiolysis/amnesia prior to or during diagnostic, therapeutic, or endoscopic procedures			✔ *†			
Sedation of intubated and mechanically ventilated patients as a component of anesthesia or during treatment in a critical care setting			✔ *			
Anxiety Disorders						
Management of anxiety disorders		✔ †		✔		
Short-term relief of symptoms of anxiety		✔ †		✔		
Sedative-Hypnotic						
Short-term management of insomnia	✔				✔	✔
Seizure Disorders						
Treatment of status epilepticus		✔ *				
Miscellaneous						
Acute alcohol withdrawal				✔		

*Injection formulation.
†Oral formulation(s).

IV. Pharmacokinetics

The pharmacokinetic parameters of the benzodiazepines are listed in Table 5.

Table 5. Pharmacokinetic Parameters of the Benzodiazepines[2]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Alprazolam	90	80	Liver	Renal (80) Feces (7)	ER: 10.7 to 15.8 IR: 6.3 to 26.9 ODT: 7.9 to 19.2
Chlordiazepoxide	Nearly complete	90 to 98	Liver	Renal (1 to 2)	10 to 48
Clobazam	87	80 to 90	Liver	Renal (82) Feces (11)	36 to 42
Clonazepam	90	85	Liver	Renal (<1)	30 to 40
Clorazepate	91	97 to 98	Liver	Renal (62 to 67) Feces (15 to 19)	2.29
Diazepam	98	95 to 99	Liver	Renal (75)	up to 48
Estazolam	Not reported	93	Not reported	Renal Feces (4)	10 to 24
Flurazepam	Not reported	97	Liver	Renal	2.3
Lorazepam	90 to 93	85 to 91	Liver (75)	Renal (88) Feces (7)	12
Midazolam	36	95	Liver	Renal (45 to 57)	1.8 to 6.4
Oxazepam	93	86 to 99	Liver	Renal (50)	2.8 to 8.6
Temazepam	Well absorbed	96	Not reported	Renal (80 to 90)	3.5 to 18.4
Triazolam	Well absorbed	89 to 94	Liver	Renal (80) Feces (9)	2.3

ER=extended-release, IR=immediate-release, ODT=orally disintegrating tablet

V. Drug Interactions

Major drug interactions with the benzodiazepines are listed in Table 6.

Table 6. Major Drug Interactions with the Benzodiazepines[2]

Generic Name(s)	Interaction	Mechanism
Benzodiazepines (alprazolam, chlordiazepoxide, clobazam, clonazepam, clorazepate, diazepam, estazolam, flurazepam, lorazepam, midazolam, oxazepam, temazepam, triazolam)	Barbiturates	Concurrent use of triazolam and barbiturates may result in additive respiratory depression.
Benzodiazepines (alprazolam, chlordiazepoxide, clobazam, clonazepam, clorazepate, diazepam, estazolam, flurazepam, lorazepam, midazolam, oxazepam, temazepam, triazolam)	Centrally acting muscle relaxants	Concurrent use of benzodiazepines and centrally acting muscle relaxants may result in additive respiratory depression.
Benzodiazepines (clobazam)	Clozapine	Delirium, sedation, sialorrhea, and ataxia may occur when certain benzodiazepines and clozapine are coadministered. Severe orthostatic hypotension and respiratory depression may occur.
Benzodiazepines (alprazolam, chlordiazepoxide, clobazam, clonazepam, clorazepate, diazepam,	Flumazenil	Concurrent use of flumazenil and benzodiazepines may result in precipitation of seizures.

Generic Name(s)	Interaction	Mechanism
estazolam, flurazepam, lorazepam, midazolam, oxazepam, temazepam, triazolam)		
Benzodiazepines (alprazolam, chlordiazepoxide, clobazam, clonazepam, clorazepate, diazepam, estazolam, flurazepam, lorazepam, midazolam, oxazepam, temazepam, triazolam)	Mirtazapine	Concurrent use of mirtazapine and benzodiazepines may result in increased risk of CNS depression.
Benzodiazepines (alprazolam, chlordiazepoxide, clobazam, clonazepam, clorazepate, diazepam, estazolam, flurazepam, lorazepam, midazolam, oxazepam, temazepam, triazolam)	Sodium oxybate	Concurrent use of sodium oxybate and benzodiazepines may result in an increase in sleep duration and central nervous system depression.
Benzodiazepines (alprazolam, chlordiazepoxide, clobazam, clonazepam, clorazepate, diazepam, estazolam, flurazepam, lorazepam, midazolam, oxazepam, temazepam, triazolam)	Tapentadol	Concurrent use of tapentadol and sedatives may result in an increase in central nervous system and respiratory depression.
Benzodiazepines (alprazolam, clorazepate, diazepam, estazolam, flurazepam, midazolam, triazolam)	Protease inhibitors	Concurrent use may lead to severe sedation and respiratory depression due to inhibition of hepatic metabolism.
Benzodiazepines (alprazolam, diazepam, midazolam, triazolam)	Azole antifungals	Increased and prolonged serum levels, central nervous system depression, and psychomotor impairment have been reported with benzodiazepines undergoing oxidative metabolism.
Benzodiazepines (diazepam)	Hydantoins	Serum hydantoin concentrations may be increased and phenytoin may increase the clearance of certain benzodiazepines.
Benzodiazepines (clonazepam, clorazepate, diazepam, estazolam, flurazepam, midazolam, triazolam)	Nefazodone	Nefazodone may increase the pharmacologic effects of certain benzodiazepines due to CYP3A4 inhibition and decreased metabolic elimination. Impaired psychomotor performance and increased sedation may result from elevated benzodiazepine plasma concentrations.
Benzodiazepines (clonazepam, clorazepate, diazepam, estazolam, flurazepam, midazolam)	Rifamycins	Pharmacologic effects of certain benzodiazepines may be decreased by rifamycins due to CYP3A4 induction and increased metabolic elimination.
Benzodiazepines (alprazolam, clonazepam)	Carbamazepine	The pharmacologic effects of certain benzodiazepines may be decreased due to CYP3A4 induction by carbamazepine.
Benzodiazepines (diazepam, estazolam, midazolam)	Macrolides and ketolides	Central nervous system depression and prolonged sedation have been reported with the concurrent use of benzodiazepines and macrolides/ketolides.
Benzodiazepines (alprazolam, chlordiazepoxide, clobazam, clonazepam, clorazepate, diazepam, estazolam, flurazepam, lorazepam, midazolam, oxazepam, temazepam, triazolam)	Opioid analgesics	Concurrent use of opioid analgesics and benzodiazepines may result in additive respiratory depression
Benzodiazepines (midazolam)	Vasopressin receptor antagonists	Plasma concentrations of midazolam may be increased by vasopressin receptor antagonists.

Generic Name(s)	Interaction	Mechanism
Benzodiazepines (midazolam)	Delavirdine	Inhibition of CYP3A4 by delavirdine may decrease the metabolic elimination of certain benzodiazepines. Plasma concentrations and pharmacologic effects of certain benzodiazepines may be increased by delavirdine. Adverse effects, including the potential for serious cardiac arrhythmias, may result.
Benzodiazepines (alprazolam, clonazepam, midazolam, triazolam)	Idelalisib	Concurrent use of idelalisib and triazolam may result in increased triazolam concentrations.
Benzodiazepines (alprazolam, midazolam, triazolam)	Cobicistat	Concurrent use of cobicistat and triazolam may result in increased triazolam plasma concentrations and increased risk for serious adverse effects including, prolonged or increased sedation or respiratory depression.
Benzodiazepines (clobazam)	Thioridazine	Concurrent use of clobazam and thioridazine may result in increased thioridazine plasma concentrations.

VI. Adverse Drug Events

The most common adverse drug events reported with the benzodiazepines are listed in Tables 7 to 8. The boxed warnings for midazolam are listed in Tables 9 to 10. The benzodiazepines share a number of similar adverse drug events. The most common adverse events are central nervous system-related, including ataxia, confusion, drowsiness, dizziness, and lightheadedness.[1-13] Long-acting benzodiazepines, or benzodiazepines with active metabolites, may have a higher incidence of residual daytime sedation and cognitive/psychomotor impairment. This may be more pronounced in elderly patients or patients with impaired elimination of benzodiazepines. Complex behaviors such as "sleep driving", as well as other behaviors, have been reported in patients who are not fully awake after taking a sedative-hypnotic.[1,2]

Misuse and dependence are a concern with the use of benzodiazepines. The risk of dependence increases with long-term therapy, high daily dose, use of high potency and rapid-onset benzodiazepines, history of substance abuse, chronic physical illness, chronic sleep disorders, and dysthymic or personality disorders.[36,37] Withdrawal symptoms may occur when benzodiazepines are discontinued, especially if therapy is abruptly stopped. Symptoms may include relapse of anxiety disorder or rebound/withdrawal syndromes. Withdrawal may occur within hours of discontinuation of a short-acting benzodiazepine or as late as one to two weeks with the use of long-acting agents. Factors that can predict the severity of withdrawal symptoms include long-term therapy, high daily dose, short benzodiazepine half-life, rapid taper rate, and concomitant substance abuse.[36,38]

Table 7. Adverse Drug Events (%) Reported with the Benzodiazepines (Drugs A to E)[1-13]

Adverse Events	Alprazolam	Chlordiazepoxide	Clobazam	Clonazepam	Clorazepate	Diazepam	Estazolam
Cardiovascular							
Chest pain	1 to 10	-	-	-	-	-	-
Flushing	-	-	-	-	-	-	1 to 10
Hypotension	1 to 10	1 to 10	-	-	✔	✔	-
Palpitations	1 to 10	-	-	✔	-	-	1 to 10
Syncope	<10	-	-	-	-	-	-
Tachycardia	1 to 10	-	-	-	-	-	-
Vasodilation	-	-	-	-	-	✔	-
Central Nervous System							
Aggressive behavior	-	-	8 to 14	-	-	-	-
Agitation	1 to 10	-	5	-	-	-	1 to 10
Akathisia	1 to 10	1 to 10	-	-	-	-	-
Amnesia	<1	-	-	✔	-	✔	1 to 10
Anxiety	-	-	✔	-	✔	-	1 to 10
Apathy	-	-	✔	-	-	-	1 to 10
Ataxia	1 to 10	>10	10	✔	✔	✔	-
Attention disturbance	1 to 10	-	-	-	-	-	-
Behavior changes	-	-	✔	✔	-	-	-
Cognitive disorder	>10	-	-	-	-	-	-
Coma	-	-	-	✔	-	-	-
Complex sleep-related behavior	-	-	-	-	-	-	<1

Adverse Events	Alprazolam	Chlordiazepoxide	Clobazam	Clonazepam	Clorazepate	Diazepam	Estazolam
Confusion	1 to 10	1 to 10	✔	✔	✔	✔	1 to 10
Coordination abnormal	>10	-	-	✔	-	-	1 to 10
Depersonalization	1 to 10	-	-	-	-	-	-
Depression	>10	-	✔	✔	✔	✔	-
Derealization	1 to 10	-	-	-	-	-	-
Disinhibition	1 to 10	-	-	-	-	-	-
Disorientation	1 to 10	-	-	-	-	-	-
Dizziness	1 to 10	1 to 10	-	✔	✔	-	1 to 10
Dream abnormalities	1 to 10	-	-	-	-	-	-
Drowsiness	>10	>10	16 to 25	✔	✔	✔	-
Dysdiadochokinesia	-	-	-	✔	-	-	-
Emotional lability	-	-	-	✔	-	-	1 to 10
Euphoria	-	-	-	-	-	-	1 to 10
Fatigue	>10	>10	3 to 5	✔	✔	✔	-
Fear	1 to 10	-	-	-	-	-	-
Fever	-	-	10 to 17	✔	-	-	<1
Hallucinations	1 to 10	-	✔	✔	-	-	-
Hangover effect	-	-	-	-	-	-	1 to 10
Headache	1 to 10	-	-	✔	✔	✔	-
Hemiparesis	-	-	-	✔	-	-	-
Homicidal ideation	<1	-	-	-	-	-	-
Hostility	-	-	-	-	-	-	1 to 10
Hypersomnia	1 to 10	-	-	-	-	-	-
Hypoesthesia	1 to 10	-	-	-	-	-	-
Hypokinesia	-	-	-	-	-	-	1 to 10
Hypomania	<1	-	-	-	-	-	-
Hypotonia	-	-	-	✔	-	-	-
Hysteria	-	-	-	✔	-	-	-
Insomnia	1 to 10	-	5 to 7	✔	✔	-	-
Intellectual ability reduced	-	-	-	✔	-	-	-
Irritability	>10	>10	3 to 11	-	✔	-	-
Lethargy	1 to 10	-	10 to 15	-	-	-	-
Lightheadedness	>10	>10	-	-	✔	-	-
Malaise	1 to 10	-	-	-	-	-	-
Mania	<1	-	-	-	-	-	-
Memory impairment	>10	-	-	✔	✔	-	-
Mental impairment	1 to 10	>10	-	-	-	-	-

Adverse Events	Alprazolam	Chlordiazepoxide	Clobazam	Clonazepam	Clorazepate	Diazepam	Estazolam
Nervousness	1 to 10	-	-	✔	✔	-	-
Nightmares	1 to 10	-	-	-	-	-	-
Paradoxical reactions	-	-	-	✔	-	✔	-
Paresthesia	1 to 10	-	-	-	-	-	1 to 10
Psychosis	-	-	-	✔	-	-	-
Restlessness	1 to 10	-	-	-	-	-	-
Sedation	>10	-	9	-	-	-	-
Seizure	1 to 10	-	-	✔	-	-	1 to 10
Sleep disturbances	-	-	-	-	-	-	1 to 10
Slurred speech	-	-	-	✔	✔	✔	-
Somnolence	>10	-	-	✔	-	-	>10
Stupor	-	-	-	-	-	-	1 to 10
Suicidal ideation/attempts	<1	-	-	✔	-	-	-
Talkativeness	1 to 10	-	-	-	-	-	-
Tremor	1 to 10	1 to 10	-	✔	✔	✔	1 to 10
Vasomotor disturbances	2	-	-	-	-	-	-
Vertigo	1 to 10	-	-	✔	-	✔	-
Dermatological							
Alopecia	-	-	-	✔	-	-	-
Dermatitis	1 to 10	1 to 10	-	-	-	-	1 to 10
Hirsutism	-	-	-	✔	-	-	-
Photosensitivity	-	1 to 10	-	-	-	-	-
Pruritus	-	-	-	-	-	-	1 to 10
Rash	1 to 10	>10	✔	✔	✔	✔	1 to 10
Stevens-Johnson Syndrome	<1	-	✔	-	-	-	-
Urticaria	-	-	✔	-	-	-	1 to 10
Gastrointestinal							
Abdominal pain	1 to 10	-	-	✔	-	-	-
Anorexia	1 to 10	-	-	✔	-	-	-
Appetite increased/decreased	>10	>10	2 to 7	✔	✔	-	-
Change in appetite	-	-	-	-	-	-	1 to 10
Constipation	>10	-	2 to 10	✔	✔	✔	1 to 10
Dehydration	-	-	-	✔	-	-	-
Diarrhea	1 to 10	-	-	✔	✔	✔	-
Dyspepsia	1 to 10	-	-	-	-	-	-
Dysphagia	-	-	5	-	-	-	-
Encopresis	-	-	-	✔	-	-	-

Adverse Events	Alprazolam	Chlordiazepoxide	Clobazam	Clonazepam	Clorazepate	Diazepam	Estazolam
Flatulence	-	-	-	-	-	-	1 to 10
Gastritis	-	-	-	✔	-	-	1 to 10
Gingival soreness	-	-	-	✔	-	-	-
Nausea	1 to 10	-	-	✔	✔	✔	-
Salivation decreased	-	>10	-	-	✔	-	-
Salivation increased	1 to 10	1 to 10	13 to 14	-	-	✔	-
Taste alteration	-	-	-	-	-	-	1 to 10
Tongue coated	-	-	-	✔	-	-	-
Vomiting	1 to 10	-	7 to 9	-	✔	-	-
Xerostomia	>10	>10	-	✔	✔	✔	1 to 10
Genitourinary							
Colpitis	-	-	-	✔	-	-	-
Dysmenorrhea	1 to 10	-	-	✔	-	-	-
Dysuria	-	-	-	✔	-	-	-
Ejaculation delayed	-	-	-	✔	-	-	-
Enuresis	-	-	-	✔	-	-	-
Impotence	-	-	-	✔	-	-	-
Incontinence	1 to 10	1 to 10	-	-	-	✔	-
Libido decreased	>10	>10	-	✔	✔	✔	-
Libido increased	1 to 10	1 to 10	-	✔	-	✔	-
Menstrual disorders	1 to 10	>10	-	-	-	-	1 to 10
Micturition difficulty	>10	>10	-	-	-	-	1 to 10
Micturition frequency	-	-	-	✔	-	-	1 to 10
Nocturia	-	-	-	✔	-	-	-
Sexual dysfunction	1 to 10	1 to 10	-	-	-	-	-
Urinary retention	-	-	✔	✔	-	✔	-
Urinary tract infection	-	-	2 to 5	✔	-	-	-
Vaginal discharge/itching	-	-	-	-	-	-	1 to 10
Hematologic							
Anemia	-	-	✔	✔	-	-	-
Eosinophilia	-	-	✔	✔	-	-	-
Leukopenia	-	-	✔	✔	-	-	-
Neutropenia	-	-	-	-	-	✔	-
Thrombocytopenia	-	-	✔	✔	-	-	-
Hepatic							
Alkaline phosphatase increased	-	-	-	✔	-	-	-
Bilirubin increased	1 to 10	-	-	-	-	-	-

Adverse Events	Alprazolam	Chlordiazepoxide	Clobazam	Clonazepam	Clorazepate	Diazepam	Estazolam
Hepatic failure	<1	-	-	-	-	-	-
Hepatitis	<1	-	-	-	-	-	-
Hepatomegaly	-	-	-	✔	-	-	-
Jaundice	<10	-	-	-	✔	✔	-
Liver enzymes increased	<10	-	✔	✔	✔	-	-
Musculoskeletal							
Arthralgia	1 to 10	-	-	✔	-	-	-
Back pain	1 to 10	-	-	✔	-	-	-
Choreiform movements	-	-	-	✔	-	-	-
Dysarthria	>10	>10	2 to 5	✔	-	✔	-
Dyskinesia	1 to 10	-	-	-	-	-	-
Dystonia	1 to 10	-	-	-	-	-	-
Muscle cramps	1 to 10	1 to 10	-	-	-	-	-
Muscle pain	-	-	-	✔	-	-	-
Muscle spasm	-	-	✔	-	-	-	<1
Muscle twitching	1 to 10	-	-	-	-	-	-
Muscle weakness	-	-	-	✔	-	-	-
Myalgia	1 to 10	-	-	✔	-	-	<1
Neck pain	-	-	-	-	-	-	<1
Rigidity	-	1 to 10	-	-	-	-	-
Weakness	1 to 10	-	-	-	-	✔	>10
Respiratory							
Allergic rhinitis	1 to 10	-	-	-	-	-	-
Apnea	-	-	-	-	-	✔	-
Asthma	-	-	-	-	-	✔	1 to 10
Bronchitis	-	-	2 to 5	✔	-	-	-
Chest congestion	-	-	-	✔	-	-	-
Cough	-	-	3 to 7	✔	-	-	1 to 10
Dyspnea	1 to 10	-	-	-	-	-	1 to 10
Hypersecretions	-	-	-	✔	-	-	-
Hyperventilation	1 to 10	-	-	-	-	-	-
Nasal congestion	>10	1 to 10	-	-	-	-	-
Pharyngitis	-	-	-	✔	-	-	-
Pneumonia	-	-	3 to 7	-	-	-	-
Respiratory depression	-	-	✔	✔	-	✔	-
Respiratory tract infection	-	-	-	✔	-	-	-
Rhinitis	-	-	-	✔	-	-	1 to 10

Adverse Events	Alprazolam	Chlordiazepoxide	Clobazam	Clonazepam	Clorazepate	Diazepam	Estazolam
Rhinorrhea	-	-	-	✔	-	-	-
Shortness of breath	-	-	-	✔	-	-	-
Sinusitis	-	-	-	✔	-	-	1 to 10
Upper respiratory infection	1 to 10	-	13 to 14	-	-	-	-
Special Senses							
Blurred vision	1 to 10	-	✔	✔	✔	✔	-
Diplopia	-	-	✔	-	✔	✔	-
Eye movements abnormal	-	-	-	✔	-	-	-
Eye pain/swelling	-	-	-	-	-	-	1 to 10
Nystagmus	-	-	-	✔	-	-	-
Other							
Allergic reaction	-	-	-	✔	-	-	<1
Anaphylaxis	-	-	-	-	-	-	<1
Angioedema	<1	-	-	-	-	-	<1
Aphonia	-	-	-	✔	-	-	-
Chills	-	-	-	-	-	-	<1
Diaphoresis	1 to 10	-	-	-	-	-	1 to 10
Drug dependence	-	-	-	-	-	-	<1
Edema	-	-	✔	✔	-	-	-
Falls	<1	-	-	-	-	-	-
Galactorrhea	<1	-	-	-	-	-	-
Gynecomastia	<1	-	-	-	-	-	-
Hyperprolactinemia	<1	-	-	-	-	-	-
Lymphadenopathy	-	-	-	✔	-	-	-
Pain with injection	-	-	-	-	-	✔	-
Peripheral edema	<1	-	-	-	-	-	-
Sleep apnea syndrome	<1	-	-	-	-	-	-
Tinnitus	<1	1 to 10	-	-	-	-	-
Weight changes	>10	>10	-	✔	-	-	-

✔ Percent not specified.
- Event not reported or incidence <1%.

Table 8. Adverse Drug Events (%) Reported with the Benzodiazepines (Drugs F to T)[1-13]

Adverse Events	Flurazepam	Lorazepam	Midazolam	Oxazepam	Temazepam	Triazolam
Cardiovascular						
Bigeminy	-	-	<1	-	-	-
Chest pain	✔	-	-	-	-	<1
Hypotension	✔	1 to 10	1 to 10	-	-	-

Adverse Events	Flurazepam	Lorazepam	Midazolam	Oxazepam	Temazepam	Triazolam
Palpitations	✔	-	-	-	-	-
Syncope	-	-	-	✔	-	-
Tachycardia	-	-	-	-	-	<1
Central Nervous System						
Abnormal thinking	-	-	-	-	-	-
Agitation	-	-	<1	-	-	-
Akathisia	-	1 to 10	-	-	-	-
Amnesia	-	1 to 10	<1	-	<1	<1
Anxiety	-	-	-	-	1 to 10	-
Apathy	-	-	-	-	-	-
Apprehension	✔	-	-	-	-	-
Ataxia	✔	1 to 10	-	✔	<1	5
Coma	✔	-	-	-	-	-
Complex sleep-related behavior	-	-	-	-	<1	<1
Confusion	✔	1 to 10	-	-	1 to 10	<1
Delirium	-	-	<1	-	-	-
Depression	✔	1 to 10	-	-	-	<1
Disinhibition	-	<1	-	-	-	-
Disorientation	-	1 to 10	-	-	-	-
Dizziness	✔	1 to 10	-	✔	1 to 10	8
Dream abnormalities	-	-	-	-	-	<1
Drowsiness	✔	-	1 to 10	✔	1 to 10	14
Dysesthesia	-	-	-	-	-	<1
Dystonia	-	-	-	-	-	-
Euphoria	✔	<1	<1	-	1 to 10	<1
Faintness	✔	-	-	-	-	-
Fatigue	-	<1	-	-	1 to 10	<1
Hallucinations	✔	-	<1	-	-	-
Hangover effect	✔	-	-	-	1 to 10	-
Headache	✔	1 to 10	1 to 10	✔	1 to 10	10
Hyperkinesia	-	-	-	-	-	-
Hypokinesia	-	-	-	-	-	-
Incoordination	-	-	-	-	-	-
Irritability	✔	-	-	-	-	-
Lethargy	-	-	-	-	1 to 10	-
Lightheadedness	✔	-	-	-	-	5
Malaise	-	-	-	-	-	-

Adverse Events	Flurazepam	Lorazepam	Midazolam	Oxazepam	Temazepam	Triazolam
Memory impairment	✔	-	-	✔	-	<1
Nervousness	✔	-	-	-	-	5
Nightmares	-	-	-	-	-	<1
Over sedation	-	-	1 to 10	-	-	-
Paradoxical reaction	✔	-	1 to 10	✔	<1	<1
Paranoid reaction	-	-	-	-	-	-
Paresthesia	-	-	-	-	-	<1
Restlessness	✔	-	-	-	-	-
Sedation	-	>10	-	-	-	<1
Seizure	-	<1	1 to 10	-	-	-
Sleep disturbances	-	-	-	-	-	-
Slurred speech	✔	-	-	-	-	<1
Speech disorder	-	-	-	-	-	-
Staggering	✔	-	-	-	-	-
Stimulation	-	-	-	-	-	-
Suicidal ideation	-	<1	-	-	-	-
Talkativeness	✔	-	-	-	-	-
Tremor	-	-	-	✔	-	-
Vertigo	-	<1	-	✔	1 to 10	-
Dermatological						
Dermatitis	-	1 to 10	-	-	-	<1
Flushing	✔	-	-	-	-	-
Pruritus	✔	-	-	-	-	-
Rash	✔	1 to 10	<1	✔	1 to 10	-
Gastrointestinal						
Abdominal pain	-	-	-	-	-	-
Anorexia	-	-	-	-	-	-
Appetite increased/decreased	✔	1 to 10	-	-	-	-
Bitter taste	✔	-	-	-	-	-
Constipation	✔	-	-	-	-	-
Cramps	-	-	-	-	-	<1
Diarrhea	✔	-	-	-	1 to 10	-
Dyspepsia	-	-	-	-	-	-
Gastrointestinal pain	✔	-	-	-	-	-
Heartburn	✔	-	-	-	-	-
Hiccups	-	-	1 to 10	-	-	-
Nausea	✔	1 to 10	1 to 10	-	-	5

Adverse Events	Flurazepam	Lorazepam	Midazolam	Oxazepam	Temazepam	Triazolam
Salivation increased	✔	<1	-	-	-	-
Taste alteration	-	-	-	-	-	-
Upset stomach	✔	-	-	-	-	-
Vomiting	✔	-	1 to 10	-	<1	5
Weight changes	✔	1 to 10	-	-	-	-
Xerostomia	✔	-	-	-	-	<1
Genitourinary						
Impotence	-	-	-	-	-	-
Incontinence	-	-	-	✔	-	-
Libido changes	-	-	-	✔	1 to 10	<1
Decreased libido	-	-	-	-	-	-
Menstrual irregularities	-	<1	-	✔	-	-
Urinary retention	-	-	-	-	-	-
Hematologic						
Blood dyscrasias	-	<1	-	✔	<1	-
Granulocytopenia	✔	-	-	-	-	-
Leukopenia	✔	-	-	✔	-	-
Hepatic						
Aspartate aminotransferase increased	✔	-	-	-	-	-
Alkaline phosphatase increased	✔	-	-	-	-	-
Alanine aminotransferase increased	✔	-	-	-	-	-
Bilirubin increased	✔	-	-	-	-	-
Hepatic dysfunction	-	-	-	✔	-	-
Jaundice	✔	-	-	✔	-	-
Musculoskeletal						
Asthenia	-	<1	-	-	-	-
Dysarthria	✔	-	-	✔	1 to 10	<1
Joint pain	✔	-	-	-	-	-
Muscle spasticity	-	-	-	-	-	-
Myoclonic jerks	-	-	1 to 10	-	-	-
Weakness	✔	1 to 10	-	-	1 to 10	<1
Respiratory						
Apnea	✔	1 to 10	-	-	-	-
Bronchospasm	-	-	<1	-	-	-
Cough	-	-	1 to 10	-	-	-
Dyspnea	✔	-	-	-	-	-
Hyperventilation	-	1 to 10	-	-	-	-

Adverse Events	Flurazepam	Lorazepam	Midazolam	Oxazepam	Temazepam	Triazolam
Laryngospasm	-	-	<1	-	-	-
Nasal congestion	-	1 to 10	-	-	-	-
Respiratory rate decreased	-	-	>10	-	-	-
Tidal volume decreased	-	-	>10	-	-	-
Special Senses						
Abnormal vision	-	-	-	-	-	-
Blurred vision	✔	-	-	✔	1 to 10	-
Cataract	-	-	-	-	-	-
Difficulty focusing	✔	-	-	-	-	-
Diplopia	-	-	-	✔	-	-
Eyes burning	✔	-	-	-	-	-
Nystagmus	-	-	1 to 10	-	-	-
Visual disturbances	-	1 to 10	-	-	-	<1
Other						
Anaphylaxis	-	-	-	-	<1	<1
Angioedema	-	-	-	-	<1	<1
Diaphoresis	✔	-	-	-	1 to 10	-
Drug dependence	✔	<1	1 to 10	✔	<1	-
Edema	-	-	-	✔	-	-
Falling	✔	-	-	-	-	-
Injection site reaction	-	-	1 to 10	-	-	-
Pain	✔	-	-	-	-	<1

✔ Percent not specified.
- Event not reported or incidence <1%.

Table 9. Boxed Warning for Midazolam Injection[1]

WARNING
Adults and pediatrics: Intravenous midazolam hydrochloride has been associated with respiratory depression and respiratory arrest, especially when used for sedation in noncritical care settings. In some cases, where this was not recognized promptly and treated effectively, death or hypoxic encephalopathy has resulted. Intravenous midazolam hydrochloride should be used only in hospital or ambulatory care settings, including physicians' and dental offices, that provide for continuous monitoring of respiratory and cardiac function (i.e., pulse oximetry). Immediate availability of resuscitative drugs and age- and size-appropriate equipment for bag/valve/mask ventilation and intubation, and personnel trained in their use and skilled in airway management should be ensured. Patients should be continuously monitored with some means of detection for early signs of hypoventilation, airway obstruction, or apnea (i.e., pulse oximetry). Hypoventilation, airway obstruction, and apnea can lead to hypoxia or cardiac arrest unless effective countermeasures are taken immediately. The immediate availability of specific reversal agents (flumazenil) is highly recommended. Vital signs should continue to be monitored during the recovery period. For deeply sedated pediatric patients, a dedicated individual, other than the practitioner performing the procedure, should monitor the patient throughout the procedure. The initial dose for sedation in adult patients may be as little as 1 mg, but should not exceed 2.5 mg in a healthy adult. Lower doses are necessary for older (over 60 years) or debilitated patients and in patients receiving concomitant narcotics or other central nervous system depressants. The initial dose and all subsequent doses should always be titrated slowly; administer over at least 2 minutes and allow an additional two or more minutes to fully evaluate the sedative effect. The use of the 1 mg/mL formulation or dilution of the 1 or 5 mg/mL formulation is recommended to facilitate slower injection. Doses of sedative medications in pediatric patients must be calculated on a mg/kg basis, and initial doses and all subsequent doses should always be titrated slowly. The initial pediatric dose of midazolam hydrochloride for sedation/anxiolysis/amnesia is age, procedure, and route dependent. Neonates: Midazolam hydrochloride should not be administered by rapid injection in the neonatal population. Rapid injection should be avoided in the neonatal population. Midazolam hydrochloride administered rapidly as an intravenous injection (less than two minutes) has been associated with severe hypotension in neonates, particularly when the patient has also received fentanyl. Likewise, severe hypotension has been observed in neonates receiving a continuous infusion of midazolam who then receive a rapid intravenous injection of fentanyl. Seizures have been reported in several neonates following rapid intravenous administration.

Table 10. Boxed Warning for Midazolam Syrup[1]

WARNING
Midazolam syrup has been associated with respiratory depression and respiratory arrest, especially when used for sedation in noncritical care settings. Midazolam syrup has been associated with reports of respiratory depression, airway obstruction, desaturation, hypoxia, and apnea, most often when used concomitantly with other central nervous system depressants (e.g., opioids). Midazolam syrup should be used only in hospital or ambulatory care settings, including physicians' and dentists' offices, that can provide for continuous monitoring of respiratory and cardiac function. Immediate availability of resuscitative drugs and age- and size-appropriate equipment for ventilation and intubation, and personnel trained in their use and skilled in airway management should be ensured. For deeply sedated patients, a dedicated individual, other than the practitioner performing the procedure, should monitor the patient throughout the procedure.

VII. Dosing and Administration

The usual dosing regimens for the benzodiazepines are listed in Table 11.

Table 11. Usual Dosing Regimens for the Benzodiazepines[1-13]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Alprazolam	Management of anxiety disorders, short-term relief of symptoms of anxiety: Oral concentrate (IR), orally disintegrating tablet (IR), tablet (IR): initial, 0.25 to 0.5 mg orally three times daily; may be increased to achieve a maximum therapeutic effect at every three to four days; maximum, 4 mg/day Treatment of panic disorder, with or without agoraphobia: Oral concentrate (IR), orally disintegrating tablet (IR), tablet (IR): initial, 0.5 mg orally three times daily; may increase dosage up to 1 mg every three to four days; usual dosage range is 1 to 10 mg/day Tablet (ER): initial, 0.5 to 1 mg orally in the morning; may increase dosage by up to 1 mg/day every three to four days; usual dosage range is 3 to 6 mg/day; maximum, 10 mg/day	Safety and efficacy in children have not been established.	Oral concentrate (IR): 1 mg/mL Orally disintegrating tablet (IR): 0.25 mg 0.5 mg 1 mg 2 mg Tablet (ER): 0.5 mg 1 mg 2 mg 3 mg Tablet (IR): 0.25 mg 0.5 mg 1 mg 2 mg
Chlordiazepoxide	Acute alcohol withdrawal: Capsule: initial, 50 to 100 mg, followed by repeated doses as needed; maximum, 300 mg/day Management of anxiety disorders, short-term relief of symptoms of anxiety: Capsule: mild-to-moderate symptoms, 5 or 10 mg three to four times daily; severe symptoms, 20 or 25 mg three to four times daily Preoperative apprehension/ anxiety: Capsule: 5 to 10 mg three to four times daily on days preceding surgery	Management of anxiety disorders, short-term relief of symptoms of anxiety ≥6 years of age: Capsule: 5 mg two to four times daily; may be increased to 10 mg two to three times daily	Capsule: 5 mg 10 mg 25 mg
Clobazam	Adjunctive treatment of seizures associated with Lennox-Gastaut syndrome:	Adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in	Oral suspension: 2.5 mg/mL

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Oral suspension, tablet: initial, 5 mg if weighing ≤30 kg or 10 mg if weighing >30 kg, titrate weekly to efficacy and tolerability; maximum, 20 kg/day if ≤30 kg or 40 mg/day if >30 kg	patients two years and older: Oral suspension, tablet: initial, 5 mg if weighing ≤30 kg or 10 mg if weighing >30 kg, titrate weekly to efficacy and tolerability; maximum, 20 kg/day if ≤30 kg or 40 mg/day if >30 kg	Tablet: 10 mg 20 mg
Clonazepam	Treatment of panic disorder, with or without agoraphobia: Orally disintegrating tablet, tablet: initial, 0.25 mg twice daily; increase by 0.125 to 0.25 mg twice daily every three days; maximum, 4 mg/day Management of patients with absence seizures who failed succinimides, monotherapy or adjunctive treatment of Lennox-Gastaut syndrome, akinetic and myoclonic seizures: Orally disintegrating tablet, tablet: initial, 1.5 mg/day divided into three doses; increase daily by 0.5 to 1 mg/day every three days; maximum, 20 mg/day	Management of patients with absence seizures who failed succinimides, monotherapy or adjunctive treatment of Lennox-Gastaut syndrome, akinetic and myoclonic seizures: Orally disintegrating tablet, tablet: ≤10 years of age (≤30 kg), 0.01 to 0.03 mg/kg/day divided two to three times daily; increase by 0.25 to 0.5 mg/day every three days; maximum, 0.2 mg/kg/day; >10 years of age (>30 kg): Initial, 1.5 mg/day divided into three doses; increase by 0.5 to 1 mg/day every three days; maximum, 20 mg/day	Orally disintegrating tablet: 0.125 mg 0.25 mg 0.5 mg 1 mg 2 mg Tablet: 0.5 mg 1 mg 2 mg
Clorazepate	Acute alcohol withdrawal: Tablet: day one: 30 mg initially, then 30 to 60 mg in divided doses for the remainder of the day; say two: 45 to 90 mg/day in divided doses; day three: 22.5 to 45 mg/day in divided doses; day four: 15 to 30 mg/day in divided doses; day five and thereafter: 7.5 to 15 mg/day in divided doses until the patient's condition is stable; maximum, 90 mg/day Management of anxiety disorders, short-term relief of symptoms of anxiety: Tablet: 15 to 60 mg/day in divided doses; usual daily dose is 30 mg/day; may be administered in a single dose at bedtime. Adjunct in partial seizures: Tablet: 7.5 mg three times daily; may increase dose by 7.5 mg/week; maximum, 90	Adjunct in partial seizures: Tablet: nine to 12 years of age, 7.5 mg twice daily; increase by 7.5 mg/week; maximum, 60 mg/day; >12 years of age: 7.5 mg three times daily; increase by 7.5 mg/week; maximum, 90 mg/day	Tablet 3.75 mg 7.5 mg 15 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	mg/day		
Diazepam	Acute alcohol withdrawal: Injection: initial, 10 mg IM/IV, then 5 to 10 mg in three to four hours, if necessary Oral concentrate, oral solution, tablet: 10 mg three to four times during the first 24 hours, reducing to 5 mg three to four times daily as needed Management of anxiety disorders, short-term relief of symptoms of anxiety: Injection: moderate symptoms: Initial, 2 to 5 mg IM/IV; repeat in three to four hours, if necessary; severe symptoms: initial, 5 to 10 mg IM/IV; repeat in three to four hours, if necessary Oral: 2 to 10 mg two to four times daily Premedication for the relief of anxiety and tension prior to cardioversion and to diminish the patient's recall of the procedure: Injection: 5 to 15 mg IV five to 10 minutes prior to the procedure Premedication for relief of anxiety and tension in patients who are to undergo surgical procedures (endoscopic procedure): Injection: 10 to 20 mg IV immediately prior to procedure or five to 10 mg IM 30 minutes prior to procedure Premedication for relief of anxiety and tension in patients who are to undergo surgical procedures: Injection: 10 mg IM (preferred route) before surgery Adjunct for the relief of skeletal muscle spasm due to reflex spasm to local pathology, spasticity caused by upper	Management of anxiety disorders, short-term relief of symptoms of anxiety: Oral concentrate, oral solution, tablet: ≥6 months of age, 1 to 2.5 mg three to four times daily; increase gradually as needed and tolerated Adjunct for the relief of skeletal muscle spasm due to reflex spasm to local pathology, spasticity caused by upper motor neuron disorders, athetosis, and stiff-man syndrome: Injection: 30 days to five years of age, 1 to 2 mg IM/IV, repeated every three to four hours, if necessary ≥5 years of age, 5 to 10 mg IM/IV, repeated every three to four hours, if necessary Oral concentrate, oral solution, tablet: ≥6 months of age, 1 to 2.5 mg three to four times daily; increase gradually as needed and tolerated Adjunctive in convulsive disorders: Oral concentrate, oral solution, tablet: ≥6 months of age: 1 to 2.5 mg three to four times daily; increase gradually as needed and tolerated Rectal gel: two to five years of age, 0.5 mg/kg; may repeat in four to 12 hours; six to 11 years of age, 0.3 mg/kg; may repeat in four to 12 hours; ≥12 years of age, 0.2 mg/kg; may repeat in four to 12 hours Adjunct in status epilepticus and severe recurrent seizures: Injection: 30 days to five years of age: 0.2 to 0.5 mg (IV preferred) every two to	Injection : 5 mg/mL Oral concentrate: 5 mg/mL Rectal gel: 2.5 mg 5-7.5-10 mg 12.5-15-17.5-20 mg Oral solution: 5 mg/5 mL Tablet: 2 mg 5 mg 10 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	motor neuron disorders, athetosis, and stiff-man syndrome: Injection: initial, 5 to 10 mg IM/IV, then 5 to 10 mg in three to four hours, if necessary. Oral: 2 to 10 mg three to four times daily Adjunctive in convulsive disorders: Oral: 2 to 10 mg two to four times daily Rectal gel: 0.2 mg/kg; may repeat in four4 to 12 hours Adjunct in status epilepticus and severe recurrent seizures: Injection: initial, 5 to 10 mg (IV preferred); may be repeated at 10 to 15 minute intervals; maximum, 30 mg	five minutes; maximum, 5 mg; ≥5 years of age: 1 mg (IV preferred) every two to five minutes; maximum, 10 mg	
Estazolam	Short-term management of insomnia: Tablet: 1 to 2 mg at bedtime	Safety and efficacy in children have not been established.	Tablet: 1 mg 2 mg
Flurazepam	Short-term management of insomnia: Capsule: 15 to 30 mg at bedtime	Safety and efficacy in children have not been established.	Capsule: 15 mg 30 mg
Lorazepam	Management of anxiety disorders, short-term relief of symptoms of anxiety: Oral concentrate, tablet: 2 to 3 mg/day divided into two to three daily doses Preanesthetic medication, producing sedation, relief of anxiety, and a decreased ability to recall events related to the day of surgery: Injection: 0.05 mg/kg IM two to three hours before procedure; maximum, 4 mg; 0.044 mg/kg or 2 mg IV (whichever is less); maximum, 0.05 mg/kg or 4 mg Treatment of status epilepticus: Injection: 4 mg IV; may repeat dose in 10 to 15 minutes if needed	Safety and efficacy in children have not been established.	Injection: 2 mg/mL 4 mg/mL Oral concentrate: 2 mg/mL Tablet: 0.5 mg 1 mg 2 mg
Midazolam	Induction of anesthesia, before administration of other anesthetic agents:	Preoperative sedation/anxiolysis/amnesia: Injection: non-neonatal: 0.1	Injection: 1 mg/mL 5 mg/mL

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Injection: unpremedicated patients, 0.3 to 0.35 mg/kg IV; premedicated patients, 0.15 to 0.35 mg/kg IV Sedation/anxiolysis/amnesia prior to or during diagnostic, therapeutic, or endoscopic procedures (amnesia maintenance): Injection: incremental injections of approximately 25% of the induction dose should be given in response to signs of lightening of anesthesia and repeated as necessary Preoperative sedation/ anxiolysis/amnesia: Injection: 0.07 to 0.08 mg/kg IM administered up to one hour before surgery; IV dosage must be individualized and titrated; some patients may respond to as little as 1 mg; no more than 2.5 mg should be given over a period of at least two minutes Sedation/anxiolysis/amnesia prior to or during diagnostic, therapeutic, or endoscopic procedures (continuous infusion): Injection: 0.01 to 0.05 mg/kg IV loading dose, followed by a continuous IV infusion at a rate of 0.02 to 0.10 mg/kg/hr	to 0.15 mg/kg IM, six months to five years of age, 0.05 to 0.1 mg/kg IV; six to 12 years of age, 0.025 to 0.05 mg/kg IV; 12 to 16 years of age: refer to adult dosing Syrup: 0.25 to 1 mg/kg; maximum, 20 mg Sedation of intubated and mechanically ventilated patients as a component of anesthesia or during treatment in a critical care setting: Injection: <32 weeks, continuous IV infusion at a rate of 0.03 mg/kg/hr; ≥32 weeks, continuous IV infusion at a rate of 0.06 mg/kg/hour; non-neonatal, 0.05 to 0.2 mg/kg IV loading dose, followed by a continuous IV infusion at a rate of 0.06 to 0.12 mg/kg/hr	Syrup: 2 mg/mL
Oxazepam	Acute alcohol withdrawal: Capsule: 15 to 30 mg three to four times daily Management of anxiety disorders, short-term relief of symptoms of anxiety: Capsule: mild-to-moderate symptoms: 10 to 15 mg three to four times daily; severe symptoms: 15 to 30 mg three to four times daily	Safety and efficacy in children <6 years of age have not been established. Absolute dosage for patients six to 12 years of age is not established. Management of anxiety disorders, short-term relief of symptoms of anxiety: Capsule: mild-to-moderate symptoms: 10 to 15 mg three to four times daily; severe symptoms: 15 to 30 mg three to four times daily	Capsule: 10 mg 15 mg 30 mg
Temazepam	Short-term management of insomnia:	Safety and efficacy in children have not been	Capsule: 7.5 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Capsule: 7.5 to 30 mg at bedtime	established.	15 mg 22.5 mg 30 mg
Triazolam	Short-term management of insomnia: Tablet: 0.125 to 0.25 mg at bedtime; maximum, 0.5 mg	Safety and efficacy in children have not been established.	Tablet: 0.125 mg 0.25 mg

ER=extended-release, IM=intramuscular, IR=immediate-release, IV=intravenous

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the benzodiazepines are summarized in Table 12.

Table 12. Comparative Clinical Trials with the Benzodiazepines

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Alcohol Withdrawal				
Holbrook et al.[39] (1999) Benzodiazepines (chlordiazepoxide, diazepam, oxazepam, lorazepam) vs alternative active treatments (bromocriptine, carbamazepine, chlorpromazine, clonidine, doxepin, ethanol, hydroxyzine, paraldehyde, propranolol, thiamine) vs placebo	MA Patients being treated for acute alcohol withdrawal	N=1,286 (11 trials) Variable duration	Primary: Improvement of withdrawal symptoms, therapeutic success (CIWA-Ar score ≤10), adverse events, dropout rates Secondary: Not reported	Primary: In three studies with a similar outcome measures, the benzodiazepines were rated as more efficacious compared to placebo in relieving the symptoms of alcohol withdrawal within the first two days of withdrawal (OR, 3.28; 95% CI, 1.30 to 8.28). There were no significant differences in efficacy between individual benzodiazepines. In the nine trials that compared benzodiazepines with alternative active agents, there was no evidence of better efficacy of any alternative agent over a benzodiazepine. Three studies reported the number of adverse events and found no significant difference between benzodiazepines and the alternative treatments examined (OR, 0.67; 95% CI, 0.34 to 1.32). Data on study dropout rates were combined from five trials and indicated that fewer patients in the benzodiazepines group compared to the alternative treatment group dropped out within the first seven days of treatment (OR, 0.68; 95% CI, 0.47 to 0.97). Secondary: Not reported
Ntais et al.[40] (2005) Benzodiazepines alone or in	MA Patients with alcohol dependence who experienced	N=4,051 Variable duration	Primary: Severity of overall alcohol withdrawal syndrome, alcohol withdrawal	Primary: Compared to placebo, there was a benefit with the benzodiazepines against alcohol withdrawal seizures (P=0.01). Benzodiazepines had similar success rates as other drugs and offered a

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
combination with other agents vs alternate benzodiazepines vs other agents (e.g., anticonvulsants) vs placebo	alcohol withdrawal		seizures, alcohol withdrawal delirium Secondary: Adverse events, discontinuation due to adverse events, withdrawal rate, mortality	benefit for seizure control against non-anticonvulsants (P=0.02), but not against anticonvulsants (95% CI, 0.46 to 8.65). Data on other comparisons were limited preventing informative quantitative synthesis for the various outcomes. Secondary: Compared to placebo, the number of withdrawals per arm tended to be less common among patients receiving benzodiazepine (P=0.22). No patients discontinued due to side effects in the benzodiazepine group and one patient discontinued treatment for this reason in the placebo group. No patients died in either the benzodiazepine groups or placebo groups. In those studies that compared benzodiazepines to other agents, there were no between-group differences in number of withdrawals per arm (P=0.54 for comparison with other drugs and P=0.75 for comparison with anticonvulsants). Two out of 901 benzodiazepine-treated patients died compared to five out of 1,275 patients receiving other agents. Patients receiving benzodiazepines had a higher incidence of side effects compared to patients receiving other agents (P=0.16) or anticonvulsants (P=0.47), though NS.
Kumar et al.[41] (2009) Lorazepam 8 mg/day (2 mg in the morning, 2 mg in the afternoon, 4 mg at night) for 2 days; the dose was reduced by 2 mg/day every 2 days vs	DB, RCT Male inpatients in a state of moderately severe, uncomplicated alcohol withdrawal	N=100 12 days	Primary: Withdrawal severity and changes in the CIWA-Ar scale Secondary: Not reported	Primary: There was no significant difference in withdrawal severity between patients receiving lorazepam or chlordiazepoxide at baseline or at any time during the study. Using an 11-item alcohol-withdrawal checklist, irritability (2.9 vs 0.4%; P<0.001), dizziness (0.9 vs 0.0%; P<0.001), and brisk reflexes (0.8 vs 0.2%; P<0.02) were more common with lorazepam than with chlordiazepoxide. Palpitations were more common with chlordiazepoxide than with lorazepam (0.9 vs 0.0%, respectively; P<0.001). The incidence of the remaining items (depressed mood, impaired concentration, anorexia, insomnia, fever, and gait ataxia) did not differ between the two groups. There were no symptoms of benzodiazepine withdrawal recorded during

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
chlordiazepoxide 80 mg/day (20 mg in the morning, 20 mg in the afternoon, 40 mg at night) for 2 days; the dose was reduced by 20 mg per day every 2 days Dosing was down-titrated to zero across 8 treatment days.				the last four days of the study, nor were there impairing adverse events reported during this period. Secondary: Not reported
Caputo et al.[42] (2014) GATE 1 Oxazepam vs sodium oxybate	DB, MC, RCT Alcohol-dependent outpatients 21 to 75 years of age affected by uncomplicated AWS with CIWA-Ar score ≥10	N=126 10 days	Primary: Reduction of symptoms of AWS measured by the change in the total CIWA-Ar score from baseline Secondary: Not reported	Primary: A significant decrease of the mean total CIWA-Ar score from the baseline to the end of the study was found both in the sodium oxybate group (adjusted mean change from baseline of −15.62 ± 0.38; ANCOVA model P<0.0001) and in the oxazepam group (adjusted mean change from baseline of −16.27 ± 0.38; ANCOVA model P<0.0001), with no significant differences between the two treatments (ANCOVA model: estimated point 0.65 (95 % CI, −0.37 to 1.66) P=0.210). Secondary: Not reported
Anxiety Disorders				
Martin et al.[43] (2007) Alprazolam, diazepam, lorazepam vs	MA Patients with generalized anxiety disorder	N=2,326 (23 trials) 2 to 24 weeks	Primary: Withdrawals for any reason and withdrawals due to adverse events Secondary: Withdrawals due to lack of efficacy	Primary: The RR of withdrawal for any reason was 0.78 (95% CI, 0.62 to 1.00; P=0.05) in favor of benzodiazepines. The RR of withdrawal due to adverse events was 1.54 (95% CI, 1.17 to 2.03; P=0.002) indicating an increased risk for the benzodiazepine group. Secondary: The RR of withdrawal due to lack of efficacy was 0.29 (95% CI, 0.18 to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				0.45; P<0.00001) in favor of benzodiazepines.
Moylan et al.[44] (2011) Alprazolam vs benzodiazepines	MA Patients ≥18 years of age with panic disorder or agoraphobia with panic attacks	N=631 (8 trials) Variable duration	Primary: PAF, HAM-A, proportion of panic attack-free patients, adverse events Secondary: Not reported	Primary: There was no significant difference in mean PAF improvement between alprazolam and other benzodiazepines (WMD in PAF of 0.6 panic attacks/week; 95% CI, -0.3 to 1.6). There was no difference in mean HAM-A improvement between alprazolam and other benzodiazepines (WMD, 0.8 points; 95% CI, -0.5 to 2.1). There was no significant difference between alprazolam and other benzodiazepines in the proportion of panic-attack free patients (RR, 1.1; 95% CI, 0.9 to 1.4). The most commonly reported adverse effect was sedation. There was no significant difference in the dropout rates due to adverse effects. There was no clinically significant difference in tolerability between alprazolam and comparative benzodiazepine. Secondary: Not reported
Mitte et al.[45] (2005) Benzodiazepines vs azaspirones vs placebo	MA Patients with generalized anxiety disorder	N=12,053 (48 trials) Variable duration	Primary: Anxiety (HAM-A), depression (HAM-D) Secondary: Not reported	Primary: Active treatment reduced both anxiety and depression symptoms better than placebo. There were no significant differences in efficacy between the benzodiazepines and azaspirones (P=NS). Significantly fewer patients in the benzodiazepine group dropped out of the study (20.5 vs 30.7%; P<0.05). Secondary: Not reported
Blanco et al.[46] (2003) Benzodiazepines,	MA Patients with social anxiety disorder	N=2,954 (23 trials) 6 to 20 weeks	Primary: Outcome data on the LSAS or a categorical	Primary: In terms of LSAS, no statistical difference was detected between medications or medication groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
SSRIs, MAOIs, RIMAs, β-blockers, gabapentin, buspirone vs placebo			measure of status Secondary: CGI score	Secondary: In terms of responders, effect sizes of each medication group were: benzodiazepines (16.61), brofaromine (6.96), phenelzine (4.10), gabapentin (3.78), SSRIs (3.22), atenolol (1.36), and moclobemide (1.27). No statistical differences were detected between these medications or medication groups.
van Balkom et al.[47] (1997) Benzodiazepines vs antidepressants vs psychological panic management vs exposure in vivo vs placebo	MA Patients with panic disorder (with or without agoraphobia)	N=5,011 (106 trials) Variable duration	Primary: Panic, agoraphobia, depression, and general anxiety Secondary: Not reported	Primary: Antidepressants, psychological panic management and antidepressants/ exposure in vivo demonstrated significant improvement in the reduction of panic, agoraphobia, depression, and anxiety compared to a control conditions. High-potency benzodiazepines showed significant improvement in panic, agoraphobia, and anxiety compared to control conditions. There were no significant differences between the treatments for panic disorder. Antidepressant test groups had significant improvements compared to other treatments except exposure in vivo in agoraphobia. A significantly greater improvement was noted in antidepressant/exposure in vivo compared to exposure in vivo alone and psychological panic management/exposure in vivo in treatment of depression and anxiety. Secondary: Not reported
Chessick et al.[48] (2006) Benzodiazepines vs	MA Patients with generalized anxiety disorder	N=5,908 (36 trials) 4 to 14 weeks	Primary: HAM-A, patient acceptability Secondary: Not reported	Primary: Using the HAM-A, lorazepam (WMD, 1.1; 95% CI, 0.29 to 1.91; P=0.008) and alprazolam (WMD, 1.1; 95% CI, 0.28 to 1.92; P=0.009) were more effective than buspirone, but diazepam was comparable in efficacy to buspirone (WMD, -0.20; 95% CI, -7.45 to 7.05; P=0.96).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
azaspirones The MA also compared the azaspirones to hydroxyzine, kava kava, placebo, venlafaxine and psychotherapy, but only the results from studies comparing the azaspirones to the benzodiazepines are reported in this review.				Significantly fewer participants dropped out on benzodiazepine therapy compared to buspirone (RR, 1.24; 95% CI, 1.01 to 1.52; P=0.04). Patients receiving buspirone reported less drowsiness (P<0.00001), fatigue (P=0.00001), nervousness (P=0.0006), depression (P<0.00001), insomnia (P=0.01) and sleep problems (P=0.02) compared to benzodiazepines. Patients receiving benzodiazepines reported less nausea (P=0.03) and dizziness (P=0.02) compared to buspirone. In the trial that discontinued either diazepam or buspirone at either six or 12 weeks, neither group had worsening symptoms of anxiety but those on diazepam did show withdrawal symptoms at six weeks compared to those on buspirone (P<0.001). In the one extension trial with a taper off, 25% of patients on ipsapirone showed rebound anxiety symptoms compared to 40% of patients on lorazepam (P<0.001). Secondary: Not reported
Insomnia				
Holbrook et al.[49] (2000) Benzodiazepines vs zopiclone, diphenhydramine, glutethimide, promethazine, cognitive behavioral therapy, placebo	MA Patients with insomnia	N=2,672 (45 trials) 1 day to 6 weeks	Primary: Sleep latency, total sleep duration, adverse effects, dropout rates, cognitive function decline Secondary: Not reported	Primary: Using sleep records, benzodiazepines demonstrated a decrease in sleep latency by 4.2 minutes compared to placebo (95% CI, -0.7 to 9.2). Benzodiazepines demonstrated a significant increase in sleep duration compared to placebo by 61.8 minutes (95% CI, 37.4 to 86.2). Benzodiazepines were more likely to be associated with complaints of daytime drowsiness (OR, 2.4; 95% CI, 1.8 to 3.4) and dizziness/ lightheadedness (OR, 2.6; 95% CI, 0.7 to 10.3) compared to placebo. No difference was observed in dropout rates between the two groups. Pooled results from three trials indicated there was no significant difference between benzodiazepines and zopiclone in sleep latency, but benzodiazepine therapy may lead to a longer sleep by 23.1 minutes (95% CI, 5.6 to 40.6). There was no significant difference in adverse events among the treatment

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				groups (OR, 1.5; 95% CI, 0.8 to 2.9). Comparisons between benzodiazepines and antihistamines did not detect any significant differences on sleep outcomes. Triazolam was found to be more effective in reducing sleep latency early in one trial, but efficacy decreased by the second week of treatment. Behavioral therapy efficacy was maintained throughout the nine-week follow-up. Secondary: Not reported
Smith et al.[50] (2002) Benzodiazepines or benzodiazepine receptor agonists vs behavioral treatment vs placebo	MA Patients with primary insomnia for ≥1 month	N=470 (21 trials) 1 to 10 weeks	Primary: Sleep latency, TST, number of awakenings, wake time after sleep onset, and sleep quality before and after treatment Secondary: Not reported	Primary: Sleep latency was reduced by 30% with pharmacological treatment compared to 43% with behavioral interventions. Pharmacotherapy increased TST by 12% compared to 6% with behavior therapy. Both pharmacotherapy and behavior therapy reduced number of awakenings per night by one. Wake time after sleep onset was reduced by 46% with pharmacotherapy and by 56% with behavior therapy. Pharmacotherapy improved sleep quality by 20% compared to 28% with behavior therapy. Overall, there were no differences in TST, number of awakenings, wake time after sleep onset, and sleep quality between benzodiazepine receptor agonists and behavioral therapy. The behavioral therapy group had a greater reduction in latency to sleep onset than the group that took the benzodiazepine receptor agonists (95% CI, 0.17 to 1.04). Secondary: Not reported
Nowell et al.[51]	MA	N=1,894	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(1997) Benzodiazepines or benzodiazepine receptor agonists vs placebo	Adults <65 years of age with chronic insomnia	(22 trials) 4 to 35 days	Sleep latency, TST, number of awakenings, sleep quality Secondary: Not reported	Zolpidem and benzodiazepines were significantly more effective than placebo with regards to sleep latency, TST, number of awakenings and sleep quality (P<0.001). Secondary: Not reported
Buscemi et al.[52] (2007) Benzodiazepines, non-benzodiazepines, antidepressants vs placebo	MA Adults with chronic insomnia	105 trials 1 night to 6 months	Primary: Sleep latency, WASO, sleep efficiency, sleep quality, TST, adverse events Secondary: Not reported	Primary: Sleep latency assessed by PSG was significantly decreased for benzodiazepines (WMD, -10.0 minutes; 95% CI, -16.6 to -3.4), non-benzodiazepines (WMD, -12.8 minutes; 95% CI, -16.9 to -8.8) and antidepressants (WMD, -7.0 minutes; 95% CI, -10.7 to -3.3). Sleep latency assessed by sleep diaries was also significantly improved for benzodiazepines (WMD, -19.6 minutes; 95% CI, -23.9 to -15.3), non-benzodiazepines (WMD, -17.0 minutes; 95% CI, -20.0 to -14.0) and antidepressants (WMD, -12.2 minutes; 95% CI, -22.3 to -2.2). MA for WASO, sleep efficiency, sleep quality and TST measured by PSG and sleep diary were statistically significant and favored benzodiazepines and non-benzodiazepines vs placebo with the exception of PSG studies measuring WASO and TST, which were marginally nonsignificant. In contrast, PSG results significantly favored antidepressants vs placebo, but sleep diary results were fewer and non-significantly favored antidepressants for WASO and non-significantly favored placebo for TST. Indirect comparisons between benzodiazepines and non-benzodiazepines resulted in no significant difference in sleep latency; however, benzodiazepines were associated with more adverse events. Indirect comparisons between benzodiazepines and antidepressants resulted in no significant difference in sleep latency or adverse events. Indirect comparisons between non-benzodiazepines and antidepressants resulted in a significantly greater sleep latency assessed by PSG but not by

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				sleep diary for non-benzodiazepines. There was no significant difference in adverse events. All drug groups had a statistically significant higher risk of harm compared to placebo, although the most commonly reported adverse events were minor. The adverse events most commonly reported in these studies were headache, drowsiness, dizziness and nausea. Secondary: Not reported
Glass et al.[53] (2008) Temazepam 15 mg for 2 weeks vs diphenhydramine 50 mg for 2 weeks vs placebo for 2 weeks	DB, PC, RCT, XO Elderly patients ≥70 years of age with primary insomnia	N=20 6 weeks	Primary: Subjective assessments of sleep recorded on sleep diaries Secondary: Morning-after psychomotor impairment (using the DSST and the MTT); morning-after memory impairment (using free-recall)	Primary: There was a significant difference in sleep quality scores with temazepam compared to diphenhydramine and placebo (both P<0.05). There was a significant difference in sleep-onset latency and TST with temazepam compared to placebo (P<0.05). There was a significant difference in the number of awakenings with diphenhydramine and temazepam compared to placebo (both P<0.05). Secondary: There were no changes in the DSST or the MTT scores with any treatment. No treatment effects could be detected on the memory assessment performed.
Piccione et al.[54] (1980) Triazolam 0.25 mg vs triazolam 0.50 mg vs	DB, XO Elderly patients >60 years of age with insomnia	N=27 5 days	Primary: Efficacy (questionnaire with subjective estimates of sleep latency, TST, number of awakenings, overall quality of sleep), side effects	Primary: The patients' global evaluation of effectiveness indicated that triazolam 0.25 and 0.50 mg improved sleep more than placebo (both P<0.05), while chloral hydrate 250 and 500 mg were not better than placebo. Triazolam 0.50 mg, but not 0.25 mg, was significantly better than chloral hydrate 250 mg (P<0.01) and 500 mg (P<0.05) in the global evaluation of effectiveness. There was no significant difference in sleep latency, TST and number of awakenings between placebo and either dose of chloral hydrate.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
chloral hydrate 250 mg vs chloral hydrate 500 mg vs placebo			Secondary: Not reported	Triazolam 0.25 mg significantly decreased sleep latency and increased TST compared to placebo (both P<0.05). Triazolam 0.50 mg significantly decreased the number of awakenings compared to placebo (P<0.01). Patients estimated their TST to be longer following the use of triazolam 0.25 mg as compared to chloral hydrate 250 or 500 mg (both P<0.05). There were no significant differences in reported side effects between the active treatments and placebo. Secondary: Not reported
Okawa et al.[55] (1978) Secobarbital 100 mg vs triazolam 0.5 mg vs placebo	DB, RCT, XO (two trials) Patients 18 to 60 years of age with a history of insomnia and two of the following: onset of sleep longer than 30 minutes, duration of sleep six hours or less, or experiencing three or more awakenings	N=76 2 nights	Primary: Patient preference questionnaire, success (defined as sleep onset in 30 minutes or less and sleep duration of six hours or more), adverse effects Secondary: Not reported	Primary: One trial compared triazolam to placebo and involved 19 patients. Sixteen patients preferred triazolam over placebo and three expressed no preference (P<0.001). Triazolam demonstrated greater efficacy over placebo in overall sleep (P<0.001), onset (P<0.001), duration (P<0.002) and number of awakenings (P<0.002). Triazolam was determined to be significantly more successful in 15 of 19 patients (P<0.004). No difference in next-morning alertness was noted between the two study groups. Seven patients receiving active treatment experienced mild-to-moderate adverse effects, with dizziness, drowsiness and headache as the most frequently reported. In comparison, three of the patients in the placebo group experienced mild-to-moderate side effects. The second trial was a combined study of 57 patients comparing triazolam and secobarbital. The results of the patient preference questionnaire were analyzed and showed a significant preference for triazolam (41 patients) over secobarbital (10 patients), with six having no preference for either agent (P<0.001). Significant improvement was seen with triazolam compared to secobarbital (P<0.001) in sleep onset, duration of sleep and number of awakenings. Feelings of alertness the next morning did not differ between treatment groups. Success was established in 73% of triazolam treated patients whereas only 30% of the secobarbital treated patients were determined successful (P<0.001). Thirteen patients in the secobarbital group reported adverse effects ranging from drowsiness and restlessness to dry mouth. More patients on triazolam reported side effects.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Seizures				
Conry et al.[56] (2014) Clobazam adjunctive therapy	ES, OL Patients 2 to 60 years of age from two RCTs taking clobazam as adjunctive therapy for Lennox-Gastaut syndrome	N=267 2 to 6 years	Primary: Changes in rates of drop seizures and total seizures Secondary: Responder rates (≥50, ≥75, or 100% decreases in seizure frequency vs baseline), sustained efficacy over time, and global evaluations; safety	Primary: The high median percentage decrease from baseline in average weekly rate of drop seizures (85 to 91%) was maintained through year five. The median percentage decrease in total seizures was also maintained, with an 85% reduction from baseline in those patients who had reached year five. Secondary: The percentages of patients with decreases of ≥50, ≥75, or 100% in their average weekly seizure rates from the previous blinded study baseline were consistent over the five-year trial span for both drop and total seizures. Over five years, 62 to 69% achieved at least a 75% reduction in drop seizures, and 50 to 65% attained a 75% or more reduction in total seizures while treated with clobazam. The majority of patients were assessed by both their physicians and caregivers as "very much improved" or "much improved" after one, two, and three years of treatment. During the open-label study, 60% of patients experienced ≥1 treatment-related adverse event. The most common adverse events during the open label extension were upper respiratory tract infection (28%) and pyrexia (19%). The upper respiratory tract infection and pneumonia events occurred predominantly in pediatric patients.
Pavlidou et al.[57] (2006) Diazepam 0.33 mg/kg every 8 hours rectally for 1 day, followed by every 12 hours on day 2 vs	PRO, RCT Children 6 months to 3 years of age who experienced a first febrile seizure	N=139 3 years	Primary: Recurrence rates Secondary: Not reported	Primary: The 36-month recurrence rates in the no treatment group compared to the diazepam group were: 83 vs 38% (high-risk patients; P=0.005), 55 vs 35% (intermediate-risk patients; P=0.341), and 46 vs 33% (low-risk patients; P=0.412). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
no treatment				
Treiman et al.[58] (1998) Phenobarbital 15 mg/kg vs diazepam 0.15 mg/kg, followed by phenytoin 18 mg/kg vs lorazepam 0.1 mg/kg vs phenytoin 18 mg/kg	DB, MC, RCT Adults with overt or subtle generalized convulsive status epilepticus	N=518 5 years	Primary: Success (defined as cessation of all motor and electrical seizure activity within 20 minutes of start of drug infusion and no recurrence of seizure activity within the next 40 minutes), side effects, outcomes 30 days posttreatment Secondary: Not reported	Primary: For treatment success in overt status epilepticus, a significant difference overall in the frequency of success was found, reported as: lorazepam, 64.9%; phenobarbital, 58.2%; diazepam/phenytoin, 55.8%; and phenytoin, 43.6% (P<0.02 between all groups). For subtle status epilepticus, no significant differences were seen between treatment groups (P<0.18). Lorazepam showed significantly higher frequency of treatment success compared to phenytoin in a pairwise comparison of patients with overt status epilepticus (P<0.002). Pairwise comparisons among other individual treatments showed no significant differences. There were no significant differences among any of the treatment groups with respect to adverse effects or 30-day posttreatment outcomes. Secondary: Not reported
Appleton et al.[59] (2002) Lorazepam intravenous or rectally (dose not specified) vs diazepam intravenous or rectally (dose not specified)	MA Children 1 month to 16 years of age with acute tonic-clonic convulsions	N=102 1 year	Primary: Efficacy (cessation of the presenting convulsion, seizure recurrence within 24 hours of initial termination, need for additional drugs), safety (adverse events, admission to intensive care unit) Secondary:	Primary: Administration of one to two intravenous doses stopped the convulsion in 70% of lorazepam-treated patients compared to 65% of patients receiving intravenous diazepam (RR, 1.09; 95% CI, 0.77 to 1.54). A single dose of rectal lorazepam stopped the convulsion in all children (6/6), compared to 6/19 children treated with rectal diazepam (RR, 3.17; 95% CI, 1.63 to 6.14). Approximately 22% of intravenous lorazepam-treated children and 35% of intravenous diazepam-treated children experienced a further convulsion within 24 hours after presentation (RR, 0.63; 95% CI, 0.27 to 1.46). Approximately 4% of patients receiving intravenous lorazepam compared to 15% of patients receiving intravenous diazepam required additional

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Not reported	antiepileptic drugs to terminate the presenting seizure (RR, 0.25; 95% CI, 0.03 to 2.03). The incidence of respiratory depression occurring in the lorazepam-treated group was 4% compared to 21% in the diazepam-treated group (RR, 0.18; 95% CI, 0.02 to 1.37). Secondary: Not reported
Chamberlain et al.[60] (2014) Lorazepam 0.1 mg/kg intravenous vs diazepam 0.2 mg/kg intravenous Half of the treatment dose repeated at five minutes if necessary. If status epilepticus continued at 12 minutes, fosphenytoin was administered.	DB, RCT Patients 3 months <18 years of age with convulsive status epilepticus	N=273 4 hours	Primary: Cessation of status epilepticus by 10 minutes without recurrence within 30 minutes, assisted ventilation Secondary: Rates of seizure recurrence and sedation	Primary: Cessation of status epilepticus for 10 minutes without recurrence within 30 minutes occurred in 101 of 140 (72.1%) in the diazepam group and 97 of 133 (72.9%) in the lorazepam group, with an absolute efficacy difference of 0.8% (95% CI, −11.4 to 9.8%). Twenty-six patients in each group required assisted ventilation (16.0 in the diazepam vs 17.6% in the lorazepam groups; absolute risk difference, 1.6%; 95% CI, −9.9 to 6.8%). Secondary: The rates of recurrent generalized convulsions within 60 minutes, excluding patients who failed the primary outcome, were 10.9% for diazepam and 10.3% for lorazepam and the rates of recurrence within four hours were 38.6 and 39.2%, respectively. The only statistically significant difference between treatment groups in any of the secondary outcomes was in the incidence of sedation, which occurred in 81 of 162 diazepam patients (50%) and 99 of 148 lorazepam patients (66.9%) (absolute risk difference, 16.9%; 95% CI, 6.1 to 27.7%).
Prasad et al.[61] (2014) Lorazepam intravenous	MA Patients with status epilepticus	N=2755 (18 studies) Variable duration	Primary: Efficacy and safety Secondary: Not reported	Primary: Intravenous diazepam demonstrated a greater reduction than placebo in the risk of non-cessation of seizures (RR, 0.73; 95% CI, 0.57 to 0.92), requirement for ventilatory support (RR, 0.39; 95% CI, 0.16 to 0.94), or continuation of status epilepticus requiring use of a different drug or general anaesthesia (RR, 0.73; 95% CI, 0.57 to 0.92). Intravenous

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs diazepam intravenous or rectally vs phenytoin intravenous vs placebo				lorazepam demonstrated a lower risk than placebo for non-cessation of seizures (RR, 0.52; 95% CI, 0.38 to 0.71) and for risk of continuation of status epilepticus requiring a different drug or general anaesthesia (RR, 0.52; 95% CI, 0.38 to 0.71). Intravenous lorazepam demonstrated a greater reduction than intravenous diazepam for the risk of non-cessation of seizures (RR, 0.64; 95% CI, 0.45 to 0.90) and had a lower risk for continuation of status epilepticus requiring a different drug or general anaesthesia (RR, 0.63; 95% CI, 0.45 to 0.88). Intravenous lorazepam demonstrated a greater reduction than intravenous phenytoin for risk of non-cessation of seizures (RR, 0.62; 95% CI, 0.45 to 0.86). Diazepam gel demonstrated a greater reduction than placebo gel in the risk of non-cessation of seizures (RR, 0.43; 95% CI, 0.30 to 0.62). Secondary: Not reported
Miscellaneous				
Leufkens et al.[62] (2007) Alprazolam XR 1 mg vs alprazolam IR 1 mg vs placebo	DB, PC, XO Healthy individuals 20 to 45 years of age	N=18 Up to 5.5 hours after administration	Primary: Comparison of effects on actual driving ability (as assessed in a standard on-the-road driving test) measured by SDLP in centimeters) Secondary: Comparison of effects on cognitive and psychomotor functioning related to driving in a controlled laboratory setting	Primary: Both drug formulations significantly increased SDLP (P<0.001 for both IR and XR). However, mean SDLP after alprazolam XR was significantly lower than alprazolam IR (23.44 vs 27.68 cm, respectively; P<0.001). SDLP increased with approximately 8 cm in the IR group and 4 cm in the XR group as compared to placebo (19.5 cm with placebo; P<0.001 for both comparisons). No overall differences were found between placebo and either formulation of alprazolam in terms of mean speed and speed variability. Ten driving tests were terminated prematurely due to patients being too drowsy to continue (7/18 rides in the IR group and 3/18 rides in the XR group). Secondary: In terms of the divided attention task, performance was significantly impaired at 1 (P<0.001), 2.5 (P<0.001), and 5.5 hours (P<0.01) after administration of alprazolam IR 1 mg. The effects of the XR preparation were less severe than the IR formulation at one hour (P<0.05) and at 2.5 hours (P<0.5) but no longer at 5.5 hours postdose. A significant impairment on target detection by alprazolam IR compared to placebo was

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				noted for all times of measurement (P<0.05). Alprazolam XR did not differ significantly from placebo one hour postdose; however, there was a significant difference at 2.5 and 5.5 hours (P<0.05 for both). In terms of the stop signal task, relative to placebo, the go reaction time was significantly longer after alprazolam IR (P<0.001) but not after alprazolam XR. In terms of the word learning test, placebo-drug comparisons demonstrated a significant impairing effect of alprazolam IR at one hour after administration but not with alprazolam XR.
Hindmarch et al.[63] (2006) Flurazepam 30 mg vs zolpidem modified release 6.25 mg vs zolpidem modified release 12.5 mg vs placebo	DB, RCT, XO Healthy volunteers ≥65 years of age	N=24 Single dose treatment	Primary: Psychometric tests performed 8 hours after study medication (CFF, CRT, word recall, CTT, DSST), subjective evaluation of sleep (LSEQ), safety, pharmacokinetics (zolpidem modified release only) Secondary: Not reported	Primary: There were no significant differences in psychometric tests between the zolpidem modified release treatment groups and placebo (P>0.05). Psychometric performance was significantly impaired with flurazepam compared to placebo for all tests with the exception of the DSST (P=0.0526). Ease of falling asleep and sleep quality were significantly improved with both doses of zolpidem modified release and with flurazepam (all P<0.05). Neither zolpidem modified release, nor flurazepam, modified perception of well-being on awakening. The frequency of adverse events was similar in all four treatment conditions. None of the adverse events was serious or led to withdrawal from the study. The plasma concentration ratio was 1.96 between the two doses of zolpidem modified release, which is consistent with dose linearity. Secondary: Not reported
Johnson et al.[64] (2006) Triazolam 0.25,	DB, XO Adults with a history of sedative	N=14 18 days	Primary: Subject-rated measures (drug liking, street value,	Primary: Triazolam showed dose-related effects on subject-rated, observer-rated, and motor and cognitive performance measures.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
0.5 or 0.75 mg vs ramelteon 16, 80 or 160 mg vs placebo	abuse		pharmacological classification), observer-rated measures (sedation, impairment), motor and cognitive performance (balance task, DSST, word recall) Secondary: Not reported	Compared to placebo, all doses of ramelteon showed no significant effect on any of the subjective effect measures, including those related to potential for abuse (all P>0.05). In the pharmacological classification, 79% of patients identified the highest dose of ramelteon as placebo. Compared to placebo, ramelteon had no effect at any dose on any observer-rated or motor and cognitive performance measure (all P>0.05). Secondary: Not reported

Study abbreviations**:** CI=confidence interval, DB=double-blind, ES=extension study, MA=meta-analysis, MC=multi-center, NS=not significant, OL=open label, PC=placebo controlled, PRO=prospective trial, OR=odds ratio, RETRO=retrospective trial, RCT=randomized controlled trial, RR=relative risk, XO=crossover, WMD=weighted mean difference
Other abbreviations: AWS=alcohol withdrawal syndrome, CGI=Clinical Global Impression, CIWA-Ar=Clinical Institute Withdrawal Assessment of Alcohol Scale, CRT=choice reaction time, CPS=complex partial seizures, DSST=digit symbol substitution task, HAM-A=Hamilton Rating Scale for Anxiety, HAM-D=Hamilton Rating Scale for Depression, IR=immediate-release, LSAS=Lebowitz Social Anxiety Scale, LSEQ=Leeds sleep evaluation questionnaire, MAOI=monoamine oxidase inhibitor, MTT=manual tracking task, PAF=panic attack frequency, PSG=polysomnogram, RIMA=reversible inhibitor of monoamine-oxidase-A, SDLP=Standard Deviation of Lateral Position, SSRI=Selective serotonin reuptake inhibitor, XR=extended-release, TST=total sleep time, WASO=wake after sleep onset

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 13. Relative Cost of the Benzodiazepines

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Alprazolam	extended-release tablet, oral concentrate, orally disintegrating tablet, tablet	Xanax®*, Xanax XR®*	$$$-$$$$$	$
Chlordiazepoxide	capsule	N/A	N/A	$
Clobazam	oral suspension, tablet	Onfi®	$$$$$	N/A
Clonazepam	orally disintegrating tablet, tablet	Klonopin®*	$$$$	$
Clorazepate	tablet	Tranxene T-Tab®*	$$$$-$$$$$	$$
Diazepam	injection, oral concentrate, oral solution, rectal gel, tablet	Diastat®*, Diastat AcuDial®*	$$$$$	$
Estazolam	tablet	N/A	N/A	$
Flurazepam	capsule	N/A	N/A	$
Lorazepam	injection, oral concentrate, tablet	Ativan®*	$$$$-$$$$$	$
Midazolam	injection, oral syrup	N/A	N/A	$
Oxazepam	capsule	N/A	N/A	$$$
Temazepam	capsule	Restoril®*	$$$$$	$
Triazolam	tablet	Halcion®*	$$$	$$

*Generic is available in at least one dosage form or strength.
N/A=Not available

X. Conclusions

The benzodiazepines are approved for the treatment of anxiety disorders and for the short-term treatment of insomnia.[1-13] In addition, some of the agents are approved for the treatment of seizure disorders, acute alcohol withdrawal, as muscle relaxants, and for the induction/maintenance of general anesthesia.[1-13] The benzodiazepines are mechanistically similar; however, they differ with regards to their pharmacokinetic properties (e.g., onset and duration of action).[15,16] All of the benzodiazepines are available in a generic formulation, with the exception of clobazam.

The benzodiazepines that are approved for the treatment of anxiety include alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, lorazepam and oxazepam. The American Psychiatric Association recommends the initial use of either a serotonin-norepinephrine reuptake inhibitor (SNRI) or a selective serotonin reuptake inhibitor (SSRI) for the treatment of panic disorder due to their favorable safety and tolerability profiles.[18] However, benzodiazepines may be preferred for patients with very distressing or impairing symptoms in whom rapid symptom control is critical. They can be used concurrently with antidepressants to help control symptoms until the antidepressant takes effect, which is then followed by a slow tapering of the benzodiazepine.[18] For the long-term treatment of generalized anxiety disorder, the National Institute for Health and Clinical Excellence recommends the use of an SSRI as first-line therapy.[17] Benzodiazepines should only be used as a short-term measure during crises.[17] Benzodiazepines have been shown to be more effective than placebo, and have demonstrated similar efficacy compared to agents in other classes for the treatment of anxiety disorders.[18,43,45-48] Guidelines do not give preference to one particular benzodiazepine over another. The risk of adverse events and physiological dependence must be considered when using the benzodiazepines.[18] Benzodiazepines are not recommended as monotherapy for the treatment of obsessive-compulsive disorder or posttraumatic stress disorder.[19-23]

Several benzodiazepines are approved for the short-term treatment of insomnia, including estazolam, flurazepam, temazepam and triazolam. The American Academy of Sleep Medicine recommends the use of a short/intermediate-acting benzodiazepine, benzodiazepine receptor agonist, or ramelteon for the initial treatment of insomnia.[24] They do not give preference to one agent over another. Symptom pattern, treatment goals, past treatment responses, patient preference, comorbid conditions, contraindications, drug interactions, and adverse events should be considered when selecting a specific agent.[24] The frequency and severity of adverse events may be lower with benzodiazepine receptor agonists (e.g., eszopiclone, zaleplon, and zolpidem) due to their shorter half-lives.[25] Hypnotic treatments should be combined with behavioral and cognitive therapies.[24] Patients should be followed every few weeks during the initial treatment period to assess for effectiveness, adverse events, and the need for ongoing medication. Chronic use of hypnotic medications may be necessary in those individuals with severe/refractory insomnia or for those with chronic comorbid illnesses.[24] Results from clinical trials demonstrate that the benzodiazepines are effective for the short-term treatment of insomnia.[24,25,49,51-54]

Benzodiazepines may also be used for the treatment of seizure disorders, either as monotherapy or adjunctive therapy. It should be noted that other antiepileptic drugs are not currently included in the Preferred Drug Program. Diazepam is available in a rectal gel formulation, which is approved for the management of selected, refractory, patients with epilepsy who require intermittent use of diazepam to control bouts of increased seizure activity.[9] Clobazam is a newly included agent indicated for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in patients two years of age or older.[5]

There is insufficient evidence to support that one brand benzodiazepine is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all benzodiazepines within the class reviewed, with the exception of diazepam rectal gel, are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use. Diazepam rectal gel provides a beneficial route of administration compared to other agents in this class. Therefore, patients should be allowed approval for this agent through the medical justification portion of the prior authorization process.

XI. Recommendations

No brand benzodiazepine is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Anxiolytics, Sedatives, and Hypnotics – Miscellaneous
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I. Overview

The miscellaneous anxiolytics, sedatives, and hypnotics are used primarily for the treatment of anxiety disorders and insomnia. Anxiety disorders include generalized anxiety disorder, panic disorder, posttraumatic stress disorder, and social phobia.[1] The agents approved for the treatment of anxiety include buspirone, hydroxyzine, and meprobamate.[2-5] The exact mechanism of action of buspirone is unknown. It lacks anticonvulsant, muscle relaxant, or sedative properties, which are seen with other agents. The anxiolytic effects of hydroxyzine may be due to a suppression of activity in key regions of the subcortical area of the central nervous system. Meprobamate has been shown to have effects at multiple sites in the central nervous system, including the thalamus and limbic system.[2-5]

The key diagnostic feature of primary insomnia is difficulty initiating or maintaining sleep for at least three months, which causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.[1] Insomnia may be classified as episodic (symptoms last at least one month but less than three months), persistent (lasting three months or longer) or recurrent (two (or more) episodes within the space of one year).[1] Eszopiclone, zaleplon, and zolpidem are approved for the treatment of insomnia.[6-11] These agents are considered benzodiazepine receptor agonists; however, they are more selective than traditional benzodiazepines when binding to the $GABA_A$ receptor complex. Compared to the benzodiazepines, they have a more rapid onset, shorter duration of action, and a lower risk of tolerance, dependence, and abuse. They are classified as Schedule IV controlled substances by federal regulation.[6-11] Ramelteon is a melatonin receptor agonist, which is also approved for the treatment of insomnia.[12] It is more selective for the melatonin type 1 (MT_1) and type 2 (MT_2) receptors as compared to the type 3 (MT_3) receptor in the suprachiasmatic nucleus of the hypothalamus.[12] The MT_1 and MT_2 receptors are thought to be involved in the maintenance of the circadian rhythm underlying the normal sleep-wake cycle. Ramelteon is not a controlled substance. Discontinuation after chronic administration did not produce withdrawal signs and it does not appear to produce physical dependence.[12] Suvorexant (Belsomra®) was Food and Drug Administration (FDA) approved in 2014 for the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance. Suvorexant is a selective antagonist of orexin receptors (OX1R and OX2R). Orexin A and orexin B are neuropeptides that promote wakefulness. Blocking the binding of orexin to the orexin receptors is thought to suppress wakefulness.[13] Suvorexant is a Schedule IV controlled substance, producing similar effects as zolpidem in an abuse liability study.[13]

Some of the miscellaneous agents are also approved for the management of acute alcohol withdrawal, for use as a sedative (e.g., preoperative, prior to procedures, and in intubated or mechanically ventilated patients), for the management of nausea/vomiting from surgical/diagnostic procedures, and for the treatment of pruritus. Dexmedetomidine is a selective $alpha_2$-adrenergic agonist with sedative properties.[14] Droperidol is a butyrophenone antipsychotic. The antiemetic effect is due to the blockade of dopamine stimulation of the chemoreceptor trigger zone.[2,3] Other effects include alpha-adrenergic blockade, peripheral vascular dilation, and reduction of the pressor effect of epinephrine.

Since the last review, Hetlioz® (tasimelteon) was FDA approved for treatment of Non-24-Hour Sleep-Wake Disorder (non-24).[15] Tasimelteon is a melatonin receptor agonist with effects at the MT_1 and MT_2 receptors. Although the precise mechanism of tasimelteon in non-24 is unknown, these receptors are thought to be involved in the control of circadian rhythms.[15] This is the first FDA approval of a treatment for non-24, a chronic circadian rhythm disorder which occurs almost exclusively in persons who are completely blind, and the effectiveness of tasimelteon was evaluated in this population.[16]

Intermezzo® (zolpidem), a sublingual zolpidem formulation, was approved by the FDA for the as needed treatment of insomnia when a middle of the night awakening is followed by difficultly returning to sleep.[11] This is the first medication to be approved for this indication.[17] Intermezzo® (zolpidem) provides a lower dose of zolpidem compared to other zolpidem agents. Furthermore, the agent is formulated as a sublingual tablet that

employs a proprietary binary buffer system. This buffer system is theorized to increase salivary pH and facilitate the rapid sublingual absorption of the drug across the oral mucosa by conversion of the medication to its lipophilic form.[11]

In January 2013, the FDA released new recommendations that the dose of zolpidem be lowered due to new data suggesting that blood levels in some patients may be high enough the morning after use to impair activities that require alertness, including driving. Women appear to be more susceptible, as they eliminate zolpidem more slowly than men.[18] The FDA required the manufacturers of Ambien®, Ambien CR®, Edluar®, and Zolpimist® to lower the recommended dose. The recommended dose of zolpidem for women should be lowered from 10 to 5 mg for immediate-release products (Ambien®, Edluar®, and Zolpimist®) and from 12.5 to 6.25 mg for extended-release products (Ambien CR®). For men, the labeling should recommend that health care professionals consider prescribing the lower doses—5 mg for immediate-release products and 6.25 mg for extended-release products.[18] In May 2014, a similar safety communication was issued for eszopiclone, based on data that the 2 and 3 mg doses may be associated with impairment of driving skills, memory, and coordination lasting more than 11 hours without subjective awareness in some patients. A starting dose of 1 mg is now recommended in all patients.[19]

The miscellaneous anxiolytics, sedatives, and hypnotics that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. All of the products are available in a generic formulation, with the exception of ramelteon, suvorexant, and tasimelteon. This class was last reviewed in May 2014.

Table 1. Miscellaneous Anxiolytics, Sedatives, and Hypnotics Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Buspirone	tablet	N/A	buspirone
Dexmedetomidine	injection	Precedex®*	dexmedetomidine
Droperidol	injection	N/A	droperidol
Eszopiclone	tablet	Lunesta®*	eszopiclone
Hydroxyzine	capsule, solution, tablet	Vistaril®*	hydroxyzine
Meprobamate	tablet	N/A	meprobamate
Ramelteon	tablet	Rozerem®	none
Suvorexant	tablet	Belsomra®	none
Tasimelteon	capsule	Hetlioz®	none
Zaleplon	capsule	Sonata®*	zaleplon
Zolpidem	extended-release tablet, sublingual tablet, tablet	Ambien®*, Ambien CR®*, Edluar®, Intermezzo®	zolpidem

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List.
N/A=Not available.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the miscellaneous anxiolytics, sedatives, and hypnotics are summarized in Table 2.

Table 2. Treatment Guidelines Using the Miscellaneous Anxiolytics, Sedatives, and Hypnotics

Clinical Guideline	Recommendation(s)

National Institute for Clinical Excellence: **Generalized Anxiety Disorder and Panic Disorder in Adults: management (2011)**[20]	Stepped care for people with generalized anxiety disorder (GAD)
	• If a person with GAD chooses drug treatment, offer a selective serotonin reuptake inhibitor (SSRI), specifically sertraline.
	• If sertraline is ineffective, offer an alternative SSRI or a serotonin–noradrenaline reuptake inhibitor (SNRI), taking into account the following factors:
	  o Tendency to produce a withdrawal syndrome (especially with paroxetine and venlafaxine).
	  o The side-effect profile and the potential for drug interactions.
	  o The risk of suicide and likelihood of toxicity in overdose (especially with venlafaxine).

Clinical Guideline	Recommendation(s)
	o The person's prior experience of treatment with individual drugs (particularly adherence, effectiveness, side effects, experience of withdrawal syndrome and the person's preference). • If the person cannot tolerate SSRIs or SNRIs, consider offering pregabalin. • Do not offer a benzodiazepine for the treatment of GAD in primary or secondary care except as a short-term measure during crises. • Do not offer an antipsychotic for the treatment of GAD in primary care. <u>Panic disorder general considerations</u> • Benzodiazepines are associated with a less effective outcome in the long term and should not be prescribed for panic disorder. • Sedating antihistamines or antipsychotics should not be prescribed for panic disorder. • Interventions with evidence for the longest duration of effect are listed in descending order, where preference of the patient should be taken into account: o Psychological therapy (i.e., cognitive behavioral therapy, structured problem solving, psychoeducation). o Pharmacological therapy (antidepressant therapy). o Self-help interventions (i.e., bibliotherapy, support groups, exercise, cognitive behavioral therapy via a computer interface). • Antidepressants should be the only pharmacologic intervention used in the longer term. • Two types of medication are considered in the guideline for the treatment of panic disorder, tricyclic antidepressants (TCAs) and SSRIs. • Unless otherwise indicated, an SSRI (e.g., paroxetine, fluvoxamine, citalopram) licensed for panic disorder should be offered. If an SSRI is not suitable or there is no improvement after a 12-week course and if further medication is appropriate, imipramine or clomipramine may be considered. • If the patient is showing improvement, the medication should be continued for at least six months after optimal dose is reached, after which the dose may be tapered slowly over an extended period of time to minimize the risk of discontinuation/withdrawal symptoms.
American Psychiatric Association: **Practice Guideline for the Treatment of Patients with Panic Disorder, Second Edition (2009)**[21]	• SSRIs, SNRIs, TCAs, and benzodiazepines have demonstrated efficacy in numerous controlled trials and are recommended for treatment of panic disorder. • Because SSRIs, SNRIs, TCAs, and benzodiazepines appear roughly comparable in their efficacy for panic disorder, selecting a medication involves considerations of side effects, pharmacological properties, potential drug interactions, prior treatment history, and comorbid medical and psychiatric conditions. • The relatively favorable safety and side effect profile of SSRIs and SNRIs makes them the best initial choice for many patients with panic disorder. • There is no evidence of differential efficacy between the SSRIs, although differences in the side-effect profile (e.g., potential for weight gain, discontinuation-related symptoms), half-life, propensity for drug interactions, and availability of generic formulations may be clinically relevant. They are safer than TCAs and monoamine oxidase inhibitors (MAOI). They are rarely lethal in overdose and have few serious effects on cardiovascular function. • Venlafaxine extended release has been shown to be effective for panic disorder. It is generally well tolerated and has a side effect profile similar to the SSRIs. No systematic data are currently available supporting the use of duloxetine, in panic disorder, although its mechanism of action suggests it might be an effective agent. • Although TCAs are effective, the side effects and greater toxicity in overdose

Clinical Guideline	Recommendation(s)
	limit their acceptability to patients and clinical utility. Given the equivalency of TCAs in treating depression, there is little reason to expect other TCAs to work less well for panic disorder. TCAs that are more noradrenergic (e.g., desipramine, maprotiline) may be less effective than agents that are more serotonergic. • SSRIs, SNRIs, and TCAs are all preferable to benzodiazepines as monotherapies for patients with comorbid depression or substance use disorders. Benzodiazepines may be especially useful adjunctively with antidepressants to treat residual anxiety symptoms. • Benzodiazepines may be preferred for patients with very distressing or impairing symptoms in whom rapid symptom control is critical. The benefit of more rapid response to benzodiazepines must be balanced against the possibilities of troublesome side effects and physiological dependence that may lead to difficulty discontinuing the medication. • MAOIs appear effective for panic disorder but, because of their safety profile, they are generally reserved for patients who have failed to respond to several first-line treatments. • Neither trazodone nor nefazodone can be recommended as a first-line treatment for panic disorder. There is minimal support for the use of trazodone in panic disorder and it appears less effective than imipramine and alprazolam. There are a few small, uncontrolled studies showing benefits of nefazodone in some patients with panic disorder; however, its use has been limited by concerns about liver toxicity. • Bupropion was effective in one small trial and ineffective in another. It cannot be recommended as a first line treatment for panic disorder. • Other medications with less empirical data may be considered as monotherapies or adjunctive treatments for panic disorder when patients have failed to respond to several standard treatments or based on other individual circumstances.
American Academy of Child and Adolescent Psychiatry: **Practice Parameter for the Assessment and Treatment of Children and Adolescents With Obsessive-Compulsive Disorder (2012)**[22]	• The psychiatric assessment of children and adolescents should routinely screen for the presence of obsessions and/or compulsions or repetitive behaviors. • If screening suggests obsessive-compulsive symptoms, clinicians should fully evaluate the child using the Diagnostic and Statistical Manual of Mental Disorders-IV-TR criteria and scalar assessment. • A complete psychiatric evaluation should be performed, including information from all available sources and compromising standard elements of history and a mental state examination, with attention to the presence of commonly occurring comorbid psychiatric disorders. • It is possible that three out of four children with obsessive-compulsive disorder (OCD) meet criteria for at least one comorbid diagnosis, and these children have lower response rates to cognitive behavioral therapy than children without comorbid diagnoses. • Identification of major depressive disorder and bipolar disorder is very important before initiating treatment with a SSRI. • Comorbid eating disorders are infrequent in younger children; however, comorbid eating disorders become more prevalent in adolescents. • A full medical, developmental, family and school history should be included with the psychiatric history and examination. • Cognitive behavioral therapy is the first-line treatment for mild to moderate OCD in children, whenever possible. • For moderate to severe OCD, medication is indicated in addition to cognitive behavioral therapy. • Serotonin reuptake inhibitors (SRIs) are the first-line medications recommended for OCD in children, including clomipramine (a TCA) and

Clinical Guideline	Recommendation(s)
	certain SSRIs (fluoxetine, fluvoxamine, paroxetine and sertraline). • There is no SRI that is proven to be more efficacious over another. • The modality of assigned treatment should be guided by empirical evidence on the moderators and predictors of treatment response. • Multimodal treatment with cognitive behavioral therapy and medication is recommended if cognitive behavioral therapy fails to achieve a clinical response after several months or in more severe cases. • Medication augmentation strategies are reserved for treatment-resistant cases in which impairments are deemed moderate in at least one important domain of function despite adequate monotherapy. • Adding clomipramine to an SSRI is a useful medication augmentation strategy. • Augmenting with an atypical neuroleptic is also a strategy employed by experts (e.g. haloperidol and risperidone combined) based on studies in adults with OCD; however, controlled data for the use of atypical antipsychotics in children with OCD does not exist. • A minimum of two adequate SSRI trials or an SSRI and clomipramine trial is recommended before atypical augmentation. • Empirically validated medication and psychosocial treatments for comorbid disorders should be considered.
American Psychiatric Association: **Practice Guideline for the Treatment of Patients with Obsessive-Compulsive Disorder (2007)**[23]	General considerations • OCD is a chronic illness which typically waxes and wanes. • Patients who have symptoms interfering with daily functioning should be treated. • Clinical remission and recovery may not always occur and will not occur rapidly. • Goals of treatment include improving symptoms, patient functioning, and quality of life. Initial treatment options • The choice of treatment depends on the patient's ability to comply with therapy, whether psychotherapy, pharmacotherapy, or both. • First-line treatments include cognitive-behavioral therapy, SRIs, or a combination of the two. The choice depends on past treatment history, comorbid psychiatric conditions, severity of symptoms, and functional limitations. • Cognitive-behavioral therapy or SRI therapy may be used alone or in combination, and combination therapy may be considered in patients who do not respond fully to monotherapy, those with severe symptoms, those with comorbid psychiatric illnesses for which an SRI is indicated, or in patients who wish to limit SRI exposure. • All SRIs appear to be equally effective, though patients may respond to agents differently. • Prescribers should consider the safety, side effects, Food and Drug Administration (FDA) warnings, drug interactions, past response to treatment, and comorbid medical conditions when choosing a medication for treatment. • Most patients do not experience a significant improvement until four to six weeks after treatment initiation, and some may ultimately respond after as many as 10 to 12 weeks. • Patients not responding after 10 to 12 weeks may respond to a higher dose of the same medication. Changing treatments and pursuing sequential treatment trials • Augmentation strategies may be preferred to switching strategies in patients who have a partial response to the initial treatment.

Clinical Guideline	Recommendation(s)
	• Augmentation of SRIs with trials of different antipsychotic medications or with cognitive-behavioral therapy or augmentation of cognitive-behavioral therapy with an SRI. • Patients who do not respond to their first SRI may have their medication switched to a different SRI. A switch to venlafaxine is less likely to produce an adequate response. • For patients who have not benefitted from their first SSRI trial, a switch to mirtazapine can be considered. • After first- and second-line treatments and well-supported augmentation strategies have been exhausted, less well-supported treatment strategies may be considered. These include augmenting SRIs with clomipramine, buspirone, pindolol, riluzole, or once- weekly oral morphine sulfate. • Evidence for beneficial effects of benzodiazepines as monotherapy for OCD is limited to case reports with clonazepam and alprazolam. Modest doses of benzodiazepines may relieve anxiety and distress in OCD without directly diminishing the frequency or duration of obsessions or compulsions. Given their limited evidence for efficacy, benzodiazepines cannot be recommended as monotherapy for OCD, except in those rare individuals who are unable or unwilling to take standard anti-OCD medications.
American Academy of Child and Adolescent Psychiatry: **Practice Parameter for the Assessment and Treatment of Children and Adolescents With Posttraumatic Stress Disorder (2010)**[24]	• The psychiatric evaluation of children and adolescents should routinely include questions about traumatic experiences and posttraumatic stress disorder (PTSD) symptoms. • If the evaluation indicates symptoms of PTSD, the clinician should formally determine if PTSD is present, the severity of PTSD symptoms and the degree of functional impairment. Caregivers should be included in the formal evaluation. • A differential diagnosis should be conducted in order to rule out diagnoses with symptoms that can mimic PTSD symptoms. • The treatment plan should be comprehensive in approach and should consider the severity of symptoms and impairment, as well as comorbid psychiatric conditions. • Trauma-focused psychotherapies should be considered first-line in children and adolescents with PTSD, including psychoanalytic, attachment and cognitive behavioral treatment models. • SSRIs can be considered for treatment of children and adolescents with PTSD. • The effect of SSRIs in children with PTSD may be more consistent with a placebo effect. • Other medications such as clonidine and propranolol may be useful in decreasing symptoms of hyperarousal, and anticonvulsants may beneficial in treating PTSD symptoms other than avoidance. • Benzodiazepines have not been found to be beneficial in treating PTSD symptoms. • School-based accommodations are recommended for children with PTSD, especially in children with school-based trauma, such as bullying. • The use of restrictive, “rebirthing,” binding or other coercive therapies are not recommended. • Screening for PTSD in the school or community should be conducted after traumatic events that affect significant numbers of children.
American Psychiatric Association: **Guideline Watch: Practice Guideline for the Treatment of Patients with Acute**	• Meta-analyses and several randomized controlled trials published since 2004 support the greater efficacy of SSRIs and SNRIs over placebo for non-combat-related PTSD. • The evidence base for pharmacological intervention in combat-related PTSD has not been significantly augmented by recent studies. Studies suggest that SSRIs may not be recommended with the previous level of confidence for the

Clinical Guideline	Recommendation(s)
Stress Disorder and Posttraumatic Stress Disorder (2009)[25]	treatment of PTSD in this particular population. Further research is needed to answer why these populations have been shown to have differential responses to SSRI treatment. • As described in the 2004 guideline, no significant differences among antidepressants, including the SSRIs, were found in the few head-to-head studies then available. Since that time, studies have been published comparing nefazodone and sertraline, venlafaxine and sertraline, the SNRI reboxetine and fluvoxamine, and fluoxetine, moclobemide, and tianeptine. These studies have generally demonstrated the greater efficacy of antidepressants to placebo but have done little to clarify the relative utility of these different antidepressants. • There is a relatively robust evidence basis for pharmacological treatment with antidepressant medications (particularly SSRIs and SNRIs for noncombat PTSD) as compared to other classes of medications. • Comparison of other treatments with the SSRIs and SNRIs is complicated by methodological differences in the available studies. SSRIs and SNRIs have mostly been studied in rigorous trials compared to placebo; other agents have been studied against "treatment as usual" or as augmentation agents in patients with refractory illness.
American Psychiatric Association: **Practice Guideline for the Treatment of Patients with Acute Stress Disorder and Posttraumatic Stress Disorder (2004)**[26]	• Goals of treatment for patients with PTSD and acute stress disorder include lessening the severity of symptoms and preventing trauma-related comorbid conditions. • Clinical trial data and randomized studies are limited and difficult to perform. • Treatment includes pharmacotherapy, psychotherapy and supportive measures. • SSRIs are first-line therapy for PTSD and acute stress disorder and if found effective, treatment should be continued in order to continue to see benefit. • Second-line treatment agents include TCAs (specifically amitriptyline and imipramine, but not desipramine) and MAOIs. • Benzodiazepines should not be used as monotherapy, but may be effective as sedatives and anxiolytics. • Atypical antipsychotics may be necessary for patients experiencing psychotic symptoms. • Anticonvulsants (divalproex, carbamazepine, topiramate and lamotrigine) have produced mixed results for treating PTSD and acute stress disorder but may prove to be beneficial. • Limited data exists for the use of adrenergic inhibitors and their use is not part of the guideline at this time. • An adequate trial of therapy requires a minimum of three months of treatment. If treatment is effective, it should be continued for up to 12 months or longer.
American Academy of Sleep Medicine: **Clinical Guideline for the Evaluation and Management of Chronic Insomnia in Adults (2008)**[27]	• The primary treatment goals are to improve sleep quality/quantity and to improve insomnia related daytime impairments. • Short-term hypnotic treatment should be supplemented with behavioral and cognitive therapies when possible. • When pharmacotherapy is utilized, the choice of a specific pharmacological agent should be directed by: symptom pattern, treatment goals, past treatment responses, patient preference, availability of other treatments, comorbid conditions, contraindications, concurrent medication interactions, and side effects. • For patients with primary insomnia, when pharmacologic treatment is utilized alone or in combination therapy, the recommended general sequence of medication trials is: o Short-intermediate acting benzodiazepine receptor agonists or ramelteon.

Clinical Guideline	Recommendation(s)
	o Alternate short-intermediate acting benzodiazepine receptor agonists or ramelteon if the initial agent has been unsuccessful. o Sedating antidepressants, especially when used in conjunction with treating comorbid depression/anxiety. Examples of these include trazodone, amitriptyline, doxepin, and mirtazapine. o Combined benzodiazepine receptor agonists or ramelteon and sedating antidepressant. o Other sedating agents. Examples include anti-epilepsy medications (gabapentin, tiagabine) and atypical antipsychotics (quetiapine and olanzapine). These medications may only be suitable for patients with comorbid insomnia who may benefit from the primary action of these drugs as well as from the sedating effect. • Over-the-counter antihistamine or antihistamine/analgesic type drugs (over-the-counter "sleep aids"), as well as herbal and nutritional substances (e.g., valerian and melatonin), are not recommended in the treatment of chronic insomnia due to the relative lack of efficacy and safety data. • Older approved drugs for insomnia including barbiturates, barbiturate-type drugs and chloral hydrate are not recommended for the treatment of insomnia. • Pharmacological treatment should be accompanied by patient education regarding treatment goals, safety concerns, potential side effects and drug interactions, other treatment modalities (cognitive and behavioral treatments), potential for dosage escalation, and rebound insomnia. • Patients should be followed on a regular basis, every few weeks in the initial period of treatment when possible, to assess for effectiveness, possible side effects, and the need for ongoing medication. • Efforts should be made to employ the lowest effective maintenance dosage of medication and to taper medication when conditions allow. Medication tapering and discontinuation are facilitated by cognitive behavioral therapy for insomnia. • Chronic hypnotic medication may be indicated for long-term use in those with severe or refractory insomnia or chronic comorbid illness. Whenever possible, patients should receive an adequate trial of cognitive behavioral treatment during long-term pharmacotherapy. • Long-term prescribing should be accompanied by consistent follow-up, ongoing assessment of effectiveness, monitoring for adverse effects, and evaluation for new onset or exacerbation of existing comorbid disorders. • Long-term administration may be nightly, intermittent (e.g., three nights per week), or as needed.
National Institutes of Health: **Manifestations and Management of Chronic Insomnia in Adults (2005)**[28]	<u>Behavioral and cognitive therapies</u> • Behavioral methods include relaxation training, stimulus control, and sleep restriction. • Cognitive therapy methods have been added to behavioral methods and include cognitive restructuring, in which anxiety-producing beliefs and erroneous beliefs about sleep and sleep loss are specifically targeted. • The combination of cognitive methods and behavioral methods has been found to be as effective as prescription medications for short-term treatment of chronic insomnia. The beneficial effects of cognitive-behavioral therapy may last well beyond the termination of active treatment. <u>Benzodiazepine receptor agonists</u> • Benzodiazepine receptor agonists include benzodiazepines (e.g., flurazepam, temazepam, and triazolam) as well as nonbenzodiazepine-structured anxiolytic agents acting at benzodiazepine receptors (e.g., eszopiclone, zaleplon, and zolpidem). • Benzodiazepine receptor agonists have been shown to be effective in the

Clinical Guideline	Recommendation(s)
	short-term management of insomnia. • The frequency and severity of the adverse effects are much lower for the newer benzodiazepine receptor agonists, most likely because these agents have shorter half-lives. • In the short term, abuse of the benzodiazepine receptor agonists is not a major problem, but problems associated with their long-term use require further study. • Barbiturates (e.g., phenobarbital) have been used in the treatment of insomnia, however, short-term and long-term studies are lacking; such drugs bear significant risks and are not recommended in the treatment of chronic insomnia. <u>Other prescription medications</u> • Other sedating medications have been used in the treatment of insomnia. These include barbiturates and antipsychotics. • Studies demonstrating the usefulness of these medications for either short- or long-term management of insomnia are lacking. • All of these agents have significant risks. Thus, their use in the treatment of chronic insomnia cannot be recommended. <u>Antidepressants</u> • Antidepressants (especially trazodone) are often prescribed for insomnia, although they are not FDA-approved for this purpose. • In short-term use, trazodone and doxepin have been shown to have some beneficial effects, but there are no studies on long-term use. • Data on other antidepressants (e.g., amitriptyline and mirtazapine) in individuals with chronic insomnia are lacking. • These guidelines were published prior to the FDA approval of ramelteon. <u>Nonprescription medications</u> • Antihistamines are the most commonly used over-the-counter treatments for chronic insomnia, but there is no systematic evidence for efficacy and there are significant concerns about risks of these medications. • Adverse effects include residual daytime sedation, diminished cognitive function, and delirium, the latter being of particular concern in the elderly. Other adverse effects include dry mouth, blurred vision, urinary retention, constipation, and risk of increased intraocular pressure in individuals with narrow angle glaucoma.
American Society for Gastrointestinal Endoscopy: **Sedation and Anesthesia in Gastrointestinal Endoscopy (2008)**[29]	• Adequate and safe sedation can be achieved in most patients undergoing routine esophagogastroduodenoscopy and colonoscopy by using an intravenous benzodiazepine and opioid combination. • In patients who are not adequately sedated with an intravenous benzodiazepine and opioid combination, the addition of other intravenous agents such as droperidol, promethazine, or diphenhydramine may allow adequate and safe sedation to be achieved. These medications potentiate the action of the benzodiazepine/narcotic regimen; thus, a deeper level of sedation may result. • Droperidol is a neuroleptic agent in the same class as haloperidol with sedative effects. Randomized trials have demonstrated the efficacy of droperidol in patients undergoing therapeutic endoscopy, particularly those who are difficult to sedate. • Use droperidol only in select patients with the inability to achieve an acceptable response or intolerance to standard sedatives, or for an anticipated long procedure. o Obtain 12-lead electrocardiogram before procedure.

Clinical Guideline	Recommendation(s)
	o Droperidol is contraindicated if the QTc is prolonged (>440 milliseconds in males, >450 milliseconds in females). o Patients should remain on a cardiac monitor during the procedure and for two to three hours afterward. o Use with caution in patients at high risk for development of prolonged QT syndrome such as congestive heart failure, bradycardia, cardiac hypertrophy, hypokalemia/magnesemia, or other drugs known to prolong the QTc interval. • Propofol has the advantages of more rapid onset of action and shorter recovery time compared to traditional sedative regimens. However, clinically important benefits in average-risk patients undergoing upper endoscopy and colonoscopy have not been consistently demonstrated with regard to patient satisfaction and safety. Therefore, the routine use of propofol in average- risk patients cannot be endorsed.
Society for Ambulatory Anesthesia: **Consensus Guidelines for the Management of Postoperative Nausea and Vomiting (2014)**[30]	Prevention of postoperative nausea and vomiting (PONV) in adults • The efficacy of dexamethasone 4 mg intravenous, ondansetron 4 mg intravenous and droperidol 1.25 mg intravenous for the prevention of postoperative nausea and vomiting appears to be similar. • Ondansetron, dolasetron, granisetron, and tropisetron are most effective in the prophylaxis of PONV when given at the end of surgery, although; some data on dolasetron suggest timing may have little effect on efficacy. Palonosetron is typically given at the start of surgery. • Aprepitant is similar to ondansetron in achieving complete response (no vomiting and no use of rescue antiemetic) for 24 hours after surgery. However, aprepitant was significantly more effective than ondansetron for preventing vomiting at 24 and 48 hours after surgery and in reducing nausea severity in the first 48 hours after surgery. It also has a greater antiemetic effect compared with ondansetron. • Systematic reviews have demonstrated that 5-HT_3 receptor antagonists in combination with dexamethasone or droperidol are more effective than monotherapy with any of the agents. • Droperidol in combination with dexamethasone is more effective than either agent as monotherapy. • Combinations that include metoclopramide have not been shown to be more effective than monotherapy. Prevention of postoperative nausea and vomiting in children • Children are at increased risk of postoperative nausea and vomiting compared to adults. • Children at moderate to high risk for postoperative nausea and vomiting should receive combination therapy with two to three prophylactic agents from different classes. • Ondansetron has been studied extensively in pediatric patients and is approved for patients as young one month of age. • There is now good evidence to suggest that 5-HT_3 antagonists and dexamethasone are the most effective antiemetics in the prophylaxis of pediatric postoperative nausea Treatment of PONV in patients who failed or did not receive prophylaxis • If prophylactic therapy fails, an agent from a different pharmacologic class should be selected for treatment. • If no prophylactic therapy was given, first-line treatment should include a low-dose 5-HT_3 antagonist.
American Gastroenterological	• In clinical studies, dimenhydrinate and meclizine, among others, have shown efficacy in the prevention and treatment of motion sickness.

Clinical Guideline	Recommendation(s)
Association: **Technical Review: Nausea and Vomiting (2001)**[31]	• Prochlorperazine may be used to treat more severe nausea and vomiting due to vertigo or motion sickness. • Trimethobenzamide has been used in the treatment of moderate to severe nausea and vomiting in a variety of clinical contexts. • Scopolamine is used principally for prophylaxis and treatment of motion sickness. • In pregnant patients with more severe symptoms and hyperemesis, hospitalization, fluid and electrolyte replacement, thiamine supplementation, and administration of antiemetics including antihistamines, such as meclizine may be used. For more severe cases of hyperemesis gravidarum, parenteral prochlorperazine may be used. • For the prevention of acute post chemotherapy- and radiation-related nausea and vomiting, the combination of a 5-HT_3 receptor antagonist and dexamethasone is the preferred option. • Scopolamine has been shown to have mild efficacy against cytotoxic chemotherapy-related nausea and vomiting and may have a role as adjunctive therapy in this context. • 5-HT_3 antagonists have been shown to be more effective than either placebo or other agents such as prochlorperazine in the prevention of radiotherapy-induced nausea and vomiting, as well as in the treatment of nausea and vomiting that is unrelated to chemotherapy and radiation therapy in cancer patients. • The various 5-HT_3 antagonists appear to be of similar efficacy and have a comparable incidence of side effects. • For postoperative nausea and vomiting, the use of a 5-HT_3 receptor antagonist and droperidol have been proven to be the most effective compared to placebo and with other agents in large randomized trials. Comparisons between the various 5-HT_3 antagonists or between members of this class of compounds and droperidol have generally found similar efficacies for all. • Dronabinol is available for use in the United States and is indicated for anorexia resulting in weight loss among patients with the acquired immunodeficiency syndrome and for refractory chemotherapy-related nausea and vomiting.
National Institute for Health and Clinical Excellence: **Alcohol-Use Disorders: Diagnosis, Assessment and Management of Harmful Drinking and Alcohol Dependence (2011)**[32] **Reaffirmed 2015**	<u>Treatment for acute alcohol withdrawal</u> • Offer pharmacotherapy to treat the symptoms of acute alcohol withdrawal. • Consider offering a benzodiazepine or carbamazepine. • Clomethiazole may be offered as an alternative to a benzodiazepine or carbamazepine. <u>Management of delirium tremens</u> • Lorazepam is considered a first-line treatment option. • If symptoms persist or oral medication is declined, give parenteral lorazepam, haloperidol or olanzapine. <u>Management of alcohol withdrawal seizures</u> • In people with alcohol withdrawal seizures, consider offering a quick-acting benzodiazepine (e.g., lorazepam) to reduce the likelihood of further seizures. • Do not offer phenytoin to treat alcohol withdrawal seizures.
American Psychiatric Association: **Treatment of Patients with Substance Use Disorders, Second Edition (2007)**[33]	<u>Alcohol use disorders: treatment principles and alternatives</u> • The treatment of patients in moderate to severe withdrawal includes efforts to reduce central nervous system irritability and restore physiological homeostasis. • Management of alcohol withdrawal generally requires the use of thiamine and fluids, benzodiazepines, and occasionally other medications such as anticonvulsants, clonidine, or antipsychotic agents.

Clinical Guideline	Recommendation(s)
	• Once clinical stability is achieved, the tapering of benzodiazepines and other medications should be carried out as necessary. • Naltrexone may attenuate some of the reinforcing effects of alcohol; however, long-term data regarding efficacy are limited. • Acamprosate may also be an effective adjunctive medication in motivated patients who are receiving psychosocial treatment. • Disulfiram is an effective adjunct to a comprehensive treatment program for reliable, motivated patients whose drinking may be triggered by events that suddenly increase alcohol craving.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the miscellaneous anxiolytics, sedatives, and hypnotics are noted in Tables 3 and 4. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Miscellaneous Anxiolytics, Sedatives, and Hypnotics (Drugs B-H)[2-15]

Indication	Buspirone	Dexmedetomidine	Droperidol	Eszopiclone	Hydroxyzine
Anxiety Disorders					
Management of anxiety disorders	✔				
Short-term relief of symptoms of anxiety	✔				
Symptomatic relief of anxiety and tension associated with psychoneurosis and as an adjunct in organic disease states in which anxiety is manifested					✔
Sedative-Hypnotic					
Sedation when used as premedication and following general anesthesia					✔
Sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting; administer by continuous infusion not to exceed 24 hours		✔			
Sedation of non-intubated patients prior to and/or during surgical and other procedures		✔			
Treatment of insomnia (shown to decrease sleep latency and improve sleep maintenance)				✔	
Miscellaneous					
Management of pruritus caused by allergic conditions such as chronic urticaria and atopic or contact dermatoses and in histamine-mediated pruritus					✔
To reduce the incidence of nausea and vomiting associated with surgical and diagnostic procedures			✔		

Table 4. FDA-Approved Indications for the Miscellaneous Anxiolytics, Sedatives, and Hypnotics (Drugs M-Z)[2-15]

Indication	Meprobamate	Ramelteon	Suvorexant	Tasimelteon	Zaleplon	Zolpidem
Anxiety Disorders						
Management of anxiety disorders	✔					
Short-term relief of symptoms of anxiety	✔					
Sedative-Hypnotic						

Indication	Meprobamate	Ramelteon	Suvorexant	Tasimelteon	Zaleplon	Zolpidem
Short-term treatment of insomnia (shown to decrease the time to sleep onset for up to 30 days in controlled clinical studies; it has not been shown to increase total sleep time or decrease the number of awakenings; the clinical trials performed in support of efficacy ranged from a single night to five weeks in duration; the final formal assessments of sleep latency were performed at the end of treatment)					✔	
Short-term treatment of insomnia characterized by difficulties with sleep initiation (shown to decrease sleep latency for up to 35 days in controlled clinical studies)						✔ *
Insomnia when a middle-of-the-night awakening is followed by difficulty returning to sleep (not indicated for the treatment of middle-of-the night awakening when the patient has fewer than four hours of bedtime remaining before the planned time of waking)						✔ †
Treatment of insomnia characterized by difficulty with sleep onset		✔				
Insomnia characterized by difficulties with sleep onset and/or sleep maintenance			✔			✔ ‡
Miscellaneous						
Treatment of Non-24-Hour Sleep-Wake Disorder				✔		

*Immediate-release formulations (oral spray, sublingual tablet [Edluar®], and tablet).
†Immediate-release formulations (sublingual tablet [Intermezzo®].
‡Extended-release formulation.

IV. Pharmacokinetics

The pharmacokinetic parameters of the miscellaneous anxiolytics, sedatives, and hypnotics are listed in Table 5.

Table 5. Pharmacokinetic Parameters of the Miscellaneous Anxiolytics, Sedatives, and Hypnotics[3]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Buspirone	Variable	86	Liver	Renal (29 to 63) Feces (18 to 38)	2.4 to 2.7
Dexmedetomidine	Not reported	94	Liver	Renal (95) Feces (4)	2 to 2.7
Droperidol	Complete	Extensive	Liver	Renal (75) Feces (22)	2
Eszopiclone	Rapidly absorbed	Not reported	Liver	Renal	5 to 6
Hydroxyzine	Rapidly absorbed orally	Not reported	Liver	Not reported	3 to 20
Meprobamate	Well absorbed	0 to 30	Liver	Renal (10 to 20)	9 to 11
Ramelteon	1.8	82	Liver	Renal (84) Feces (4)	1.0 to 2.6
Suvorexant	82	>99	Liver	Renal (23) Feces (66)	12
Tasimelteon	38.3	90	Liver	Renal (80) Feces (4)	1.3
Zaleplon	30	60	Liver	Renal (71) Feces (17)	1
Zolpidem	70	93	Liver	Renal (<1)	2.5 to 3.0

V. Drug Interactions

Major drug interactions with the miscellaneous anxiolytics, sedatives, and hypnotics are listed in Table 6.

Table 6. Major Drug Interactions with the Miscellaneous Anxiolytics, Sedatives, and Hypnotics[3]

Generic Name(s)	Interaction	Mechanism
Buspirone	Linezolid	Serotonin syndrome (e.g., agitation, altered consciousness, ataxia, myoclonus, overactive, reflexes, shivering) may occur in some patients. Unless patients are carefully observed for signs and symptoms of serotonin syndrome, do not coadminister.
Buspirone	Tranylcypromine	Concurrent use of buspirone and tranylcypromine may result in hypertensive crisis.
Buspirone	Phenelzine	Concurrent use of phenelzine and buspirone may result in hypertensive crisis.
Buspirone	Isocarboxazid	Concurrent use of isocarboxazid and buspirone may result in hypertensive crisis.
Buspirone	Monoamine oxidase inhibitors	Concurrent use of buspirone and monoamine oxidase inhibitors may result in hypertensive crisis.
Buspirone	Clozapine	Concurrent use of clozapine and buspirone may result in an increased risk of gastrointestinal bleeding and hyperglycemia.
Buspirone	Procarbazine	Concurrent use of buspirone and procarbazine may result in hypertensive crisis.
Droperidol	Ziprasidone	The combination of ziprasidone and droperidol may have cause additive prolongation of the QT interval.
Droperidol	Neuroleptics (molindone, clozapine,	Concurrent use of droperidol and neuroleptics may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).

Generic Name(s)	Interaction	Mechanism
	perphenazine, triflupromazine, remoxipride, acetophenazine, bromperidol, tiapride, pipamperone)	
Droperidol	Fluoroquinolones	Concurrent use of droperidol and fluoroquinolones may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
Droperidol	Tricyclic antidepressants, monoamine oxidase inhibitors, phenothiazines	Concurrent use of droperidol and tricyclic antidepressants may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
Droperidol	Class I and III antiarrhythmics	Concurrent use of droperidol and antiarrhythmic agents may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
Droperidol	Diuretics	Concurrent use of droperidol and diuretics may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
Droperidol	Laxatives	Concurrent use of droperidol and laxatives may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
Droperidol	Antimalarials	Concurrent use of droperidol and antimalarials may result in an increased risk of cardiotoxicity (QT prolongation, torsade de pointes, cardiac arrest).
Droperidol	Calcium channel blockers	Concurrent use of droperidol and calcium channel blockers may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
Droperidol	Tyrosine kinase inhibitors	Concurrent use of droperidol and tyrosine kinase inhibitors may result in an increased risk of QT interval prolongation.
Eszopiclone, zaleplon	Ketoconazole	Concurrent use of eszopiclone or zaleplon and ketoconazole may result in increased plasma concentrations of eszopiclone or zaleplon.
Eszopiclone	Selected strong CYP3A4 inhibitors (nelfinavir, saquinavir, delavirdine, lopinavir, tipranavir, posaconazole, boceprevir, telaprevir, cobicistat, atazanavir)	Concurrent use of eszopiclone and selected strong CYP3A4 inhibitors may result in increased plasma concentrations of eszopiclone.
Ramelteon	Fluvoxamine	Plasma concentrations of ramelteon/zolpidem may be increased by coadministration of fluvoxamine. Inhibition of CYP1A2 by fluvoxamine may decrease the metabolic elimination of ramelteon/zolpidem.
Suvorexant	CYP3A4 inhibitors	Concurrent use of suvorexant and selected CYP3A4 inhibitors may result in increased plasma concentrations of suvorexant.
Suvorexant	CNS depressants	Concurrent use of suvorexant and CNS depressants may result in CNS depression.

Generic Name(s)	Interaction	Mechanism
Tasimelteon	Selected strong CYP1A2 inhibitors (abiraterone, ciprofloxacin, enoxacin, fluvoxamine)	Concurrent use of tasimelteon and selected strong CYP1A2 inhibitors may result in increased tasimelteon exposure and increased risk of tasimelteon adverse events.
Tasimelteon	Selected strong CYP1A2 inducers (phenytoin, carbamazepine, primidone, phenobarbital, rifampin, rifabutin, fosphenytoin, st john's wort, rifapentine, enzalutamide)	Concurrent use of tasimelteon and selected strong CYP3A4 inducers may result in decreased tasimelteon exposure with reduced tasimelteon efficacy.
Zolpidem	Human immunodeficiency virus protease inhibitors	Inhibition of CYP3A4 by protease inhibitors may decrease the metabolic elimination and increase plasma concentrations of eszopiclone and zolpidem.
Zolpidem	Sedatives	Concurrent use of zolpidem and sedatives may result in an increase in central nervous system depressant effects.
Zolpidem	Carbamazepine	Concurrent use of carbamazepine and zolpidem may result in decreased zolpidem plasma concentrations.

VI. Adverse Drug Events

The most common adverse drug events reported with the miscellaneous anxiolytics, sedatives, and hypnotics are listed in Tables 7 and 8. The boxed warning for droperidol is listed in Table 9. Chloral hydrate, meprobamate, eszopiclone, suvorexant, zaleplon, and zolpidem are classified as Schedule IV controlled substances by federal regulation because of their abuse potential. The risk of abuse and dependence increases with the dose, duration of treatment, and concomitant use of other psychoactive drugs. The risk is also greater for patients who have a history of alcohol/drug abuse or psychiatric disorders.

Table 7. Adverse Drug Events (%) Reported with the Miscellaneous Anxiolytics, Sedatives, and Hypnotics (A to H)[2]

Adverse Events	Buspirone	Dexmedetomidine	Droperidol	Eszopiclone	Hydroxyzine
Cardiovascular					
Arrhythmia	-	✔	-	-	-
Atrial fibrillation	-	4 to 5	-	-	-
Atrioventricular block	-	✔	-	-	-
Bradycardia	<1	5 to 14	-	-	-
Cardiac arrest	-	✔	✔	-	-
Cardiomyopathy	<1	-	-	-	-
Chest pain	≥1	-	-	1 to 10	-
Extrasystoles	-	✔	-	-	-
Heart block	-	✔	-	-	-
Heart failure	<1	-	-	-	-
Hypertension	<1	✔	✔	<1	-
Hypotension	<1	24 to 54	✔	-	-
Hypovolemia	-	3	-	-	-
Myocardial infarction	<1	✔	-	-	-
Peripheral edema	-	-	-	1 to 10	-
QTc prolongation	-	-	✔	-	-
Supraventricular tachycardia	-	✔	-	-	-
Syncope	<1	-	-	-	-
T-wave inversion	-	✔	-	-	-
Tachycardia	-	-	✔	-	-
Torsades de pointes	-	-	✔	-	-
Ventricular arrhythmia	-	✔	-	-	-
Ventricular tachycardia	-	✔	✔	-	-
Central Nervous System					
Abnormal gait	-	-	-	<1	-
Agitation	-	✔	-	<1	-
Anger	2	-	-	-	-
Anxiety	-	-	✔	1 to 3	-
Ataxia	<1	-	-	<1	-
Cerebrovascular attack	<1	-	-	-	-
Chills	-	-	✔	-	-

Adverse Events	Buspirone	Dexmedetomidine	Droperidol	Eszopiclone	Hydroxyzine
Complex sleep-related activities	-	-	-	<1	-
Confusion	2	✔	-	≤3	-
Delirium	-	✔	-	-	-
Depression	-	-	✔	1 to 4	-
Dizziness	12	✔	✔	5 to 7	✔
Dream disturbances	≥1	-	-	1 to 3	-
Drowsiness	10	-	✔	-	✔
Dysphoria	-	-	✔	-	-
Emotional lability	-	-	-	<1	-
Euphoria	-	-	-	<1	-
Excitement	2	-	-	-	-
Extrapyramidal symptoms	<1	-	✔	-	-
Fever	-	✔	-	<1	-
Hallucinations	<1	✔	✔	1 to 3	✔
Headache	6	✔	-	15 to 21	✔
Hostility	-	-	-	<1	-
Hyperactivity	-	-	✔	-	-
Illusion	-	✔	-	-	-
Incoordination	1	-	-	-	-
Involuntary movements	-	-	-	-	✔
Lightheadedness	3	-	-	-	-
Memory impairment	-	-	-	<1	-
Malaise	-	-	-	<1	-
Migraine	-	-	-	1 to 10	-
Nervousness	5	-	-	≤5	✔
Neuralgia	-	✔	-	≤3	-
Neuritis	-	✔	-	<1	-
Neuroleptic malignant syndrome	-	-	✔	-	-
Neuropathy	-	-	-	<1	-
Neurosis	-	-	-	<1	-
Numbness	2	-	-	-	-
Paresthesia	1	-	-	<1	✔
Parkinsonism	<1	-	-	-	-
Personality disorders	<1	-	-	-	-
Psychosis	<1	-	-	-	-
Restlessness	-	-	✔	-	-
Seizure	<1	✔	-	-	✔
Somnolence	-	-	-	8 to 10	-
Speech disorder	-	✔	-	-	-
Suicidal ideation	<1	-	-	-	-
Tremor	1	-	-	<1	✔

Adverse Events	Buspirone	Dexmedetomidine	Droperidol	Eszopiclone	Hydroxyzine
Vertigo	-	-	-	<1	-
Dermatological					
Alopecia	-	-	-	<1	-
Contact dermatitis	-	-	-	<1	-
Ecchymosis	<1	-	-	-	-
Eczema	-	-	-	<1	-
Erythema multiforme	-	-	-	<1	-
Maculopapular rash	-	-	-	<1	-
Photosensitivity reaction	-	-	-	<1	-
Pruritus	-	-	-	1 to 4	✔
Rash	1	-	-	3 to 4	✔
Urticaria	-	-	-	<1	✔
Vesiculobullous rash	-	-	-	<1	-
Endocrine and Metabolic					
Acidosis	-	✔	-	-	-
Breast enlargement	-	-	-	<1	-
Breast neoplasm	-	-	-	<1	-
Cholelithiasis	-	-	-	<1	-
Galactorrhea	<1	-	-	-	-
Gout	-	-	-	<1	-
Gynecomastia	-	-	-	≤3	-
Mastitis	-	-	-	<1	-
Thyroid abnormality	<1	-	-	-	-
Gastrointestinal					
Abdominal pain	-	✔	-	-	-
Anorexia	<1	-	-	<1	-
Colitis	-	-	-	<1	-
Dehydration	-	-	-	<1	-
Diarrhea	2	✔	-	2 to 4	-
Dysgeusia	-	-	-	8 to 34	-
Dyspepsia	-	-	-	2 to 6	-
Dysphagia	-	-	-	<1	-
Gastrointestinal ulcer	-	-	-	<1	-
Irritable colon	<1	-	-	-	-
Melena	-	-	-	<1	-
Nausea	8	3 to 9	-	4 to 5	-
Rectal hemorrhage	<1	-	-	<1	-
Thirst	-	✔	-	-	-
Tongue edema	-	-	-	<1	-
Ulcerative stomatitis	-	-	-	<1	-
Vomiting	-	✔	-	≤3	-

Adverse Events	Buspirone	Dexmedetomidine	Droperidol	Eszopiclone	Hydroxyzine
Xerostomia	-	3 to 4	-	3 to 7	✔
Genitourinary					
Amenorrhea	-	-	-	<1	-
Cystitis	-	-	-	<1	-
Dysmenorrhea	-	-	-	≤3	-
Dysuria	-	-	-	<1	-
Enuresis	<1	-	-	-	-
Hematuria	-	-	-	<1	-
Kidney calculus	-	-	-	<1	-
Kidney pain	-	-	-	<1	-
Libido decreased	-	-	-	≤3	-
Menorrhagia	-	-	-	<1	-
Menstrual irregularities	<1	-	-	-	-
Oliguria	-	✔	-	<1	-
Pelvic inflammatory disease	<1	-	-	-	-
Pyelonephritis	-	-	-	<1	-
Urethritis	-	-	-	<1	-
Urinary frequency	-	-	-	<1	-
Urinary incontinence	-	-	-	<1	-
Urinary retention	-	1	-	-	-
Urinary tract infection	-	-	-	≤3	-
Vaginal hemorrhage	-	-	-	<1	-
Vaginitis	-	-	-	<1	-
Vulvovaginal dryness	-	-	-	-	-
Hematologic					
Anemia	-	✔	-	-	-
Eosinophilia	<1	-	-	-	-
Leukopenia	<1	-	-	-	-
Thrombocytopenia	<1	-	-	-	-
Thrombophlebitis	-	-	-	<1	-
Hepatic					
Alkaline phosphatase increased	-	✔	-	-	-
Alanine transaminase increased	-	✔	-	-	-
Aspartate aminotransferase increased	-	✔	-	-	-
Gamma-glutamyl transpeptidase increased	-	✔	-	-	-
Hepatic impairment	-	✔	-	-	-
Hepatitis	-	-	-	<1	-
Hepatomegaly	-	-	-	<1	-
Hyperbilirubinemia	-	✔	-	-	-
Liver damage	-	-	-	<1	-

Adverse Events	Buspirone	Dexmedetomidine	Droperidol	Eszopiclone	Hydroxyzine
Transaminases increased	<1	-	-	-	-
Laboratory Test Abnormalities					
Blood urea nitrogen increased	-	✔	-	-	-
Hypercholesterolemia	-	-	-	<1	-
Hyperkalemia	-	✔	-	-	-
Hypocalcemia	-	1	-	-	-
Hypoglycemia	-	✔	-	-	-
Hypokalemia	-	-	-	<1	-
Musculoskeletal					
Cogwheel rigidity	<1	-	-	-	-
Dyskinesia	<1	-	-	-	-
Dystonia	<1	-	-	-	-
Muscle spasms	<1	-	-	-	-
Myasthenia	-	-	-	<1	-
Myopathy	-	-	-	<1	-
Neck rigidity	-	-	-	<1	-
Restless leg syndrome	<1	-	-	-	-
Rigors	-	✔	-	-	-
Weakness	2	-	-	-	-
Respiratory					
Apnea	-	✔	-	-	-
Asthma	-	-	-	<1	-
Bronchitis	-	-	-	<1	-
Bronchospasm	-	✔	✔	-	-
Dyspnea	<1	✔	-	<1	-
Epistaxis	<1	-	-	<1	-
Hypercapnia	-	✔	-	-	-
Hyperventilation	<1	-	-	-	-
Hypoventilation	-	✔	-	-	-
Hypoxia	-	✔	-	-	-
Laryngospasm	-	-	✔	-	-
Nasal congestion	≥1	-	-	-	-
Pleural effusion	-	2	-	-	-
Pulmonary congestion	-	✔	-	-	-
Respiratory acidosis	-	✔	-	-	-
Respiratory depression	-	37	-	-	✔
Throat irritation	≥1	-	-	-	-
Upper respiratory tract infection	-	-	-	-	-
Wheezing	-	≤1	-	-	-
Special Senses					
Blurred vision	2	-	-	-	✔

Adverse Events	Buspirone	Dexmedetomidine	Droperidol	Eszopiclone	Hydroxyzine
Conjunctivitis	<1	-	-	<1	-
Dry eyes	-	-	-	<1	-
Mydriasis	-	-	-	<1	-
Nystagmus	-	-	-	<1	-
Photophobia	-	-	-	<1	-
Photopsia	-	✔	-	-	-
Tinnitus	≥1	-	-	<1	-
Vestibular disorder	-	-	-	<1	-
Visual disturbance	<1	✔	-	-	-
Other					
Accidental injury	-	-	-	≤3	-
Allergic reaction	<1	-	-	<1	✔
Anaphylaxis	-	-	✔	<1	-
Angioedema	<1	-	-	<1	-
Diaphoresis	1	✔	-	<1	-
Edema	<1	-	-	<1	-
Facial edema	-	-	-	<1	-
Heat stroke	-	-	-	<1	-
Hemorrhage	-	✔	-	-	-
Herpes zoster	-	-	-	<1	-
Infection	-	-	-	5 to 10	-
Pain	1	✔	-	4 to 5	-
Serotonin syndrome	<1	-	-	-	-
Shivering	-	-	✔	-	-
Twitching	-	-	-	<1	-
Viral infection	-	-	-	3	-

✔ Percent not specified.
- Event not reported or incidence <1%.

Table 8. Adverse Drug Events (%) Reported with the Miscellaneous Anxiolytics, Sedatives, and Hypnotics (M to Z)[2]

Adverse Events	Meprobamate	Ramelteon	Suvorexant	Tasimelteon	Zaleplon	Zolpidem
Cardiovascular						
Angina	-	-	-	-	<1	-
Arrhythmia	✔	-	-	-	-	-
Bigeminy	-	-	-	-	<1	-
Bundle branch block	-	-	-	-	<1	-
Cardiospasm	-	-	-	-	<1	-
Chest pain	-	-	-	-	≥1	1 to 10
Electrocardiogram changes	✔	-	-	-	-	-
Hypertension	-	-	-	-	<1	<1

Adverse Events	Meprobamate	Ramelteon	Suvorexant	Tasimelteon	Zaleplon	Zolpidem
Hypotension	-	-	-	-	<1	<1
Hypotensive crisis	✔	-	-	-	-	-
Palpitation	✔	-	-	-	<1	1 to 10
Pericardial effusion	-	-	-	-	<1	-
Peripheral edema	✔	-	-	-	≤1	-
Syncope	✔	-	-	-	<1	<1
Tachycardia	✔	-	-	-	-	<1
Vasodilation	-	-	-	-	<1	-
Ventricular extrasystoles	-	-	-	-	<1	-
Ventricular tachycardia	-	-	-	-	<1	-
Central Nervous System						
Abnormal dreams	-	-	2	10	-	-
Abnormal thinking	-	-	✔	-	≥1	-
Agitation	-	-	-	-	-	<1
Amnesia	-	-	✔	-	2 to 4	1 to 10
Anxiety	-	-	✔	-	≤1	1 to 10
Apathy	-	-	-	-	-	1 to 10
Ataxia	✔	-	-	-	<1	1 to 10
Attention disturbance	-	-	-	-	-	1 to 10
Burning sensation	-	-	-	-	-	1 to 10
Cerebrovascular attack	-	-	-	-	<1	<1
Chills	✔	-	-	-	-	-
Central nervous system stimulation	-	-	-	-	<1	-
Cognition decreased	-	-	-	-	-	<1
Complex sleep-related activities	-	✔	-	-	<1	<1
Concentration decreased	-	-	-	-	-	<1
Confusion	-	-	-	-	≤1	1 to 10
Delusions	-	-	-	-	<1	-
Depersonalization	-	-	-	-	<1 to 2	1 to 10
Depression	-	2	-	-	≥1	1 to 10
Disinhibition	-	-	-	-	-	1 to 10
Disorientation	-	-	-	-	-	1 to 10
Dizziness	✔	4 to 5	3	-	7 to 9	1 to 12
Dream disturbances	-	-	-	-	-	1 to 10
Drowsiness	✔	-	2 to 12	-	-	1 to 10
Drugged feeling	-	-	-	-	-	1 to 10
Emotional lability	-	-	-	-	-	<1
Euphoria	✔	-	-	-	-	1 to 10
Excitement	✔	-	-	-	-	-
Fatigue	-	3 to 4	-	-	-	1 to 10
Fever	✔	-	-	-	≥1	1 to 10

Adverse Events	Meprobamate	Ramelteon	Suvorexant	Tasimelteon	Zaleplon	Zolpidem
Hallucinations	-	-	✔	-	≤1	1 to 10
Headache	✔	-	7	17	30 to 42	3 to 19
Hypoesthesia	-	-	-	-	<1 to 2	1 to 10
Illusion	-	-	-	-	-	<1
Insomnia	-	3	-	-	-	1 to 10
Lethargy	-	-	-	-	-	1 to 10
Lightheadedness	-	-	-	-	-	1 to 10
Memory impairment	-	-	-	-	-	1 to 10
Malaise	-	-	-	-	<1 to 2	-
Migraine	-	-	-	-	≥1	<1
Mood disorder	-	-	-	-	-	1 to 10
Nervousness	-	-	-	-	≥1	-
Overstimulation	✔	-	-	-	-	-
Paresthesia	✔	-	-	-	3	<1 to 10
Sleep disorder	-	-	-	-	-	1 to 10
Somnolence	-	3 to 5	-	-	5 to 6	6 to 15
Speech disorder	✔	-	-	-	-	<1
Stress	-	-	-	-	-	1 to 10
Stupor	-	-	-	-	-	<1
Suicidal ideation	-	-	✔	-	-	-
Temperature regulation altered	-	-	-	-	-	1 to 10
Tremor	-	-	-	-	2	1 to 10
Vertigo	✔	-	-	-	≤1	1 to 10
Dermatological						
Alopecia	-	-	-	-	<1	-
Contact dermatitis	✔	-	-	-	-	-
Ecchymosis	✔	-	-	-	<1	-
Erythema multiforme	✔	-	-	-	-	-
Petechiae	✔	-	-	-	-	-
Photosensitivity reaction	-	-	-	-	≤1	-
Pruritus	-	-	-	-	≥1	<1
Purpura	✔	-	-	-	<1	-
Rash	✔	-	-	-	≥1	1 to 10
Stevens-Johnson syndrome	✔	-	-	-	-	-
Urticaria	-	-	-	-	-	1 to 10
Wrinkling	-	-	-	-	-	1 to 10
Endocrine and Metabolic						
Cholelithiasis	-	-	-	-	<1	-
Cyanosis	-	-	-	-	<1	-
Diabetes mellitus	-	-	-	-	<1	-
Goiter	-	-	-	-	<1	-

Adverse Events	Meprobamate	Ramelteon	Suvorexant	Tasimelteon	Zaleplon	Zolpidem
Ketosis	-	-	-	-	<1	-
Gastrointestinal						
Abdominal pain	-	-	-	-	6	1 to 10
Anorexia	-	-	-	-	<1 to 2	-
Appetite disorder	-	-	-	-	-	1 to 10
Bleeding gums	-	-	-	-	<1	-
Colitis	-	-	-	-	≤1	-
Constipation	-	-	-	-	≥1	1 to 10
Dehydration	-	-	-	-	-	-
Diarrhea	✔	-	2	-	-	1 to 10
Dysgeusia	-	2	-	-	≥1	-
Dyspepsia	-	-	-	-	≥1	1 to 10
Dysphagia	-	-	-	-	-	<1
Flatulence	-	-	-	-	-	1 to 10
Gastroenteritis	-	-	-	-	<1	1 to 10
Gastroesophageal reflux	-	-	-	-	-	1 to 10
Gastrointestinal ulcer	-	-	-	-	<1	-
Hiccup	-	-	-	-	-	1 to 10
Intestinal obstruction	-	-	-	-	<1	-
Nausea	✔	3	-	-	6 to 8	1 to 10
Proctitis	✔	-	-	-	-	-
Rectal hemorrhage	-	-	-	-	<1	-
Stomatitis	✔	-	-	-	-	-
Tongue edema	-	-	-	-	<1	-
Ulcerative stomatitis	-	-	-	-	<1	-
Vomiting	✔	-	-	-	-	1 to 10
Xerostomia	-	-	2	-	≥1	1 to 10
Genitourinary						
Anuria	✔	-	-	-	-	-
Cystitis	-	-	-	-	-	<1
Dysmenorrhea	-	-	-	-	3 to 4	-
Dysuria	-	-	-	-	<1	1 to 10
Hematuria	-	-	-	-	<1	-
Impotence	-	-	-	-	<1	-
Incontinence	-	-	-	-	<1	<1
Menorrhagia	-	-	-	-	-	1 to 10
Oliguria	✔	-	-	-	-	-
Renal failure	-	-	-	-	-	<1
Urinary retention	-	-	-	-	<1	-
Urinary tract infection	-	-	-	7	-	1 to 10
Vaginitis	-	-	-	-	-	<1

Adverse Events	Meprobamate	Ramelteon	Suvorexant	Tasimelteon	Zaleplon	Zolpidem
Vulvovaginal dryness	-	-	-	-	-	1 to 10
Hematologic						
Agranulocytosis	✔	-	-	-	-	-
Anemia	-	-	-	-	<1	<1
Aplastic anemia	✔	-	-	-	-	-
Eosinophilia	✔	-	-	-	<1	-
Leukocytosis	-	-	-	-	<1	-
Leukopenia	✔	-	-	-	-	<1
Lymphadenopathy	-	-	-	-	<1	<1
Lymphocytosis	-	-	-	-	<1	-
Porphyria exacerbation	✔	-	-	-	-	-
Thrombocytopenic purpura	✔	-	-	-	-	-
Thrombophlebitis	-	-	-	-	<1	-
Hepatic						
Abnormal hepatic function	-	-	-	-	-	<1
Alanine transaminase increased	-	-	-	10	<1	-
Aspartate aminotransferase increased	-	-	-	-	<1	-
Hyperbilirubinemia	-	-	-	-	<1	-
Liver function tests abnormal	-	-	-	-	<1	-
Laboratory Test Abnormalities						
Cortisol decreased	-	1	-	-	-	-
Hypercholesterolemia	-	-	✔	-	-	-
Hyperglycemia	-	-	-	-	<1	<1
Hyperuricemia	-	-	-	-	<1	-
Hypoglycemia	-	-	-	-	<1	-
Hypothyroidism	-	-	-	-	<1	-
Prolactin increased	-	✔	-	-	-	-
Testosterone decreased	-	✔	-	-	-	-
Musculoskeletal						
Arthralgia	-	2	-	-	≥1	1 to 10
Arthritis	-	-	-	-	≥1	-
Back pain	-	-	-	-	≥1	1 to 10
Balance disorder	-	-	-	-	-	1 to 10
Dysarthria	-	-	-	-	<1	-
Dystonia	-	-	-	-	<1	-
Hypertonia	-	-	-	-	1	-
Involuntary muscle contractions	-	-	-	-	-	1 to 10
Myalgia	-	2	-	-	≥1	1 to 10
Myasthenia	-	-	-	-	<1	-
Myositis	-	-	-	-	<1	-
Neck pain	-	-	-	-	-	1 to 10

Adverse Events	Meprobamate	Ramelteon	Suvorexant	Tasimelteon	Zaleplon	Zolpidem
Osteoporosis	-	-	-	-	<1	-
Psychomotor retardation	-	-	-	-	-	1 to 10
Weakness	✔	-	✔	-	5 to 7	1 to 10
Respiratory						
Bronchitis	-	-	-	-	≥1	-
Bronchospasm	✔	-	-	-	-	-
Cough	-	-	2	-	-	-
Dyspnea	-	-	-	-	-	<1
Epistaxis	-	-	-	-	≤1	-
Pharyngitis	-	-	-	-	-	1 to 10
Pulmonary embolus	-	-	-	-	<1	-
Sinusitis	-	-	-	-	-	1 to 10
Throat irritation	-	-	-	-	-	1 to 10
Upper respiratory tract infection	-	3	2	7	-	1 to 10
Special Senses						
Accommodation impaired	✔	-	-	-	-	-
Asthenopia	-	-	-	-	-	1 to 10
Blurred vision	-	-	-	-	-	1 to 10
Conjunctivitis	-	-	-	-	≥1	-
Depth perception altered	-	-	-	-	-	1 to 10
Diplopia	-	-	-	-	-	1 to 10
Ear pain	-	-	-	-	≤1	-
Eye pain	-	-	-	-	3 to 4	-
Eye redness	-	-	-	-	-	1 to 10
Glaucoma	-	-	-	-	<1	-
Hyperacusis	-	-	-	-	1 to 2	-
Parosmia	-	-	-	-	1 to 2	-
Photophobia	-	-	-	-	<1	-
Ptosis	-	-	-	-	<1	-
Scleritis	-	-	-	-	-	<1
Tinnitus	-	-	-	-	-	1 to 10
Visual disturbance	-	-	-	-	<1 to 2	1 to 10
Other						
Allergic reaction	-	-	-	-	-	1 to 10
Anaphylaxis	✔	✔	-	-	<1	<1
Angioedema	-	✔	-	-	<1	<1
Angioneurotic edema	✔	-	-	-	-	-
Binge eating	-	-	-	-	-	1 to 10
Diaphoresis	-	-	-	-	-	<1
Drug dependence	-	-	✔	-	-	-
Edema	-	-	-	-	-	<1

Adverse Events	Meprobamate	Ramelteon	Suvorexant	Tasimelteon	Zaleplon	Zolpidem
Facial paralysis	-	-	-	-	<1	-
Falling	-	-	-	-	-	<1
Flu-like syndrome	-	-	-	-	-	1 to 10
Hypersensitivity	✔	-	-	-	-	-
Influenza	-	1	-	-	-	-
Lactose intolerance	-	-	-	-	<1	-
Somnambulism	-	-	-	-	-	<1
Thrombosis	-	-	-	-	-	<1

✔ Percent not specified.
- Event not reported or incidence <1%.

Table 9. Boxed Warning for Droperidol[2]

WARNING
Cases of QT prolongation and/or torsade de pointes have been reported in patients receiving droperidol at doses at or below recommended doses. Some cases have occurred in patients with no known risk factors for QT prolongation, and some cases have been fatal. Due to its potential for serious proarrhythmic effects and death, reserve droperidol for use in the treatment of patients who fail to show an acceptable response to other adequate treatments, either because of insufficient effectiveness or the inability to achieve an effective dose due to intolerable adverse effects from those drugs. Cases of QT prolongation and serious arrhythmias (e.g., torsade de pointes) have been reported in patients treated with droperidol. Based on these reports, all patients should undergo a 12-lead electrocardiogram prior to administration of droperidol to determine if a prolonged QT interval (i.e., QTc greater than 440 msec for males or 450 msec for females) is present. If there is a prolonged QT interval, do not administer droperidol. For patients in whom the potential benefit of droperidol treatment is felt to outweigh the risks of potentially serious arrhythmias, perform electrocardiogram monitoring prior to treatment and continue for two to three hours after completing treatment to monitor for arrhythmias. Droperidol is contraindicated in patients with known or suspected QT prolongation, including patients with congenital long QT syndrome. Administer droperidol with extreme caution to patients who may be at risk for development of prolonged QT syndrome (e.g., congestive heart failure, bradycardia, use of a diuretic, cardiac hypertrophy, hypokalemia, hypomagnesemia, or administration of other drugs known to increase the QT interval). Other risk factors may include age greater than 65 years, alcohol abuse, and use of agents such as benzodiazepines, volatile anesthetics, and intravenous opiates. Initiate droperidol at a low dose and adjust upward, with caution, as needed to achieve the desired effect.

VII. Dosing and Administration

The usual dosing regimens for the miscellaneous anxiolytics, sedatives, and hypnotics are listed in Table 10.

Table 10. Usual Dosing Regimens for the Miscellaneous Anxiolytics, Sedatives, and Hypnotics[2-15]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Buspirone	Management of anxiety disorders; short-term relief of symptoms of anxiety: Tablet: 7.5 mg twice daily; increase by 5 mg/day every two to three days as needed; maximum, 60 mg/day	Safety and efficacy in children have not been established.	Tablet: 5 mg 7.5 mg 10 mg 15 mg 30 mg
Dexmedetomidine	Sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting; administer by continuous infusion not to exceed 24 hours: Injection: 1 µg/kg intravenous over 10 minutes, then 0.2 to 0.7 µg/kg/hour Sedation of non-intubated patients prior to and/or during surgical and other procedures: Injection: 1 µg/kg intravenous over 10 minutes, then 0.2 to 1.0 µg/kg/hour	Safety and efficacy in children have not been established.	Injection: 200 µg/2 mL 200 µg/50 mL 400 µg/100 mL 80 µg/20 mL

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Droperidol	To reduce the incidence of nausea and vomiting associated with surgical and diagnostic procedures: Injection: 2.5 mg; additional 1.25 mg doses may be given to achieve desired effect	To reduce the incidence of nausea and vomiting associated with surgical and diagnostic procedures in patients two to 12 years of age: Injection: 0.1 mg/kg To reduce the incidence of nausea and vomiting associated with surgical and diagnostic procedures in patients >12 years of age: Injection: 2.5 mg	Injection: 2.5 mg/mL
Eszopiclone	Treatment of insomnia: Tablet: 1 mg immediately before bedtime; maximum, 3 mg	Safety and efficacy in children have not been established.	Tablet: 1 mg 2 mg 3 mg
Hydroxyzine	Symptomatic relief of anxiety and tension associated with psychoneurosis and as an adjunct in organic disease states in which anxiety is manifested: Injection: 50 to 100 mg intramuscular stat, then every four to six hours as needed Capsule, syrup, tablet: 50 to 100 mg four times daily Management of pruritus caused by allergic conditions such as chronic urticaria and atopic or contact dermatoses and in histamine-mediated pruritus: Capsule, syrup, tablet: 25 mg three to four times per day Sedation when used as premedication and following general anesthesia: Injection: 25 to 100 mg intramuscular Capsule, syrup, tablet: 50 to 100 mg	Symptomatic relief of anxiety and tension associated with psychoneurosis and as an adjunct in organic disease states in which anxiety is manifested in patients ≥6 years of age: Capsule, syrup, tablet: 50 to 100 mg daily in divided doses Symptomatic relief of anxiety and tension associated with psychoneurosis and as an adjunct in organic disease states in which anxiety is manifested in patients <6 years of age: Capsule, syrup, tablet: 50 mg daily in divided doses Management of pruritus caused by allergic conditions such as chronic urticaria and atopic or contact dermatoses and in histamine-mediated pruritus in patients ≥6 years of age: Capsule, syrup, tablet: 50 to 100 mg daily in divided doses	Capsule: 25 mg 50 mg 100 mg Oral solution: 10 mg/5 mL 50 mg/25 mL Tablet: 10 mg 25 mg 50 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
		Management of pruritus caused by allergic conditions such as chronic urticaria and atopic or contact dermatoses and in histamine-mediated pruritus in patients <6 years of age: Capsule, syrup, tablet: 50 mg daily in divided doses Sedation when used as premedication and following general anesthesia: Injection: 0.5 mg/lb Capsule, syrup, tablet: 0.6 mg/kg	
Meprobamate	Management of anxiety disorders, short-term relief of symptoms of anxiety: Tablet: 1,200 to 1,600 mg/day in three to four doses; maximum, 2,400 mg	Management of anxiety disorders, short-term relief of symptoms of anxiety in patients six to 12 years of age: Tablet: 200 to 600 mg/day in two to three divided doses	Tablet: 200 mg 400 mg
Ramelteon	Treatment of insomnia characterized by difficulty with sleep onset: Tablet: 8 mg within 30 minutes of going to bed; maximum, 8 mg	Safety and efficacy in children have not been established.	Tablet: 8 mg
Suvorexant	Insomnia characterized by difficulties with sleep onset and/or sleep maintenance: Tablet: 10 mg taken no more than once per night and within 30 minutes of going to bed, with ≥7 hours remaining before awakening; maximum, 20 mg once daily	Safety and efficacy in children have not been established.	Tablet: 5 mg 10 mg 15 mg 20 mg
Tasimelteon	Treatment of Non-24-Hour Sleep-Wake Disorder: Capsule: 20 mg taken before bedtime, at the same time every night	Safety and efficacy in children have not been established.	Capsule: 20 mg
Zaleplon	Short-term treatment of insomnia: Capsule: 10 mg immediately before bedtime; maximum, 20 mg	Safety and efficacy in children have not been established.	Capsule: 5 mg 10 mg
Zolpidem	Short-term treatment of insomnia characterized by difficulties with sleep initiation: Immediate release sublingual tablet (Edluar®), tablet: 5 mg for women and 5 or 10 mg for men,	Safety and efficacy in children have not been established.	Extended release tablet (Ambien CR®): 6.25 mg 12.5 mg Immediate release

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	immediately before bedtime with at least seven to eight hours remaining before the planned time of awakening Insomnia when a middle-of-the-night awakening is followed by difficulty returning to sleep: Immediate release sublingual tablet (Intermezzo®): 1.75 mg for women and 3.5 mg for men, taken only once per night if needed; take only if four hours of bedtime remain before the planned time of waking Insomnia characterized by difficulties with sleep onset and/or sleep maintenance: Extended release tablet: 6.25 mg for women, and 6.25 or 12.5 mg for men, immediately before bedtime with at least seven to eight hours remaining before the planned time of awakening		tablet (Ambien®): 5 mg 10 mg Sublingual tablet: 1.75 mg (Intermezzo®) 3.5 mg (Intermezzo®) 5 mg (Edluar®) 10 mg (Edluar®)

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the miscellaneous anxiolytics, sedatives, and hypnotics are summarized in Table 11.

Table 11. Comparative Clinical Trials with the Miscellaneous Anxiolytics, Sedatives, and Hypnotics

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Anxiety				
Gammans et al.[34] (1992) Buspirone 10 to 60 mg/day vs placebo	MA Adult outpatients with generalized anxiety disorder	N=509 (8 trials) 4 weeks	Primary: HAM-A score, HAM-D score, CGI score to determine responders Secondary: Not reported	Primary: Overall, patients treated with buspirone demonstrated significant (P<0.001) improvement over baseline in total HAM-A scores compared to placebo. Significantly more buspirone-treated patients (54%) were classified as responders than placebo-treated patients (28%) (P<0.001). Patients with GAD and concurrent depressive symptoms exhibited significantly greater improvement with buspirone compared to placebo (P<0.01 to P<0.03 depending upon the parameter measured and severity of depressive symptoms). Weekly ratings indicated that buspirone produced a progressively increasing anxiolytic response relative to placebo throughout the four-week DB treatment period in patients with GAD and coexisting depressive symptoms (P<0.05 at week one for HAM-D and P<0.05 at week two for HAM-A). Secondary: Not reported
Lader et al.[35] (1998) Buspirone 20 mg/day vs hydroxyzine 50 mg/day	DB, MC, PC, RCT Adult outpatients with GAD	N=244 6 weeks	Primary: HAM-A scores Secondary: CGI, MADRS, HAD Scale, FARD, Tyrer Withdrawal Symptom Scale	Primary: Hydroxyzine (P<0.02), but not buspirone (P=NS), significantly improved HAM-A scores over placebo after 28 days of treatment. HAM-A scores were not significantly different between hydroxyzine and buspirone. Secondary: Significantly (P<0.02) more patients on hydroxyzine improved CGI scores than placebo. There was no significant difference between buspirone and placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				With respect to the MADRS, both buspirone and hydroxyzine patients were significantly better than placebo (P<0.001). HAD scores for both depression (P<0.01 for buspirone, P<0.02 for hydroxyzine) and anxiety (P<0.001 for both buspirone and hydroxyzine) were significantly better with the active drugs compared to placebo. The FARD total scores (P<0.001 for both buspirone and hydroxyzine) were also significantly better than placebo. There was no rebound with respect to HAM-A or other efficacy variables following placebo substitution at day 28. Both the buspirone and hydroxyzine patients continued to improve. No significant withdrawal symptoms for either active drug were detected on the Tyrer Scale. Both active treatments were well tolerated. The only side effects affecting more than 5% of the exposed patients were headache and migraine (6.1%) in the buspirone-treated patients (0% in hydroxyzine and 2.5% in placebo patients) and somnolence in the hydroxyzine group (9.9%) as compared to 4.9% in the buspirone and none in the placebo group.
Llorca et al.[36] (2002) Hydroxyzine 50 mg/day or bromazepam* 6 mg/day vs placebo	DB, MC, PG, RCT Adult outpatients with GAD	N=334 18 weeks	Primary: HAM-A scores Secondary: Responder and remission rates, change in CGI-S scale score and HAD scale score, maintenance of treatment efficacy, evaluation of rebound and withdrawal symptoms, safety	Primary: Mean change in HAM-A scores from baseline was significantly greater for hydroxyzine (-12.16) compared to placebo (-9.64; P=0.019). Bromazepam was also significantly more effective than placebo in decreasing HAM-A scores (P<0.03). Secondary: Results at endpoint for percentage of responders (P=0.003), remission rates (P=0.028), change in CGI-S scale score (P=0.001), HAD scale score (P=0.008), and maintenance of efficacy (P=0.022) on day 84 also confirmed the efficacy of hydroxyzine over placebo. The study showed no statistically significant difference between hydroxyzine and bromazepam; however, the study was not designed or powered to detect differences between these two active treatments. Efficacy was significantly maintained vs placebo in 86.5% of patients in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				the hydroxyzine group (P=0.022) and in 88.1% of patients in the bromazepam group (P=0.010) until day 84. In the placebo, hydroxyzine, and bromazepam groups, only 10.1%, 14.7% and 14.0% of patients, respectively, experienced at least one adverse event considered to be related to treatment. Safety results were comparable in the 3 groups with the exception of drowsiness, which was reported most frequently in the bromazepam group (7.9%), followed by hydroxyzine (3.9%) and then placebo (1.8%). There were no statistically significant differences between each treatment group with regards to rebound effect. Differences in withdrawal symptoms that reached statistical significance were the following: hydroxyzine induced more sweating than placebo (P=0.048) and bromazepam induced more sleep disturbances than placebo (P=0.002).
Blanco et al.[37] (2003) Benzodiazepines, SSRIs, MAOIs, RIMAs, β-blockers, gabapentin, buspirone vs placebo	MA Patients with social anxiety disorder	N=2,954 (23 trials) 6 to 20 weeks	Primary: Outcome data on the LSAS or a categorical measure of status Secondary: CGI score	Primary: In terms of LSAS, no statistical difference was detected between medications or medication groups. Secondary: In terms of responders, effect sizes of each medication group were: benzodiazepines (16.61), brofaromine (6.96), phenelzine (4.10), gabapentin (3.78), SSRIs (3.22), atenolol (1.36), and moclobemide (1.27). No statistical differences were detected between these medications or medication groups.
Insomnia				
Zammit et al.[38] (2004) Eszopiclone 2 to 3 mg vs	DB, MC, PC, RCT Adults 21 to 64 years of age with chronic primary insomnia	N=308 6 weeks	Primary: Efficacy (PSG and patient reports), next day residual effects (DSST), tolerance, rebound insomnia, safety	Primary: Eszopiclone 2 and 3 mg had significantly less time to sleep onset ($P \leq 0.001$ and $P \leq 0.0001$, respectively), more TST ($P \leq 0.01$ and $P \leq 0.0001$), better SE ($P \leq 0.001$ and $P \leq 0.0001$), and enhanced quality and depth of sleep (both $P < 0.05$) across the DB period compared to placebo. Eszopiclone 3 mg ($P \leq 0.01$) but not 2 mg significantly improved sleep maintenance compared to placebo.

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placebo			Secondary: Not reported	Median DSST scores showed no decrement in psychomotor performance relative to baseline and did not differ from placebo in either eszopiclone group. There was no evidence of tolerance or rebound insomnia after therapy discontinuation. Treatment was well tolerated; unpleasant taste was the most common adverse event reported with eszopiclone. Secondary: Not reported
Krystal et al.[39] (2003) Eszopiclone 3 mg vs placebo	DB, MC, PC, RCT Adults with chronic insomnia	N=788 6 months	Primary: SL, WASO, NAW, TST, quality of sleep, next-day ratings of ability to function, daytime alertness, sense of physical well-being, safety Secondary: Not reported	Primary: At the first week and each month for the study duration, eszopiclone produced significant and sustained improvements in SL, WASO, NAW, number of nights awakened per week, TST, and quality of sleep compared to placebo (all $P \leq 0.003$). Monthly ratings of next-day function, alertness, and sense of physical well-being were also significantly better with the use of eszopiclone than with placebo (all $P \leq 0.002$). There was no evidence of tolerance and the most common adverse events were unpleasant taste and headache. Secondary: Not reported
Walsh et al.[40] (2007) Eszopiclone 3 mg vs placebo	DB, MC, PC, RCT Adults 21 to 64 years of age with primary insomnia	N=830 26 weeks	Primary: Patient-reported sleep measures (SL, WASO, TST, NAW, sleep quality, daytime alertness, ability to concentrate, physical well-	Primary: Patient-reported sleep and daytime function improved more with eszopiclone than with placebo at all months ($P<0.001$). Eszopiclone reduced ISI scores to below clinically meaningful levels for 50% of patients (vs 19% of patients with placebo; $P<0.05$) at six months. Lower mean scores on the FSS and the ESS were observed in the eszopiclone group relative to placebo for each month and the month one to

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			being, and ability to function), ISI, FSS, ESS, Medical Outcomes Study SF-36, Work Limitations Questionnaire, safety (assessments performed at baseline, treatment months one to six, and two weeks after discontinuation of treatment) Secondary: Not reported	six average (P<0.05). SF-36 domains of Physical Functioning, Vitality, and Social Functioning were improved with eszopiclone vs placebo for the month one to six average (P<0.05). Similarly, improvements were observed for all domains of the Work Limitations Questionnaire with eszopiclone vs placebo for the month one to six average (P<0.05). There was no evidence of rebound insomnia after discontinuation of eszopiclone as SL, WASO and TST remained significantly improved from baseline (all P<0.001). There were no between-treatment differences observed during the discontinuation period except for a significantly greater SL on the first night after discontinuation with eszopiclone vs placebo (45 vs 30 minutes; P=0.015). No significant group differences were observed in mean Benzodiazepine Withdrawal Symptom Questionnaire scores (3.0 with eszopiclone and 2.3 with placebo; P=0.12), or overall adverse event rates (15.2% for eszopiclone and 11.1% for placebo; P value not reported). Unpleasant taste (19.7 vs 1.1%; P<0.001), somnolence (8.8 vs 3.2%; P=0.0029), and myalgia (6.0 vs 2.9; P=0.047) were reported in significantly more patients receiving eszopiclone than those receiving placebo. Secondary: Not reported
Joffe et al.[41] (2009) Eszopiclone 3 mg for 4 weeks vs placebo for 4 weeks Each treatment	DB, PC, RCT, XO Perimenopausal and postmenopausal women 40 to 65 years of age with sleep-onset and/or sleep-maintenance insomnia co-occurring with hot flashes and depressive and/or	N=59 11 weeks Each treatment period was separated by a 2-week washout period	Primary: Changes in the ISI scale Secondary: Diary-based sleep parameters (WASO, SE, sleep-onset latency, TST, NAW); number of hot flashes/night sweats, depressive	Primary: The ISI score was reduced by 8.7 more points with eszopiclone than with placebo (P<0.0001). The ISI score was 7 or less after four weeks of treatment in 87% of women on eszopiclone and in 34% of women on placebo. Secondary: SL was reduced by 17.8 more minutes with eszopiclone than with placebo (P=0.04). For both treatment periods together, WASO was reduced by 37.7 minutes more with eszopiclone than placebo (P=0.05), SE improved by 14.6% more with eszopiclone than with placebo (P=0.01), and TST increased by 66.5 minutes more with eszopiclone than with placebo

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
period was separated by a 2-week washout period.	anxiety symptoms		symptoms (via MADRS), anxiety symptoms (assessed via BAI), MENQOL, and functional impairment, safety	(P=0.01). Among patients with anxiety symptoms at baseline, BAI scores were reduced by a mean of 1.5 more with eszopiclone than with placebo (P=0.03). Quality of life (P=0.0002) and functional disability (P=0.09) improved more on eszopiclone than on placebo. Among those with depressive symptoms at baseline, MADRS scores were reduced by a mean of 7.4 more points with eszopiclone than with placebo (P=0.0004). Compared to placebo, eszopiclone had a significant effect on depressive symptoms during the second (P=0.003), but not first, treatment period. There was a significant reduction in nighttime hot flashes with eszopiclone compared to placebo (reduction by 1.5 nighttime hot flashes; P=0.047), but the effect on daytime symptoms was not different. Compared to placebo, eszopiclone had a significant effect on nighttime hot flashes during the second (P=0.0006), but not first, treatment period. Overall, the treatment was well tolerated. The only adverse event occurring in >5% of the population was metallic taste on eszopiclone (25%).
Scharf et al.[42] (2005) Eszopiclone 1 to 2 mg vs placebo	DB, MC, PC, RCT Community-dwelling elderly patients (mean age 72.3 years) with primary insomnia	N=231 2 weeks	Primary: Patient-reported efficacy (SL, TST) Secondary: WASO, NAW, number and length of naps, quality of sleep, depth of sleep, ratings of daytime alertness, sense of physical well-being, morning sleepiness, ability	Primary: Patients treated with eszopiclone 1 and 2 mg had a significantly shorter SL compared to placebo (P<0.05 and P=0.0034, respectively). The eszopiclone 2-mg group (P=0.0003) but not the 1-mg group (P>0.1) had significantly longer TST compared to placebo. Secondary: Compared to placebo, patients receiving eszopiclone 2 mg had significantly less WASO but similar NAW per night (P>0.1). Patients receiving eszopiclone 2 mg had significantly fewer (P=0.028) and shorter in duration (P=0.011) daytime naps, higher ratings of sleep quality (P=0.0006) and depth (P=0.0015), better daytime alertness (P=0.022) and sense of physical well-being (P=0.047) compared to patients receiving

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			to function, quality of life (Q-LES-Q), safety	placebo. The differences between eszopiclone 2 mg and placebo were marginally significant for morning sleepiness (P=0.055) and ability to function (P=0.058). Duration of nap was significantly shorter in the eszopiclone 1-mg group compared to the placebo group (P<0.05); however, there were no other significant differences in any other secondary efficacy endpoints. Compared to placebo, the eszopiclone 2-mg group had significantly higher quality of life scores on five of the 16 Q-LES-Q domains (physical health, mood, household activities, leisure time activities and medications; P<0.05). The differences between eszopiclone 2 mg and placebo were marginally significant for the Q-LES-Q global score (P=0.064). There were no significant differences between eszopiclone 1 mg and placebo for any of the Q-LES-Q dimensions. Eszopiclone was well tolerated with unpleasant taste reported as the most frequent treatment-related adverse event.
Ancoli-Israel et al.[43] (2010) Eszopiclone 2 mg vs placebo	DB, MC, PC, RCT Patients 65 to 85 years of age with primary insomnia	N=388 12 weeks Treatment was followed by a two week, SB run out period	Primary: Change from baseline sTST Secondary: Change from baseline in sSL and WASO	Primary: After 12 weeks, the mean sTST was 360.08 minutes with eszopiclone compared to 297.86 minutes at baseline (mean change of 63.24 minutes). This was significantly greater than placebo (P<0.0001). Secondary: There was a greater improvement in sSL with eszopiclone compared to placebo (mean decrease of 24.62 vs 19.92 minutes; respectively; P=0.0014). Patients receiving eszopiclone experienced a greater decrease in WASO compared to those receiving placebo (mean decrease of 36.4 vs 14.8 minutes; P<0.0001). The reported NAW per night was reduced (P≤0.01), and the quality (P<0.001) and depth of sleep (P≤0.001) was improved at all time points with eszopiclone compared to placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There was a significantly greater decrease in naps per week over the first three weeks of treatment with eszopiclone (1.2 naps per week decrease) vs placebo (0.4 naps per week; P=0.006), but not at subsequent time points. Similar results were obtained for total nap time per week. Patients receiving eszopiclone had significantly greater improvements in ISI total scores than those receiving placebo at all time points (all P<0.001). The percentage of patients with ISI total scores categorized as "no insomnia" and "sub-threshold insomnia" was greater in the eszopiclone group (78.0% at week 12) than in the placebo group (61.1%; P<0.05). Changes in self-reported daytime alertness, ability to function, ability to concentrate, and sense of physical well-being were significantly increased with eszopiclone compared to placebo at all times points (all P≤0.001). Patients receiving eszopiclone had significant improvements in the vitality scale of the SF-36 at week six (P=0.04) and week 12 (P=0.008), and in the general health scale at week 12 (P=0.009) compared to placebo. There were no significant differences on the other SF-36 individual scale scores, or on the mental or physical component summary scores among the treatment groups. On the SDS, there were significant improvements observed in the eszopiclone group compared to the placebo group for the social life and family life/home responsibilities items (both P≤0.03) at week six, but not at week 12. There was no significant difference on the work/school item at either time point. The overall incidence of adverse events was 59.3% for eszopiclone and 50.5% for placebo. The most common adverse events reported in the eszopiclone group were headache (13.9 vs 12.4% for placebo), unpleasant taste (12.4 vs 1.5% for placebo), and nasopharyngitis (5.7 vs 6.2% for placebo).

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Lettieri et al.[44] (2009) Eszopiclone 3 mg 30 minutes prior to PSG (premedication) vs placebo30 minutes prior to PSG (premedication)	DB, PC, RCT Patients 18 to 64 years of age with newly diagnosed obstructive sleep apnea who were initiating CPAP	N=117 4-6 weeks	Primary: CPAP compliance during the initial four to six weeks of therapy Secondary: CPAP titration quality as assessed by WASO), TST, total arousal index, SL, SE, AHI	Primary: CPAP was used on a higher percentage of nights in the eszopiclone group than in the placebo group (75.9 vs 60.1%, respectively; P=0.005). Eszopiclone was associated with more hours of use per night during nights used (4.8 vs 3.9 hours, respectively; P=0.03) and for more hours per night for all nights of the study period (4.0 vs 2.9 hours, respectively; P=0.03). The percentage of days with >4 hours of use also was greater among the eszopiclone group (59.2 vs 37.0%, respectively; P=0.007). Good compliance (>4 hours of use per night on >70% of nights) was observed in more patients pretreated with eszopiclone than with placebo (53.1 vs 27.1%, respectively; P=0.009). Secondary: Premedication with eszopiclone improved the quality of CPAP titration PSG compared to placebo as evidenced by shortened SL (19.4 vs 31.8 minutes, respectively; P=0.08), improved SE (87.8 vs 80.1%, respectively; P=0.002), expanded TST (350.9 vs 319.7 minutes, respectively; P=0.007), and decreased WASO (39.3 vs 59.9 minutes, respectively; P=0.009). The residual AHI tended to be lower following eszopiclone premedication (6.4 vs 12.8 events/hour, respectively; P=0.08).
Lettieri et al.[45] (2009) Eszopiclone 3 mg for 2 weeks vs placebo for 2 weeks To promote adherence with CPAP, OL use of	DB, PC, RCT Patients 18 to 64 years of age with newly diagnosed obstructive sleep apnea who were initiating CPAP	N=160 24 weeks	Primary: Adherence to CPAP at week 24 Secondary: Rate of CPAP discontinuation and OL use of sedative-hypnotic agents	Primary: Patients receiving eszopiclone used CPAP for 64.4% of nights compared to 45.2% of nights in those receiving placebo (P=0.003). In the eszopiclone and placebo groups, CPAP was used for 3.57 vs 2.42 hours per night, respectively for all study nights (P=0.005) and for 4.05 vs 3.02 hours per night, respectively for nights when CPAP was used (P=0.019). Secondary: The mean duration of regular use of CPAP was 13.3 weeks for the placebo group and 17.6 weeks for the eszopiclone group (P=0.005). The mean time to discontinuation of CPAP for the placebo and eszopiclone groups was 17.2 and 19.7 weeks, respectively (P=0.033).

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sedative-hypnotic agents was allowed after the first 4 weeks of treatment.				A total of 24.7% of patients requested OL non-benzodiazepines. This request was more frequent among those receiving placebo than eszopiclone (31% vs 19%; P=0.084). The mean duration of hypnotic use (9.7 days) was similar for both groups. Adverse events were reported in 7.1% of patients and did not differ between the groups.
Menza et al.[46] (2010) Eszopiclone 2 to 3 mg vs placebo	DB, MC, PC, PG, RCT Patients 35 to 85 years of age with Parkinson's disease and sleep maintenance insomnia or SL insomnia, as well as clinically significant daytime distress or impairment secondary to insomnia	N=30 6 weeks	Primary: Patient-reported TST Secondary: WASO, NAW and SII, quality of sleep, quality of life (assessed via PDQ-8), motor function (assessed via UPDRS), severity and change (assessed via CGI), ability to function, daytime alertness, fatigue severity (assessed via FSS), caregiver quality of life and depression (assessed via MCBI and CES-D)	Primary: There was no significant difference in the improvement seen in TST among the groups (66.5 minutes with eszopiclone vs 47.0 minutes with placebo; P=0.1099). Secondary: There were significant differences in NAW (P=0.035), quality of sleep (P=0.018), and CGI-improvement in sleep (P=0.035) among the groups. There was no significant difference in WASO (P=0.071). There were no differences in the UPDRS motor, activities of daily living, therapeutic complications, mood or Schwab subscales. There were no significant differences in SL, FSS, SII, PDQ-8, Ability to Function Scale, the MCBI caregiver burden, the CES-D, or the Daytime Alertness Scale. Overall, 30% of patients reported adverse events; 33% of patients receiving eszopiclone and 27% of patients receiving placebo.
Pollack et al.[47] (2011) Eszopiclone 3 mg for 3 weeks	DB, PC, RCT, XO Patients 18 to 64 years of age with PTSD with associated sleep	N=24 7 weeks	Primary: Changes in scores on the SPRINT and PSQI scales Secondary:	Primary: Eszopiclone was associated with significant improvement in PTSD symptomatology as measured by the SPRINT compared to placebo (P=0.032). Eszopiclone was associated with a significantly greater reduction in PSQI

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo for 3 weeks Each treatment period was separated by a 1-week washout period.	disturbance		CAPS, SL and TST	score compared to placebo (P=0.011). Secondary: In phase 1, the CAPS was also significantly reduced with eszopiclone compared to placebo (P=0.003). SL was significantly reduced with eszopiclone compared to placebo (P=0.044). There was no significant difference in TST among the treatment groups (P=0.061). Adverse events with eszopiclone were of mild to moderate severity, with the most common comprising unpleasant taste (32%), sedation (16%), and headaches (12%).
McCall et al.[48] (2010) Eszopiclone 3 mg vs placebo All patients started with one week of OL fluoxetine; patients experiencing insomnia after this period were randomized to 8 weeks of eszopiclone or placebo in addition to the OL fluoxetine.	DB, PC, RCT Patients 18 to 70 years of age with depression and insomnia	N=60 8 weeks	Primary: DLRF subscale of the Basis-32 Secondary: Safety	Primary: Final DLRF scores were better (lower) in the eszopiclone group than in the placebo group (0.81±0.64 vs 1.2±0.72). Secondary: The only meaningful adverse event reported, was unpleasant taste, and it occurred in 46% of patients treated with eszopiclone.

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Rosenberg et al.[49] (2005) Eszopiclone 1, 2, 3 or 3.5 mg vs placebo	DB, PC, RCT Healthy adult volunteers with transient insomnia	N=436 1 night	Primary: Efficacy and next-morning effects evaluated by PSG, DSST and self report Secondary: Not reported	Primary: Patients treated with eszopiclone had significantly less PSG LPS (all doses except 1 mg; P≤0.0001), WASO (all doses; P≤0.05) and NAW (3 and 3.5 mg doses; P<0.005), and greater SE (all doses; P≤0.02) compared to placebo. Self-reported efficacy results were similar to PSG. Self-reported morning sleepiness scores were significantly better for eszopiclone 3 and 3.5 mg compared to placebo (P<0.05). Treatment was well tolerated by patients, and the most common treatment-related adverse event was unpleasant taste. Secondary: Not reported
Krystal et al.[50] (2012) Eszopiclone 3 mg vs placebo	Post hoc analysis of a 6-month PC, RCT Patients diagnosed with chronic primary insomnia	N=195 6 months	Primary: Determination of the distribution of baseline WASO; continuous analysis of the relationship between baseline WASO severity and drug-placebo difference at month one and six; and categorical efficacy analyses of subgroups delimited by the following WASO thresholds: 0, 30, 45, 60, and 90 minutes Secondary:	Primary: The baseline WASO distribution was: <30 minutes, 32.2%; >0 to <45 minutes, 41.5%; >30 to <90 minutes, 33.0%; >45 to <90 minutes, 23.7%; >90 minutes, 22.6%. A relationship between greater baseline WASO severity and a significantly greater drug-placebo difference in efficacy for WASO was evident. Eszopiclone was found to have significant sleep maintenance efficacy at each time point across the entire range of WASO severity studied. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Not reported	
Uchimura et al (abstract).[51] (2011) Ramelteon 4 and 8 mg vs placebo	DB, PC, RCT Japanese adults with chronic insomnia	N=1,130 Duration not reported	Primary: Not reported Secondary: Not reported	Primary: Not reported Secondary: Not reported There was no statistically significant difference between ramelteon and placebo in the change in subjective SL (P value not reported). Significant improvement was observed in the change in subjective TST with ramelteon 8 mg at week one (P value not reported). Post hoc analyses indicated that treatment with ramelteon 8 mg resulted in a reduction in subjective SL in individuals with smaller fluctuations (within ±30 minutes) of subjective SL at baseline, in those with a shorter (<1 year) history of insomnia, and in individuals who had not used benzodiazepines (P value not reported). Ramelteon was safe and well tolerated up to 16 mg nightly.
Kohsaka et al (abstract).[52] (2011) Ramelteon 4, 8, 16, or 32 mg vs placebo	DB, PC, XO Japanese patients with chronic insomnia	N=65 Each dose was given for two nights over five study periods	Primary: Not reported Secondary: Not reported	Primary: Not reported Secondary: Not reported Ramelteon 8 and 32 mg significantly shortened the mean LPS when compared to placebo (P value not reported). Overall changes in sleep architecture were modest (<3% changes vs placebo; P value not reported), with increases in stage 1 and decreases in stage 3/4. When compared to SL data from a similarly designed United States study, there was no evidence of any ethnic differences in the efficacy of ramelteon between Japanese and United States patients. Overall, ramelteon 8 mg showed the most favorable balance between sleep-promoting effects and tolerability (P value not reported). Ramelteon was well tolerated, the most common adverse effect was somnolence, which was similar to placebo at doses up to 8 mg, but

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				increased with higher doses (P value not reported). Next-day residual effects occurred no more frequently with ramelteon at any dose than with placebo (P value not reported).
Wang-Weigand et al.[53] (2011) Ramelteon 8 mg vs placebo	PC, RCT Adults 18 to 64 years of age with chronic insomnia	N=552 Nightly treatment for 3 weeks with a one week, placebo run-out period to assess rebound insomnia	Primary: Patient reported SL at week three Secondary: Patient reported SL at week one and two, patient reported TST, patient reported WASO, patient reported NAW, and sleep quality (all assessed each week), safety	Primary and secondary: There was a reduction in the average patient reported SL (as measured by the PSQ-IVRS) at weeks one, two, and three, when compared to placebo; however, none of these reductions reached statistical significance (P value not reported). There were no significant differences seen between ramelteon and placebo at any time point regarding the following patient-reported parameters: TST, WASO, NAW, or sleep quality (P value not reported). There was no evidence of rebound insomnia detected during the placebo run-out period for the groups that had received placebo or ramelteon. Headache and somnolence occurred in more than 3% of subjects in either group. Overall, the proportion of subjects with any treatment-related adverse events was similar between the ramelteon and placebo-groups (16.5 vs 15.4%, respectively; P-value not reported).
Wang-Weigand et al.[54] (2009) Ramelteon 8 mg vs placebo	DB, PC, RCT (pooled analysis of 4 trials) Patients 18 to 83 years of age with chronic insomnia	N=1,122 Duration varied among included trials	Primary: LS mean LPS for nights one and two for each included trial Secondary: Safety	Primary: At nights one and two, mean LPS was 43.3 minutes for the placebo group and 30.2 minutes, resulting in a between-group difference of 13.1 minutes (P<0.001). Secondary: The total number of adverse events was similar for ramelteon 8 mg (209 [36.5%]) and placebo (192 [34.3%]) (P value not reported). The most common adverse events were headache and somnolence.
Zammit et al.[55] (2009) Ramelteon 8 or 16 mg vs placebo	DB, MC, PC, RCT, SD Healthy patients 18 to 64 years of age	N=289 1 night	Primary: LPS assessed by PSG Secondary: PSG assessed endpoints include TST, WASO, and NAW after persistent sleep	Primary: Treatment with ramelteon 8 mg resulted in a significant decrease in LS mean LPS when compared to placebo (12.2 vs 19.7 minutes; P=0.004). Treatment with ramelteon 16 mg resulted in a numeric decrease in LS mean LPS when compared to placebo; however, this decrease did not reach statistical significance (14.8 vs 19.7 minutes; P=0.065). Secondary: Treatment with ramelteon 8 and 16 mg resulted in significant increases in the LS mean TST when compared to placebo (8 mg: 436.8 vs 419.7

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			onset; subjective measures include SL, TST, WASO, NAW after persistent sleep onset, and overall sleep quality, safety	minutes; P=0.009 and 16 mg: 433.1 vs 419.7 minutes; P=0.043). There were no significant changes in any other objective or subjective measures of sleep. A total of 31 subjects (10.7%) reported at least one adverse event during the study. The incidence rates were 12.4, 13.3, and 6.4% for the placebo, ramelteon 8 and 16 mg groups, respectively. Most adverse events were mild or moderate in severity and the most commonly reported adverse event was somnolence.
Erman et al.[56] (2006) Ramelteon 4 to 32 mg vs placebo	DB, MC, PC, RCT, 5-period XO Men and non-pregnant, non-lactating women 18 to 64 years of age with chronic insomnia	N=107 2 nights per treatment	Primary: Mean LPS Secondary: TST, WASO, percentage of sleep time in each sleep stage, subjective sleep quality, next-day performance and alertness, safety	Primary: All tested doses of ramelteon resulted in statistically significant reductions in LPS compared to placebo (P<0.001). Secondary: All tested doses of ramelteon resulted in statistically significant increases in TST compared to placebo (P=0.001). No significant differences in WASO (P=0.470), percentage of time spent in the different sleep stages and subjective sleep quality (P=0.525) were reported between the ramelteon groups and the placebo group. There were no differences between the placebo group and any ramelteon dose group on next-day performance and alertness (P values not reported). The safety of ramelteon at each dose was similar to that of placebo and the most commonly reported adverse events were headache, somnolence, and sore throat.
Mayer et al.[57] (2009) Ramelteon 8 mg vs placebo	DB, PC, RCT Patients ≥18 years of age with chronic primary insomnia	N=451 6 months	Primary: LPS (measured by PSG) Secondary: TST (measured by PSG), total time spent in each sleep stage, latency to REM, self-reported	Primary: Greater reductions in LPS occurred with ramelteon compared to placebo (P<0.05 for each time point). A greater change from baseline occurred with ramelteon (54 to 56%) compared to placebo (30 to 47%). Secondary A greater increase in TST occurred with ramelteon (381.1 minutes) compared to placebo (365.7 minutes) at week one (P<0.001), but not at any other time points.

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			efficacy	There were no significant changes in percent of time spent in Stage 1 or REM sleep with ramelteon vs placebo. There was a significant increase in percent of time spent in Stage 2 sleep and a significant decrease in time spent in Stage 3/4 with ramelteon compared to placebo (P values not reported). There was a greater reduction in subjective SL with ramelteon compared to placebo at week one, as well as months one and five (P<0.05). There were no significant reductions at other time points between the treatment groups. There were no significant differences between ramelteon and placebo at any time point on the following measures: subjective TST, subjective NAW and sleep quality. No significant differences in sWASO was observed between ramelteon (90.89 minutes) and placebo (79.54 minutes) at any time point except month six (P=0.036). There were no significant differences on measures of morning level of alertness and ability to concentrate, or immediate/delayed morning recall between the treatment groups. No rebound insomnia was observed during the placebo run-out period. There were no differences between the treatment groups with regards to measures of withdrawal during the placebo run-out period.
Uchiyama et al.[58] (2011) Ramelteon 8 mg vs placebo	DB, MC, PC, RCT Japanese patients 20 to 85 years of age with primary insomnia	N=1,605 2 weeks	Primary: Mean patient-reported SL during week one of treatment Secondary: Mean SL during week two of treatment, mean patient-reported	Primary: The mean SL was reduced in week one in both the ramelteon and placebo groups (-15.98 and -11.73 minutes, respectively; P=0.0010). Secondary: The mean SL decreased further in week two in both groups; however, the difference between the groups of -2.36 minutes in favor of ramelteon did not achieve statistical significance (P=0.1093). Ramelteon increased TST significantly more than placebo at week one (difference in LS mean, 4.2 minutes; P=0.0484), but not at week two (2.4

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			TST for week one and for week two, patient's global impression of treatment, rebound insomnia, and safety	minutes; P=0.2378). The mean NAW reported by patients in the ramelteon group was significantly less than that in the placebo group at week two (difference in LS mean of -0.07; P=0.0469) but not for week 1 (-0.04; P=0.2592). The mean sleep quality score with ramelteon was significantly smaller than that with placebo for week one (difference in LS mean, -0.12; P=0.0174), but not week two (-0.06; P=0.2059). There was no evidence of rebound insomnia with ramelteon during the run-out period. The mean total score for patients' global impression of treatment improved significantly with ramelteon compared to placebo at the end of week one (1.52 vs 1.59; P=0.0041) and week two (1.45 vs 1.53; P=0.0028). The proportion of patients scoring individual items as ''improved'' was significantly higher for ramelteon than placebo at weeks one and two for time to fall asleep (week one, 53.1 vs 44.3%; P=0.0100, week two, 58.3 vs 52.5%; P=0.0434), TST (week one, 42.0 vs 34.0%; P=0.0121, week two, 47.6 vs 38.8%; P=0.0031), sleep quality (week one, 56.4 vs 48.2%; P=0.0115, week two, 62.5 vs 56.1%; P=0.0463), and usefulness of treatment (week one, 58.2 vs 47.6%; P=0.0008, week two, 64.6 vs 56.8%; P=0.0123), but not for daytime distress (week one, 33.4 vs 31.9%; P=0.9116, week two, 42.7 vs 37.7%; P=0.0881). A total of 26.4% of patients in the ramelteon group and 20.5% of patients in the placebo group reported at least one treatment-emergent adverse event. All events were mild or moderate in severity. The most common adverse event leading to discontinuation was nasopharyngitis.
Uchiyama et al.[59] (2011) Ramelteon 4 to 16 mg	MC, SB Japanese patients 20 to 85 years of age with primary insomnia	N=222 24 weeks	Primary: Adverse events, residual effects, rebound insomnia, withdrawal symptoms, and dependence	Primary: During the study, 77.4% of patients reported adverse events. The most frequent reported adverse events were nasopharyngitis, inflammation of upper respiratory tract, eczema, elevated γ-glutamyltransferase, laryngopharyngitis, and headache. Endocrine adverse events that were considered drug-related included metrorrhagia, dysmenorrhea, polymenorrhea, increased estradiol, increased cortisol, and decreased

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			Secondary: Subjective SL and TST	cortisol. The mean change in next-morning residual scores significantly improved from baseline with ramelteon (P<0.05). The mean change from baseline in SL at week 24 and the placebo run-out period using the full analysis set with 8 mg were -30.4 and -28.6 minutes in the group continuously treated with ramelteon, which confirms the lack of rebound insomnia. Ramelteon was not associated with withdrawal symptoms and there was no evidence of dependence. Secondary: Mean subjective SL decreased significantly during the study. In the group that continuously received ramelteon 8 mg, it decreased from a baseline of 70.5 to 54.4 minutes after one week (P<0.0001) and 33.8 minutes after 20 weeks (P<0.0001), then plateaued until the end of the study. The mean subjective TST was 5.52 hours at baseline, increasing to 5.78 hours at week one (P<0.0001) and 6.30 hours at week 20 (P<0.0001), and remained stable until the end of the study.
Gooneratne et al.[60] (2010) Ramelteon 8 mg vs placebo	DB, PC, RCT Patients ≥60 years of age with obstructive sleep apnea and insomnia symptoms	N=21 4 weeks	Primary: Objective change in SOL using PSG Secondary: PSQI, (ISI, FOSQ, quality of life (SF-36)	Primary: Using PSG, there was a 10.7 minute decrease in SOL in the ramelteon arm compared to a 17.8 minute increase in the placebo arm (difference, 28.5 minutes; P=0.008). For self-reported SOL, there was no significant difference among the two study arms (−1.3 minutes; P=0.9). Neither objective nor subjective SE differed significantly between study arms. Secondary: There were no significant differences in the PSQI, ISI, FOSQ, or SF-36 among the treatment groups. The adverse events reported with ramelteon were diarrhea, skin ulcer, sinusitis, and fracture after being hit by a bicyclist. For placebo, the

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				adverse events were abdominal pain and nausea. All adverse events were thought to be unrelated to study drug treatments, and none were serious adverse events.
Liu et al.[61] (2012) Ramelteon vs placebo	MA Patients with chronic insomnia	N=8 trials Duration varied	Primary: Subjective and polysomnographic SL, TST and latency to REM Secondary: Not reported	Primary: There were significant improvements in all outcomes (subjective and polysomnographic SL, TST and latency to REM), except for the percentage of REM. By subgroup analysis, subjective SL was reduced only in the patients 18 to 64 years of age. For the safety, ramelteon was not associated with higher risk ratio of any frequent adverse events comparing with control. Secondary: Not reported
Dobkin et al.[62] (2009) Ramelteon 8 mg	OL, PRO Patient population not specified	N=20 6 weeks	Primary: Patient reported LPS Secondary: Patient reported endpoints include TST, WASO, total number of nighttime awakenings, SE, and number of hot flashes/ night sweats; other secondary endpoints include sleep impairment (assessed via the SII), daytime functioning, daytime alertness,	Primary: Treatment with ramelteon resulted in improvements in LPS at week six when compared to baseline (24.0±15.0 vs 46.2±19.8 minutes; P<0.001). The average improvement across all participants was 22 minutes. Secondary: Treatment with ramelteon 8 mg resulted in improvements at week six when compared to baseline in the following parameters: TST (420±38 vs 336±62 minutes; P<0.001), SE (0.91±0.06 vs 0.80±0.10; P<0.001), night time awakenings (1.86±1.53 vs 2.32±1.36; P<0.05), and hot flashes (1.52±1.32 vs 2.31±1.95; P<0.05). There were no significant improvements in WASO at any time period throughout the study when compared to baseline. Significant improvements were observed in patient reported sleep quality (P<0.001), daytime dysfunction (P<0.01), daytime alertness (P<0.001), SII scores (P<0.001), MENQOL scores (P<0.01), BDI scores (P<0.001), and anxiety (P<0.001). At the end of this trial, 55% of women were considered “responders” according to the CGI-I scale. Insomnia severity, assessed by the CGI-S,

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			quality of life (assessed via the MENQOL), mood (assessed via the BDI), CGI-S, and CGI-I, safety	also improved over baseline (3.14 vs 4.65; P<0.001). Of the subjects treated with ramelteon in this trial, 40% reported side effects. The most frequently reported side effects included headaches, daytime fatigue/fogginess, dry mouth, lightheadedness, and dizziness. Most side effects were mild and transient.
Richardson et al.[63] (2009) Ramelteon 8 or 16 mg Subjects >65 years of age received 8 mg/day, subjects 18 to 64 years of age received 16 mg/day.	OL, PRO Adults with primary insomnia	N=1,213 48 weeks	Primary: Adverse events, changes in vital signs, laboratory values, 12-ECG, and results of physical examination Secondary: Safety	Primary: There were no noteworthy changes in vital signs, physical examinations, clinical chemistry, hematology, or urinalysis values. There were also no ECG changes to suggest adverse cardiac effects. Consistent statistically significant (P≤0.05) decreases in free thyroxine and free testosterone (in older men) were detected. Duration of menses increased by approximately one day. In both groups, those older and younger than 65, subjective SL and TST improved by month one and was sustained during the one-year period. At six months and one year, CGI indices were improved. During the placebo run-out period, SL did increase but did not return to baseline. Secondary: A total of 69.8% of patients reported at least one adverse event. There was no difference in adverse event incidence between those older and younger than 65 (P value not reported). The overall incidence of adverse events was similar at six months and one year.
Gross et al.[64] (2009) Ramelteon 8 mg All patients continued to take their antidepressant; dose reductions were permitted at any time but no	OL, PRO Patients 18 to 80 years of age with GAD and related insomnia	N=27 10 weeks	Primary: CGI-I, CGI-S, daytime sleepiness (assessed via ESS), HAMA, and patient reported sleep diaries Secondary: Safety	Primary: The addition of ramelteon 8 mg resulted in significant improvement over baseline in the following study parameters: time to fall asleep (34.67±29.26 vs 77.52±47.73 minutes; P<0.001), TST (7.52±1.22 vs 5.02±0.96 hours; P<0.001), CGI-S Insomnia (1.67±0.73 vs 4.30±0.47; P<0.001), CGI-I Insomnia (1.59±0.64 vs 3.85±0.36; P<0.001), HAMA (3.96±2.97 vs 8.26±2.94; P<0.001), ESS (5.48±3.27 vs 11.56±2.14; P<0.001), CGI-S Anxiety (1.25±0.64 vs 2.85±0.66; P<0.001), CGI-I Anxiety (1.41±0.50 vs 2.33±0.78; P<0.001). Secondary: The most common adverse events regarding ramelteon use were headache

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dose increases were permitted during the study period.				upon stopping ramelteon (7.4%), daytime tiredness (3.7%), and depression (3.7%). All side effects were reported as transient.
Roth et al.[65] (2006) Ramelteon 4 mg vs ramelteon 8 mg vs placebo	DB, PC, RCT Patients 64 to 93 years of age with chronic primary insomnia	N=829 5 weeks	Primary: SL at week one Secondary: TST at weeks one, three and five; reductions in SL at weeks three and five; sleep diaries; rebound insomnia and withdrawal effects during the seven-day placebo run out	Primary: Significant reductions in SL at week one were reported with both ramelteon 4 mg (70.2 vs 78.5 minutes; P=0.008) and 8 mg (70.2 vs 78.5 minutes; P=0.008) compared to placebo. Secondary: Patients continued to report reduced SL at week three with ramelteon 8 mg (P=0.003) and at week five with ramelteon 4 and 8 mg (P=0.028 and P<0.001, respectively) compared to placebo. Patient-reported TST at weeks one and three was significantly longer compared to placebo for ramelteon 4 mg (324.6 vs 313.9 minutes; P=0.004 and 336.0 vs 324.3 minutes; P=0.007, respectively). TST for ramelteon 4 mg at five weeks and for ramelteon 8 mg at weeks one, three and five were longer than placebo but did not reach statistical significance (P values >0.05). Analyses of other sleep parameters obtained via sleep diaries (e.g., NAW, ease of falling back asleep after an awakening and sleep quality) yielded no statistically significant differences among groups at weeks one, three and five. There was no evidence of significant rebound insomnia or withdrawal effects following treatment discontinuation. Incidence of adverse events was 51.5, 54.8 and 58.0% of patients in the placebo, 4 and 8 mg ramelteon groups, respectively.
Roth et al.[66] (2005) Ramelteon 16 mg vs	DB, PC, MC, RCT Healthy adult volunteers with transient insomnia (35 to 60 years of	N =375 1 night	Primary: Mean LPS as measured by PSG Secondary: TST, WASO,	Primary: Participants who had received either ramelteon dosage had significantly shorter LPS relative to placebo (both P<0.001). Secondary: Participants who had received ramelteon 16 or 64 mg had significantly

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ramelteon 64 mg vs placebo Doses were given 30 minutes before bedtime.	age with total sleep duration 6.5 to 8.5 hours, a usual SL of 30 minutes or less, a habitual bedtime between 8:30 PM and midnight)		percentage of sleep time in each sleep stage, NAW, residual effects assessed by DSST and postsleep questionnaire, safety	longer TST compared to participants who had received placebo (P=0.007 and P=0.033, respectively). There were no significant differences between the ramelteon groups and placebo with regard to WASO, percentage of sleep time in each sleep stage, and NAW. No significant differences in DSST scores were reported among the groups, but ramelteon 64 mg was associated with statistically significant declines in subjective levels of alertness (P=0.020) and ability to concentrate (P=0.043) compared to placebo. No serious adverse events were reported.
Michelson et al.[67] (2014) Suvorexant 30 mg nightly for elderly patients and 40 mg nightly for non-elderly patients vs placebo	DB, PC, RCT Patients ≥18 years of age with primary insomnia	N=779 1 year	Primary: Safety and tolerability Secondary: sTST, sTSO	Primary: Similar proportions of patients treated with suvorexant or placebo discontinued because of adverse events. The most common adverse events that were increased for suvorexant versus placebo were somnolence, fatigue, and dry mouth. Somnolence was the adverse event with the highest incidence for discontinuations, (suvorexant 20/521 [4%] vs placebo 2/258 [1%]). Somnolence was most common in the first three months (57/527 [11%] for suvorexant vs 6/258 [2%] for placebo) and was less commonly reported by the second three months (11/425 [3%] for suvorexant vs 1/254 [<1%] for placebo). There were no clinically meaningful differences between groups in vital signs or laboratory values. Secondary: Over the first month, the suvorexant group showed significant improvements in sTST and sTSO compared with the placebo group. The improvements were maintained throughout the one-year phase.
Scharf et al.[68] (1994) Zolpidem 10 to 15 mg vs	DB, MC, PC, PG, RCT Adults with chronic insomnia	N=75 5 weeks	Primary: LPS, SE, sleep maintenance, sleep quality, effects on sleep stages, residual drug effects, safety	Primary: Zolpidem had a significant (P<0.05) effect on LPS and SE from weeks two through five in the 10-mg group and at weeks two through six in the 15-mg group. Polysomnographic measures of sleep maintenance were not significantly different among the three treatment groups (P>0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo			Secondary: Not reported	Patients receiving zolpidem 15 mg reported significantly better quality of sleep than those receiving the 10 mg dose at week two and placebo at week five. Stages 1, 2, and 3 to 4 sleep were not significantly affected by either the 10- or 15-mg doses of zolpidem compared to placebo. However, there were significant (P<0.05) decreases in REM sleep at weeks three and four with zolpidem 15 mg compared to placebo. There was no evidence of residual effect with zolpidem 10 or 15 mg. There was no evidence of tolerance at either dose. The only significant treatment difference was in the percent of time in Stage 3 to 4 sleep (P<0.05 for both zolpidem doses compared to placebo). There were no significant treatment differences between the 10-mg zolpidem group and the placebo group in LPS, SE, WTDS or sleep quality during the post treatment period when zolpidem was discontinued. The 15-mg zolpidem group did not differ significantly from the placebo group on LPS or SE on the first night post treatment, but did result in a significantly greater WTDS and poorer quality of sleep (P<0.05 compared to placebo) during the first night post treatment. Comparison of the subsequent two nights post treatment showed no significant differences between zolpidem 15 mg and placebo on any of these variables. Overall, the incidence of treatment emergent adverse events in the zolpidem groups was similar to those in the placebo group. While none of the adverse events were severe, two patients in the 15-mg zolpidem group withdrew from the study: one patient experienced drowsiness, dizziness, and nausea; and one patient experienced visual disturbance and over sedation. The 15-mg zolpidem dosage provided no clinical advantage over the 10 mg zolpidem dosage. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Roehrs et al.[69] (2011) Zolpidem 10 mg vs placebo	DB, PC, RCT Patients 21 to 70 years of age with primary insomnia	N=33 12 months	Primary: Number of zolpidem or placebo choices made, total number of zolpidem or placebo capsules chosen, and given a placebo or zolpidem choice on a given night, the nightly number of capsules taken Secondary: Not reported	Primary: On weekly telephone interviews, patients reported taking 73 to 89% of the single nightly capsules each month while at home. The groups did not differ in the average percentage of capsules used over the 12 months (placebo, 81% vs zolpidem, 84%). Over the three one-week laboratory self-administration assessments, the zolpidem group selected zolpidem (80.3%) more often than placebo (P<0.020). The placebo group showed no color preference, choosing the red capsule 51% of opportunities and the blue capsule 49% of opportunities. Overall, the zolpidem group self-administered more zolpidem capsules than placebo capsules (P<0.001). In the zolpidem group, the total number of capsules chosen, whether placebo or zolpidem, did not differ over months one, four, and 12. The total number of placebo capsules self-administered by the placebo group increased significantly during month four and month 12 compared to month one (P<0.02). Within the zolpidem group, the nightly number of placebo vs zolpidem capsules self-administered each month did not differ. On average, the zolpidem group self-administered a 9.1 mg dose nightly in month one, a 9.4 mg dose in month four, and a 9.4 mg dose in month 12. In the placebo group, the nightly number of capsules increased over time (P<0.02). The percent of patients increasing the dose did not differ between the zolpidem and placebo groups and did not change from month four to month 12. A significantly greater percent of patients receiving zolpidem compared to placebo decreased the dose they self-administered in month four and month 12 compared to month one (P<0.001). The self-administration rates did not differ when at the laboratory vs at home for patients receiving zolpidem. These rates also did not differ over the three assessments. Secondary: Not reported

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Roth et al.[70] (1995) Zolpidem 5, 7.5, 10, 15, 20 mg vs placebo Statistical analyses were primarily performed between zolpidem 7.5 and 10 mg and placebo.	DB, PC, PG, RCT Healthy adult volunteers with transient insomnia	N=462 SD	Primary: SL, sleep duration, SE (TST divided by time in bed) NAW (sleep maintenance), effect on sleep stages, next day psychomotor performance and alertness (DSST, Symbol Copying Tests, Visual Analog Scales on the Morning Questionnaire) Secondary: Not reported	Primary: Compared to placebo, zolpidem 7.5 and 10 mg significantly decreased SL, increased sleep duration and efficiency, and reduced the NAW (all P<0.05). Subjective quality of sleep was also rated significantly better with both doses of zolpidem compared to placebo (both P<0.001). Increasing the dose above 10 mg did not result in a corresponding increase in hypnotic efficacy. Treatment with zolpidem had no effect on stage 1, stage 2 and stages 3 to 4 sleep. Significantly less REM sleep was reported in the zolpidem groups compared to the placebo group (both P<0.001). Zolpidem 7.5 or 10 mg had no significant effect on next day psychomotor performance and alertness. No statistically significant differences in the overall side effects were found between zolpidem doses of 7.5 mg (4.9%) or 10 mg (6.7%) and placebo (7.8%). Higher doses of zolpidem were associated with more side effects (17.6% with 15 mg [P=0.069 vs placebo] and 31.4% with 20 mg [P<0.001 vs placebo]). Secondary: Not reported
Randall et al.[71] (2012) Zolpidem 5 or 10 mg vs placebo	DB, PC, RCT Adults 23 to 70 years of age with chronic primary insomnia	N=91 8 months	Primary: Polysomnographic sleep parameters and morning subject assessments of sleep on two nights in months one and eight Secondary: Not reported	Primary: Relative to placebo, zolpidem significantly increased overall TST and SE, reduced SL and wake after sleep onset when assessed at months one and eight. Overall, subjective evaluations of efficacy were not shown among treatment groups. Secondary: Not reported
Krystal et al.[72](2008)	DB, MC, PC, RCT	N=1,025	Primary: Score on the PGI,	Primary: At week 12, PGI, Item 1 (aid to sleep) was scored as favorable (i.e.,

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Zolpidem ER 12.5 mg vs placebo Treatments were taken 3 to 7 nights per week.	Patients 18 to 64 years of age with chronic primary insomnia	26 weeks	Item 1, (aid to sleep) at week 12 of the treatment period in the ITT population Secondary: Scores on CGI-I, PGI, PMQ, TST, WASO, SOL, quality of sleep, and NAW in the ITT population	"helped me sleep") by 89.8% of zolpidem patients vs 51.4% of placebo patients (P<0.0001). Secondary: The percentage of patients who reported a treatment benefit on the PGI (Items 1 to 4) was higher in the zolpidem ER group compared to placebo at each four-week interval during the 24-week treatment period (all P<0.0001). The percentage of patients who obtained a positive evaluation on the CGI-I scale was greater in the zolpidem ER group compared to the placebo group at all four-week intervals during the 24-week treatment period (all P<0.0001). At every time point, results on the PMQ were greater for patients in the zolpidem ER group compared to the placebo group for the TST (P<0.0001), WASO (P<0.0001), SOL (P≤0.0014), quality of sleep (P<0.0001), and NAW (month one; P=0.0515, months two to six; P<0.0001). Patients in the zolpidem ER group demonstrated improvements in their ability to concentrate in the morning at each month throughout the treatment period, as compared to those in the placebo group (months one to five; P<0.0001, month six; P=0.0014). Patients in the zolpidem ER group had sustained reductions in their level of sleepiness in the morning compared to placebo at each month throughout the treatment period (P<0.0001). The most common adverse events occurring at a higher frequency in the zolpidem extended-release group than in the placebo group were headache, anxiety, somnolence, dizziness, fatigue, disturbance inattention, irritability, nausea, and sinusitis.
Fava et al.[73] (2011) Zolpidem ER 12.5	DB, MC, PC, PG, RCT Patients 21 to 64	N=358 24 weeks	Primary: Change from baseline in subjective TST	Primary: Phase 1 During phase 1, treatment with zolpidem ER led to significantly greater improvements in TST when compared to treatment with placebo

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mg vs placebo Patients were also receiving OL escitalopram 10 mg daily.	years of age with major depressive disorder and associated insomnia	Two phases were included Phase 1 was 8 weeks; responders (≥50% in 17-item $HDRS_{17}$) at week 8 continued to receive an additional 16 weeks of therapy in phase 2	Secondary: Subjective LSO, NAW, WASO, sleep quality, sleep-related next-day functioning, $HDRS_{17}$ SIS score, PGI-IT, CGI-I, CGI-S, MGH-CPFQ, Q-LES-Q, safety	(P<0.0001). Phase 2 During phase 2, treatment with zolpidem ER led to improvements in TST that were significant at weeks 12 and 16 (P<0.05 for both), but not at weeks 20 and 24 (P value not reported). Secondary: Phase 1 Treatment with zolpidem ER led to significantly greater improvement in TST at each assessment. The LSM difference between the treatment groups in the change from baseline TST ranged from 37.9 to 45.5 minutes (P<0.0001 for all comparisons). The group receiving zolpidem ER had a TST of approximately seven hours at week eight, compared to approximately five hours at baseline (P<0.0001 vs placebo for improvement over baseline). Treatment with zolpidem ER led to significantly greater improvements in WASO, LSO, NAW, and sleep quality when compared to treatment with placebo (P<0.001 for all comparisons at all time points). Total improvement in insomnia-only $HDRS_{17}$ was also significantly greater in the group receiving zolpidem ER compared to those receiving placebo (P<0.001 for all time points). Treatment with zolpidem ER also produced favorable results on all domains of the SIS, except mental fatigue, when compared to treatment with placebo at week eight (P<0.05). There were no significant differences at week eight between the two groups on the improvement in functioning and quality of life on the Q-LES-Q; however, at week eight, there were greater improvements seen in the MGH-CPFQ total score, wakefulness/alertness, energy, memory/recall, and mental acuity in those patients receiving zolpidem ER compared to those receiving placebo (P<0.05). There were no significant improvements found with zolpidem ER compared to placebo on motivation/enthusiasm, attention focus/sustain, or ability to find words, at week eight. Treatment with zolpidem ER was also associated with greater improvements than placebo in some aspects of sleep-related next-day functioning, including morning

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				energy, sleep impact on daily activities, and morning concentration ability. Decreases seen in the $HDRS_{17}$ scores at week eight were comparable between the two treatment groups; at the end of phase 1 58.4 and 63.7% of patients in the placebo and zolpidem ER groups, respectively, met the criteria for depression treatment response. PGI-IT scores were superior in the group receiving zolpidem ER compared to those in the placebo group (P<0.001) and both CGI-S and CGI-I scores were comparable between the groups throughout phase 1. Phase 2 During phase 2, treatment with zolpidem ER continued to show significantly greater improvement at each visit in the NAW and sleep quality, when compared to treatment with placebo (P value not reported). For WASO, treatment with zolpidem ER resulted in significant improvements over treatment with placebo at weeks 16 and 20 and there were no significant differences between the treatment groups in LSO during phase 2 (P value not reported). The $HDRS_{17}$ total score of insomnia-only items demonstrated significantly greater improvement in the zolpidem ER group throughout phase 2 (P<0.05 for all time points). Treatment with zolpidem ER was associated with significant differences on all of the SIS domain scores at week 24, except mental fatigue (P<0.05). There were no differences between the groups in any of the MGH-CPFQ subscales at week 24 (P-value not reported). Treatment with zolpidem ER resulted in improvements over placebo on the physical health/activities and medication satisfaction subscales of Q-LES-Q (P<0.05); however, treatment with placebo resulted in improvements over zolpidem ER on the school/course work subscale (P<0.05). Both groups experienced improvements in depression treatment remission and depression symptoms; however, these improvements were not significantly different between groups (P value not reported).

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				PGI-IT scores indicated insomnia treatment was rated higher with zolpidem ER compared to placebo (P<0.001). Ratings of severity and mental illness by clinicians were comparable between the two groups throughout phase 2. A greater percentage of patients treated with zolpidem ER experienced at least one adverse event during phase 1 when compared to patients treated with placebo (72.9 vs 66.3%; P value not reported). The most common adverse events that occurred more frequently in the group receiving zolpidem ER, compared to the placebo group, include nausea, somnolence, dry mouth, dizziness, fatigue, upper respiratory tract infection, and decreased libido. During phase 2, 57.3% of zolpidem ER-treated patients and 60% of placebo-treated patients experienced an adverse event (P value not reported). The most frequently reported events among both treatment groups include headache, diarrhea, and nasopharyngitis.
Fava et al.[74] (2009) Zolpidem ER 12.5 mg vs placebo All patients received OL escitalopram 10 mg/day.	DB, MC, PC, PG, RCT Patients 21 to 64 years of age with insomnia and comorbid GAD	N=383 8 weeks	Primary: Change from baseline to week eight in subjective TST Secondary: Subjective SOL, NAW, WASO, sleep quality, HAMA, BAI, SIS, MGH-CPFQ, SDS, safety	Primary: At week eight, the mean TST increased from baseline by 106 minutes in the group receiving zolpidem ER and by 68.2 minutes in the placebo group (LSM in the change from baseline between groups 39.4 minutes, 90% CI, 24.81 to 53.99; P<0.0001). Secondary: From week one through week eight, mean TST was significantly greater in the group receiving zolpidem ER when compared to those receiving placebo (P<0.0001). Significant improvements in SOL, WASO, NAW, and quality of sleep were observed throughout the treatment period with zolpidem ER vs placebo based on the difference in LSM change from baseline (P<0.0001 for all comparisons). Significant improvements were also seen with MSQ measures of sleep-related next-day symptoms, including morning energy, morning concentration, and impact of sleep on daily activities (P<0.0001 for all comparisons). The change from baseline in PGI-IT for the zolpidem ER-treated group was significantly greater when compared to the placebo-treated group (P<0.0001 for all comparisons). At week two, there was a significant difference in favor of treatment with zolpidem ER on all seven items of

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				the SIS (P<0.0001 for six comparisons; P<0.01 for one comparison). This improvement was sustained to week eight on four of the seven items: daily activities (P=0.107), emotional impact (P<0.0001), energy/fatigue (P<0.001), and satisfaction with sleep (P<0.0001). Between group differences in the total MGH-CPFQ score were significant at week four but not at week eight (P=0.0586). There were statistically significant differences between groups at one or both of the time points for three of seven items. There was statistically significantly greater improvement in the zolpidem ER group on three items (motivation, wakefulness/alertness, and energy) at week four (P<0.05) and on two items (wakefulness/alertness and energy) at week eight (P<0.01). The mean HAMA total scores decreased for both groups throughout the study. At week eight, HAMA total scores for both the group receiving zolpidem ER and the group receiving placebo showed comparable reductions (-13.3 vs -12.5, respectively; P=0.4095). Rates of treatment response in the group receiving zolpidem ER and the group receiving placebo were similar at week eight (63.4 vs 64.2%, respectively; P=0.8564). Both treatment groups demonstrated at least a 40% reduction in the BAI at week one and continued to improve throughout the study. By week six, there was a difference in favor of the placebo group that as also present at week eight. There were no significant differences in Q-LES-Q between groups at week eight and there were no significant differences between groups in SDS scores at any time point measured. Treatment-emergent adverse events that occurred in at least 10% of patients and either group but with a higher incidence in the group receiving zolpidem ER included dizziness, nausea, and fatigue. Six patients receiving zolpidem ER experienced seven events of non-global amnesia between two and 59 days of taking the study medication. One patient in each group experienced one serious adverse event. Laboratory values, vital signs, and physical examination findings revealed no

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				meaningful changes or clinically relevant differences between groups.
Erman et al.[75] (2008) zolpidem ER 12.5 mg vs placebo Zolpidem ER or placebo was to be taken nightly or at least 3 times per week.	DB, PC, RCT (subset analysis) Adults under 65 years of age with chronic insomnia	N=1,012 24 weeks	Primary: Change from baseline to week 12 in the Time Management and Output scales of the WLQ Secondary: Change from baseline to week four and to week 24 in the Time Management and Output scales of the WLQ, or premature discontinuation	Primary: At week 12, treatment with zolpidem ER 12.5 resulted in a 4.86 point reduction in the Output Scale (95% CI, -8.37 to -1.36; P=0.0066) and a 7.29 point reduction in the Time Management Scale (95% CI, -10.77 to -3.81; P<0.0001) vs placebo. Secondary: At week four, scores for the Output Scale and the Time Management Scale were significantly lower than at baseline (P value not reported). The decrease was significantly greater with zolpidem ER than for placebo for both the Output Scale (-9.59 vs -2.16; P<0.0001) and the Time Management Scale (-12.22 vs -3.85; P<0.0001).
Roth et al.[76] (2013) Zolpidem SL tablets 3.5 mg vs placebo	DB, MC, PC, PG, RCT Adults with primary insomnia and difficulty returning to sleep after MOTN	N=295 28 nights	Primary: LSO after MOTN, adverse events Secondary: Not reported	Primary: Zolpidem SL tablets significantly (P<0.0001) decreased LSO over four weeks (baseline, 68.1 minutes; zolpidem SL tablets, 38.2 minutes) compared to placebo (baseline, 69.4 minutes; placebo, 56.4 minutes). Ratings of morning sleepiness/alertness significantly (P=0.0041) favored the zolpidem SL tablets group on nights medication was taken but not on other nights. Participants in the zolpidem SL tablets group took the study drug on 62% of nights during the four weeks; members of the placebo group took study medication on 64% of nights. Adverse events were generally mild and at the same rate (19.3% of participants) in both groups. There were no treatment-related serious adverse events, and one adverse event-related study discontinuation from the placebo group. Dosing/week did not increase across the study. Secondary: Not reported

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Roth et al.[77] (2008) Zolpidem 1.75 or 3.5 mg SL vs placebo Subjects were awakened 4 hours after lights out, dosed with zolpidem SL or placebo, kept awake for 30 minutes, and then returned to bed for 30 minutes.	DB, PC, XO Adults with insomnia characterized by difficulty returning to sleep following MOTN awakenings	N=82 3 2-night treatment periods Each treatment period consisted of 2 consecutive nights of dosing separated by a washout of 5 to 12 days.	Primary: LPS following MOTN comparing zolpidem SL 3.5 mg to placebo Secondary: TST, SE, sleep quality, subjective SOL, subjective TST, and mean LPS for zolpidem SL 1.75 compared to placebo (all assessed after MOTN); according to the statistical analysis plan, if any test of a secondary endpoint did not attain statistical significance, then inferential analyses of secondary endpoints would cease and no further inferential assessment of remaining secondary endpoints would be made, safety	Primary: Treatment with zolpidem SL 3.5 mg resulted in a significant improvement in LPS after MOTN compared to treatment with placebo (9.69 vs 28.12 minutes; P<0.001 vs placebo, P<0.001 vs zolpidem SL 1.75 mg). Secondary: Treatment with zolpidem SL 1.75 mg resulted in a significant improvement in LPS after MOTN compared to treatment with placebo (16.89 vs 28.12 minutes; P<0.001). Treatment with zolpidem SL 1.75 mg resulted in improvements in the following parameters: TST after MOTN (197.80 vs 183.12 minutes; P<0.001), subjective SOL after MOTN (28.58 vs 40.43 minutes; P<0.001), and subjective TST after MOTN (162.36 vs 148.61 minutes; P<0.011). Treatment with zolpidem SL 3.5 mg resulted in improvements in the following parameters: TST after MOTN (208.99 vs 183.12 minutes; P<0.001 vs placebo, P=0.005 vs zolpidem SL 1.75 mg), subjective SOL after MOTN (25.23 vs 40.43 minutes; P<0.001), and subjective TST after MOTN (172.51 vs 148.61 minutes; P<0.011). The endpoints of WASO after MOTN and NAW after MOTN failed to reach significance for either dose of zolpidem SL compared to placebo. Treatment with zolpidem SL 3.5 mg resulted in the greater improvement in sleep quality compared to treatment with placebo (P<0.001) and compared to treatment with zolpidem SL 1.75 mg (P=0.018). Sleep quality ratings in the group receiving zolpidem SL 1.75 mg were not significantly different than the group receiving placebo. No serious adverse events occurred and no subject discontinued the study due to an adverse event. Out of the 82 included subjects, 14 reported an adverse event. All adverse events were mild in severity and transient.
Staner et al.[78] (2010) Zolpidem 10 mg	DB, MC, RCT, XO Patients 18 to 65 years of age with	N=70 SD	Primary: LPS, SOL, time spent in sleep stage 1	Primary: Zolpidem SL shortened the LPS by about 34% or 10.3 minutes (P=0.001), SOL with about 8.6 minutes (P<0.01) and time spent in sleep stage 1with about 7.4 minutes (P<0.01) compared to zolpidem.

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SL tablet vs zolpidem 10 mg tablet	primary insomnia		Secondary: TST, WASO, SE index, total time spent awake, time spent in stage 2, time spent in slow wave sleep; time spent in REM sleep; REM SL, LSEQ, DSST, CFF Test	Secondary: There were no significant differences on in TST and WASO among the treatment groups. The TST was 432 minutes for zolpidem SL and 425 minutes for zolpidem. WASO was 31 and 30 minutes for zolpidem SL and zolpidem, respectively. There was a significant difference in SE index (P<0.05) and total time spent awake (P<0.05), favoring zolpidem SL. No differences were found between the treatments for the sleep architecture parameters time spent in sleep stage 1, slow wave sleep, REM and REM SL. The difference found for time spent in stage 2 reached statistical significance (P<0.05), favoring zolpidem SL. There were no significant differences in LSEQ scores among the treatment groups. There were no significant differences in the way patients rated their subjective feelings of alertness, contentedness and calmness on the visual analog scale. There were no significant differences in DSST between the two treatments. CFF Test results indicated that, during the descending runs, patients had a lower flicker fusion threshold after zolpidem SL than after zolpidem (P<0.05). There were no between-treatment differences for the ascending runs. Both routes of administration were well tolerated with a similar overall incidence of adverse events. The most common adverse events with zolpidem SL were somnolence and dysgeusia. Nausea, dysgeusia, somnolence and dizziness were the most common adverse events with zolpidem.
Valente et al.[79] (2013) Zolpidem 5 and 10 mg SL vs	DB, DD, OL, RCT Healthy volunteers	N=58 Duration not specified	Primary: PSG and post-sleep questionnaires Secondary: Not reported	Primary: A significant main treatment effect was evident considering the SOL and persistent SL. An earlier sleep onset was induced by SL zolpidem 10 mg (SOL; P<0.004 and persistent SL; P<0.006) and SL zolpidem 5 mg (SOL; P<0.025 and persistent SL; P<0.046) compared to oral zolpidem 10 mg. Subjects that received SL zolpidem 10 mg reported an earlier sleep onset (latency to sleep and latency until persistent sleep) when compared to

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zolpidem 10 mg oral				subjects from other groups (P<0.005). Secondary: Not reported
Staner et al.[80] (2009) Zolpidem 5 mg SL tablet vs zolpidem 10 mg SL tablet vs zolpidem 10 mg tablet	OL, RCT, XO Healthy volunteers in a post-nap model of insomnia	N=21 SD	Primary: LPS, SOL, latency to stage 1, TST, SE, awakening after sleep onset, REM SL, stage 4 duration Secondary: Not reported	Primary: For zolpidem 10 mg SL tablets, LPS was significantly decreased by 6.11 minutes as compared to zolpidem 10 mg tablets (P<0.05). Zolpidem 10 mg SL tablets decreased SOL by 5.81 minutes as compared to zolpidem 10 mg tablets (P<0.05). Zolpidem 10 mg SL tablets decreased latency to stage 1 by 6.17 minutes as compared to zolpidem 10 mg tablets (P<0.05). Similar differences were demonstrated for sleep initiation parameters between zolpidem 5 and 10 mg SL tablets (7.28 minute difference for LPS, 6.69 minute difference for SOL and 6.06 minute difference for latency to stage 1; all P<0.05). There were no significant differences in the three sleep initiation parameters between zolpidem 5 and 10 mg SL tablets. There were no significant differences between the three treatments for sleep maintenance parameters, including TST, SE or awakening after sleep onset. There were no differences in sleep maintenance between zolpidem 5 and 10 mg SL tablets. Significant treatment effects were evidenced for REM SL and stage 4 duration. Both REM SL and stage 4 duration were similar with zolpidem 5 and 10 mg SL tablets. Both parameters were significantly shorter in patients receiving zolpidem 5 mg SL tablets compared to zolpidem 10 mg tablets (REM SL, -19.22 minutes; P<0.01, stage 4 duration, -11.89 minutes; P<0.01). There were no differences in sleep architecture between zolpidem 5 and 10 mg SL tablets. No differences were detected in subjective sleep parameters as indicated by a lack of significant treatment effect on any of the LSEQ variables. Next-day residual effects were comparable between treatments. Vigilance,

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				psychomotor performances, attention and concentration were comparable between treatments. The most frequent adverse events were somnolence, headache and fatigue. All were of moderate or mild intensity and resolved spontaneously. Secondary: Not reported
Elie et al.[81] (1999) Zaleplon 5 to 20 mg or zolpidem 10 mg vs placebo	DB, MC, PC, RCT Adults with primary insomnia or insomnia associated with mild nonpsychotic psychiatric disorders	N=615 4 weeks	Primary: Patient's assessment of SL Secondary: Patient's assessment of sleep duration, sleep quality, NAW, rebound insomnia, withdrawal effects, safety	Primary: Median SL was significantly lower with zaleplon 10 and 20 mg than with placebo during all four weeks of treatment, and with zaleplon 5 mg and zolpidem 10 mg for the first three weeks. Secondary: Zaleplon 20 mg significantly (P<0.05) increased sleep duration compared to placebo in all but week three of the study, while zolpidem 10 mg significantly (P<0.05) increased sleep duration at all time points. Mean scores for sleep quality were significantly (P<0.05) better than with placebo during week one with zaleplon 10 mg and 20 mg, and for all weeks with zolpidem 10 mg. No significant differences were observed in NAW between the placebo and active treatment groups. The number of patients treated with zaleplon showing rebound insomnia was not significantly different from placebo on the first night after discontinuation of four weeks of treatment. Significant differences in SL (P<0.05) and NAW (P<0.01) were noted in patients treated with zolpidem 10 mg. On the second night after discontinuation of treatment, there were significantly more patients (P<0.05) showing rebound insomnia for the NAW with zaleplon 10 and 20 mg than with placebo, and on the third night there were significantly fewer patients (P<0.05) showing rebound for the NAW with zaleplon 20 mg.

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				There was no evidence of withdrawal symptoms after discontinuation of four weeks of zaleplon treatment. Significantly more patients who had received zolpidem than placebo reported withdrawal effects on the first night after treatment was discontinued; however, there was no statistically significant difference on the second or third night between the two groups. The frequency of adverse events in the active treatment groups did not differ significantly from that in the placebo group. The study did not report any direct comparisons between the zaleplon.
Huedo et al.[82] (2012) Eszopiclone, zaleplon, or zolpidem vs placebo	MA DB, PG, PC, RCTs of eszopiclone, zaleplon, or zolpidem	N=4,378 Duration varied	Primary: Polysomnographic and subjective SL Secondary: Waking after sleep onset, NAW, TST, SE, and subjective sleep quality	Primary: Significant improvements (reductions) in primary outcomes were documented: polysomnographic SL (weighted standardized mean difference; 95% CI, -0.57 to -0.16) and subjective SL (-0.33, -0.62 to -0.04) compared to placebo. Analyses of weighted mean raw differences showed that the active agents decreased polysomnographic SL by 22 minutes (-33 to -11 minutes) compared to placebo. Secondary: No significant results were identified in the secondary outcomes.
Uchimura et al.[83] (2012) Eszopiclone 1, 2, and 3 mg vs zolpidem 10 mg vs placebo	DB, PC, RCT, XO Japanese patients with primary insomnia	N=72 10 nights	Primary: Sleep measures from PSG and subjective patient reports Secondary: Not reported	Primary: All active treatments produced significant improvement in objective and subjective SL compared to placebo (P<0.05 for all comparisons); linear dose-response relationships were observed for eszopiclone. PSG-determined WASO, SE, and NAW, and patient-reported measures of WASO, NAW, sleep quality, sleep depth, and daytime functioning significantly improved following treatment with eszopiclone 2 mg and 3 mg and zolpidem 10 mg vs placebo (P<0.05). Eszopiclone at all doses increased TST and stage 2 sleep time (P<0.001 for both comparisons), but did not alter REM or slow-wave sleep. Eszopiclone was generally well tolerated; the most frequently reported adverse event was mild dysgeusia. Secondary: Not reported

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Erman et al.[84] (2008) Eszopiclone 1 mg for 2 nights vs eszopiclone 2 mg for 2 nights vs eszopiclone 2.5 mg for 2 nights vs eszopiclone 3 mg for 2 nights vs zolpidem 10 mg for 2 nights vs placebo for 2 nights There was a 3 to 7 day washout between XO treatments	MC, RCT, XO Patients 21 to 64 years of age with primary insomnia; with a 3 to 7 day washout between XO treatments	N=65 2 nights for each treatment	Primary: LPS Secondary: SE, WASO, WTDS, NAW, and patient-reported variables	Primary: All active treatments reduced median LPS by 42 to 55% compared to placebo (P<0.05). The median LPS was 13.1 minutes for eszopiclone 3 mg and zolpidem 10 mg. The median LPS was 29.0, 16.8, 15.5, and 13.8 minutes for the placebo, eszopiclone 1, 2, and 2.5 mg dose groups, respectively. The two highest doses of eszopiclone (2.5 and 3 mg) and zolpidem demonstrated significantly lower LPS when compared to eszopiclone 1 mg (P<0.05). Secondary: Significant differences were found between all active treatments in SE compared to placebo (P<0.05). Eszopiclone 2, 2.5, and 3 mg, and zolpidem 10 mg demonstrated significantly higher SE when compared to eszopiclone 1 mg (P<0.05). Treatment with eszopiclone 3 mg resulted in significant differences compared to treatment with placebo for WASO, WTDS, and NAW. Eszopiclone 2.5 mg demonstrated significant differences compared to placebo for WASO and WTDS. Neither of the lower doses of eszopiclone nor zolpidem 10 mg was different from placebo for WASO or WTDS. Comparisons of eszopiclone 3 mg and zolpidem 10 mg were not significantly different for WASO (P=0.12), for WTDS (P=0.07), or for NAW (P=0.10). Treatment with eszopiclone 2 and 3 mg and zolpidem 10 mg showed improvements in patient-reported measures of sleep relative to placebo. Both doses of eszopiclone and zolpidem 10 mg significantly improved sSL, sTST, quality of sleep, and depth of sleep relative to placebo (P<0.05). Eszopiclone 2 and 3 mg and zolpidem 10 mg were significantly different from placebo for subject reported NAW and sWASO (P<0.05). Morning sleepiness was significantly less with eszopiclone 3 mg compared to placebo (P<0.05). Evening ratings of daytime alertness were significantly increased with eszopiclone 2 mg and with zolpidem 10 mg compared to placebo (P<0.05), and daytime ability to function was significantly improved for eszopiclone 2 and 3 mg and zolpidem 10 mg compared to placebo (P<0.05).

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				The most common adverse events were headache, unpleasant taste, somnolence, dizziness, and nausea. The overall rate of central nervous system adverse events was 7.9% for placebo, 6.2 to 12.5% for the eszopiclone groups, and 23.4% for zolpidem 10 mg.
Zammit et al.[85] (2009) Ramelteon 8 mg vs zolpidem 10 mg vs placebo Subjects were administered the study drug 30 minutes prior to bedtime and were awakened 2 hours after dosing to evaluate balance.	DB, MC, PC, XO Adults over the age of 65 with self-reported chronic insomnia	N=33 Each study drug was taken for one night each with a 4 to 10 day washout period between treatments.	Primary: SOT composite score Secondary: Equilibrium scores on the SOT, SOT ratios, SQTT scores, and memory tests, safety	Primary: There were no differences between placebo and ramelteon on the SOT (P=0.837). Secondary: There were no significant differences between placebo and ramelteon on turn time (P=0.776) or turn sway (P=0.982). Treatment with zolpidem, the positive control, did result in significant impairments on the SOT, turn time, and turn sway (P<0.001 for all). Immediate and delayed memory recall were not significantly different with ramelteon (P=0.683 and P=0.650, respectively); however, immediate recall declined significantly with zolpidem (P=0.002). Adverse events were infrequent and none were serious. The same proportion of subjects in the ramelteon and placebo groups reported adverse events (21.2%) compared to 39.4% of subjects in the zolpidem group. Adverse events that occurred in at least two subjects in any group include dizziness, headache, nausea, and somnolence.
Huang et al.[86] (2011) Zaleplon 10 mg vs zolpidem 10 mg	AC, DB, RCT Patients 20 to 65 years of age with primary insomnia	N=48 2 weeks	Primary: Change in subjective SL from baseline to week two Secondary: Sleep duration, NAW, sleep quality and incidence of	Primary: There was a significant reduction in subjective SL in the zaleplon group (reduced from 63.0 minutes to 31.6 minutes; P<0.05) and zolpidem group (reduced from 61.9 minutes to 30.0 minutes; P<0.05). There was no significant difference between the zaleplon group and zolpidem group in SL (P=0.084). Secondary: There was no significant difference in sleep duration, NAW, or sleep quality among the groups. None of the patients experienced rebound insomnia.

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			rebound insomnia	The most frequently reported adverse effects were headache, dizziness, anxiety and urinary tract infection. There was no significant difference in the frequency of each adverse effect between the zaleplon and zolpidem groups.
Dunbar et al.[87] (2004) Zaleplon 5 to 20 mg vs zolpidem 5 to 10 mg	MA Patients 16 to 85 years of age with insomnia	N=1,539 (6 trials) 2 nights to 4 weeks	Primary: SOL, TST, quality of sleep, adverse events, rebound insomnia Secondary: Not reported	Primary: Of the two studies that directly compared SOL, one study reported a significantly shorter SL with zaleplon (P<0.001), whereas the other study reported results in favor of zolpidem (P=0.03). Of the two studies that directly compared TST, one study reported that sleep duration was significantly less in the zaleplon group (290.7 vs 308.6 minutes for zolpidem; P=0.05) but another study found no difference (eight hours for zaleplon vs 8.3 hours on zolpidem). Patients on zaleplon were less likely to experience an improvement in sleep quality than those on zolpidem (OR, 0.66; 95% CI, 0.51 to 0.87). There was no statistically significant difference in the frequency of treatment-emergent adverse events (OR, 0.86; 95% CI, 0.62 to 1.20). One study reported that patients taking zaleplon were less likely to suffer withdrawal symptoms on the first night of the placebo run-out phase than those on zolpidem (1.5 and 7.1% respectively; P=0.01). Combined results from two trials noted that patients receiving zaleplon were less likely to experience rebound insomnia compared to those on zolpidem (SL OR, 0.27; 95% CI, 0.17 to 0.44, sleep duration OR, 0.25; 95% CI, 0.15 to 0.41, and NAW OR, 0.34; 95% CI, 0.18 to 0.61). In a XO study, 62.3% of patients favored zolpidem compared to 37.7% of patients who favored zaleplon (P=0.08). Secondary: Not reported
Zammit et al.[88] (2006)	DB, PC, RCT, XO	N=37	Primary: LPS and TST,	Primary: LPS after the administration of zaleplon 10 mg, zolpidem 10 mg, and

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Zaleplon 10 mg for 2 nights vs zolpidem 10 mg for 2 nights vs placebo for 2 nights Each treatment period was separated by a 5- or 12-day washout period.	Patients 18 to 65 years of age with primary sleep-maintenance insomnia	2 nights	daytime SL Secondary: Not reported	placebo was 14.9, 11.7, and 42.2 minutes, respectively (overall P<0.001), which made the LPS with active agents shorter by approximately 27 and 31 minutes (P<0.001 for both comparisons). TST was significantly longer with zaleplon 10 mg and zolpidem 10 mg than placebo by approximately 22 and 30 minutes, respectively (overall P<0.001). Daytime SL was not significantly different between the zaleplon 10 mg and placebo groups (P>0.136); however, it was shorter with zolpidem 10 mg compared to placebo (overall P<0.001) when tested at four (P<0.001), five (P<0.001), and seven (P<0.05) hours, respectively, after dose administration. There was no significant difference between the zaleplon 10 mg and placebo in patients' subjective level of alertness or ability to concentrate. Patients reported significantly less alertness after the SLT performed at four hours after dosing with zolpidem 10 mg compared to placebo (overall P=0.005). Daytime subjective reports of ability to concentrate following zolpidem 10 mg were significantly worse than following placebo when tested after the SLT at four, five, and six hours after treatment (overall P<0.05). Secondary: Not reported
Danjou et al.[89] (1999) Zaleplon 10 mg vs zolpidem 10 mg vs	DB, XO Healthy volunteers, mean age 29.5 years	N=36 13 days	Primary: Subjective and objective measurements of residual effects when study drug was given five, four, three, or two hours before morning awakening, tests	Primary: No residual effects were demonstrated after zaleplon 10 mg, when administered as little as two hours before waking, on either subjective or objective assessments. Zolpidem 10 mg showed significant residual effects on DSST and memory after administration up to five hours before waking and CRT, CFF threshold and Sternberg Memory Scanning Task after administration up to four hours before waking. Residual effects of zolpidem were apparent in all objective and subjective measurements when the drug was administered later in the night.

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placebo			included DSST, CFF threshold, CRT, Memory Test, Sternberg Memory Scanning Task, LARS, LSEQ, adverse events Secondary: Not reported	There were no serious adverse experiences during the study; all adverse events were mild-to-moderate. Overall, the number of subjects who reported any adverse experience after administration of study drug was similar for zaleplon and placebo (11 and 33% regardless of the time of drug administration) but was significantly higher following zolpidem (56 to 72%) when zolpidem was administered two, three, four, and five hours before awakening (P values not reported). Secondary: Not reported
Verster et al.[90] (2002) Zaleplon 10 mg vs zaleplon 20 mg vs zolpidem 10 mg vs zolpidem 20 mg vs placebo This was a 2-part study with the first part evaluating the effect of ethanol and the second part	DB, XO Healthy volunteers with mean age 24.0 years	N=30 SD with at least a 5-day washout period	Primary: Driving ability (standard deviation of the lateral position, standard deviation of speed, memory, psychomotor performance) (subjects given study medication five hours after going to bed and awakened three hours after dose, driving test performed four hours after awakened, memory and psychomotor tests performed six hours after awakened) Secondary: Not reported	Primary: Zaleplon 10 and 20 mg did not significantly impair driving ability four hours after middle-of-the-night administration (significant difference defined as P<0.0125). Relative to placebo, after zolpidem 10 mg, standard deviation of the lateral position (amount of weaving of the car) was significantly elevated but the magnitude of the difference was small and not likely to be of clinical importance (difference, 2.87 cm; P<0.005). Standard deviation of speed (speed variability) was not significantly different for zolpidem 10 mg than placebo (P=0.256). Zolpidem 20 mg significantly increased SDLP and speed variability (both P<0.001). Memory and psychomotor test performances were unaffected after both doses of zaleplon and zolpidem 10 mg. Zolpidem 20 mg significantly impaired performance on psychomotor and memory tests. (Note: the recommended dose for zolpidem is 10 mg immediately before bedtime.) Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
evaluating the effects of zaleplon and zolpidem. Only the second part of the study was reported in this review.				
Piccione et al.[91] (1980) Triazolam 0.25 mg vs triazolam 0.50 mg vs chloral hydrate 250 mg vs chloral hydrate 500 mg vs placebo	DB, XO Elderly patients >60 years of age with insomnia	N=27 5 days	Primary: Efficacy (questionnaire with subjective estimates of SL, TST, NAW, overall quality of sleep), side effects Secondary: Not reported	Primary: The patients' global evaluation of effectiveness indicated that triazolam 0.25 and 0.50 mg improved sleep more than placebo (both P<0.05), while chloral hydrate 250 and 500 mg were not better than placebo. Triazolam 0.50 mg, but not 0.25 mg, was significantly better than chloral hydrate 250 mg (P<0.01) and 500 mg (P<0.05) in the global evaluation of effectiveness. There was no significant difference in SL, TST and NAW between placebo and either dose of chloral hydrate. Triazolam 0.25 mg significantly decreased SL and increased TST compared to placebo (both P<0.05). Triazolam 0.50 mg significantly decreased the NAW compared to placebo (P<0.01). Patients estimated their TST to be longer following the use of triazolam 0.25 mg as compared to chloral hydrate 250 or 500 mg (both P<0.05). There were no significant differences in reported side effects between the active treatments and placebo. Secondary: Not reported
Johnson et al.[92] (2006) Triazolam 0.25, 0.5 or 0.75 mg	DB, XO Adults with a history of sedative abuse	N=14 18 days	Primary: Subject-rated measures (drug liking, street value, pharmacological classification),	Primary: Triazolam showed dose-related effects on subject-rated, observer-rated, and motor and cognitive performance measures. Compared to placebo, all doses of ramelteon showed no significant effect on any of the subjective effect measures, including those related to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs ramelteon 16, 80 or 160 mg vs placebo			observer-rated measures (sedation, impairment), motor and cognitive performance (balance task, DSST, word recall) Secondary: Not reported	potential for abuse (all P>0.05). In the pharmacological classification, 79% of patients identified the highest dose of ramelteon as placebo. Compared to placebo, ramelteon had no effect at any dose on any observer-rated or motor and cognitive performance measure (all P>0.05). Secondary: Not reported
Hindmarch et al.[93] (2006) Flurazepam 30 mg vs zolpidem modified release 6.25 mg vs zolpidem modified release 12.5 mg vs placebo	DB, RCT, XO Healthy volunteers ≥65 years of age	N=24 SD treatment	Primary: Psychometric tests performed 8 hours after study medication (CFF, CRT, word recall, CTT, DSST), subjective evaluation of sleep (LSEQ), safety, pharmacokinetics (zolpidem modified release only) Secondary: Not reported	Primary: There were no significant differences in psychometric tests between the zolpidem modified release treatment groups and placebo (P>0.05). Psychometric performance was significantly impaired with flurazepam compared to placebo for all tests with the exception of the DSST (P=0.0526). Ease of falling asleep and sleep quality were significantly improved with both doses of zolpidem modified release and with flurazepam (all P<0.05). Neither zolpidem modified release, nor flurazepam, modified perception of well-being on awakening. The frequency of adverse events was similar in all four treatment conditions. None of the adverse events was serious or led to withdrawal from the study. The plasma concentration ratio was 1.96 between the two doses of zolpidem modified release, which is consistent with dose linearity. Secondary: Not reported
Holbrook et al.[94] (2000) Benzodiazepines	MA Patients with insomnia	N=2,672 (45 trials) 1 day to	Primary: SL, total sleep duration, adverse effects, dropout	Primary: Using sleep records, benzodiazepines demonstrated a decrease in SL by 4.2 minutes compared to placebo (95% CI, -0.7 to 9.2).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs zopiclone, diphenhydramine, glutethimide, promethazine, cognitive behavioral therapy, placebo		6 weeks	rates, cognitive function decline Secondary: Not reported	Benzodiazepines demonstrated a significant increase in sleep duration compared to placebo by 61.8 minutes (95% CI, 37.4 to 86.2). Benzodiazepines were more likely to be associated with complaints of daytime drowsiness (OR, 2.4; 95% CI, 1.8 to 3.4) and dizziness/ lightheadedness (OR, 2.6; 95% CI, 0.7 to 10.3) compared to placebo. No difference was observed in dropout rates between the two groups. Pooled results from three trials indicated there was no significant difference between benzodiazepines and zopiclone in SL, but benzodiazepine therapy may lead to a longer sleep by 23.1 minutes (95% CI, 5.6 to 40.6). There was no significant difference in adverse events among the treatment groups (OR, 1.5; 95% CI, 0.8 to 2.9). Comparisons between benzodiazepines and antihistamines did not detect any significant differences on sleep outcomes. Triazolam was found to be more effective in reducing SL early in one trial, but efficacy decreased by the second week of treatment. Behavioral therapy efficacy was maintained throughout the nine-week follow-up. Secondary: Not reported
Buscemi et al.[95] (2007) Benzodiazepines, non-benzodiazepines, antidepressants vs placebo	MA Adults with chronic insomnia	105 trials 1 night to 6 months	Primary: SL, WASO, SE, sleep quality, TST, adverse events Secondary: Not reported	Primary: SL assessed by PSG was significantly decreased for benzodiazepines (WMD, -10.0 minutes; 95% CI, -16.6 to -3.4), non-benzodiazepines (WMD, -12.8 minutes; 95% CI, -16.9 to -8.8) and antidepressants (WMD, -7.0 minutes; 95% CI, -10.7 to -3.3). SL assessed by sleep diaries was also significantly improved for benzodiazepines (WMD, -19.6 minutes; 95% CI, -23.9 to -15.3), non-benzodiazepines (WMD, -17.0 minutes; 95% CI, -20.0 to -14.0) and antidepressants (WMD, -12.2 minutes; 95% CI, -22.3 to -2.2). MA for WASO, SE, sleep quality and TST measured by PSG and sleep

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				diary were statistically significant and favored benzodiazepines and non-benzodiazepines vs placebo with the exception of PSG studies measuring WASO and TST, which were marginally nonsignificant. In contrast, PSG results significantly favored antidepressants vs placebo, but sleep diary results were fewer and non-significantly favored antidepressants for WASO and non-significantly favored placebo for TST. Indirect comparisons between benzodiazepines and non-benzodiazepines resulted in no significant difference in SL; however, benzodiazepines were associated with more adverse events. Indirect comparisons between benzodiazepines and antidepressants resulted in no significant difference in SL or adverse events. Indirect comparisons between non-benzodiazepines and antidepressants resulted in a significantly greater SL assessed by PSG but not by sleep diary for non-benzodiazepines. There was no significant difference in adverse events. All drug groups had a statistically significant higher risk of harm compared to placebo, although the most commonly reported adverse events were minor. The adverse events most commonly reported in these studies were headache, drowsiness, dizziness and nausea. Secondary: Not reported
Smith et al.[96] (2002) Benzodiazepines or benzodiazepine receptor agonists vs behavioral treatment	MA Patients with primary insomnia for ≥1 month	N=470 (21 trials) 1 to 10 weeks	Primary: SL, TST, NAW, WASO, and sleep quality before and after treatment Secondary: Not reported	Primary: SL was reduced by 30% with pharmacological treatment compared to 43% with behavioral interventions. Pharmacotherapy increased TST by 12% compared to 6% with behavior therapy. Both pharmacotherapy and behavior therapy reduced NAW per night by one. WASO was reduced by 46% with pharmacotherapy and by 56% with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				behavior therapy. Pharmacotherapy improved sleep quality by 20% compared to 28% with behavior therapy. Overall, there were no differences in TST, NAW, WASO, and sleep quality between benzodiazepine receptor agonists and behavioral therapy. The behavioral therapy group had a greater reduction in LSO than the group that took the benzodiazepine receptor agonists (95% CI, 0.17 to 1.04). Secondary: Not reported
Nowell et al.[97] (1997) Benzodiazepines or benzodiazepine receptor agonists vs placebo	MA Adults <65 years of age with chronic insomnia	N=1,894 (22 trials) 4 to 35 days	Primary: SL, TST, NAW, sleep quality Secondary: Not reported	Primary: Zolpidem and benzodiazepines were significantly more effective than placebo with regards to SL, TST, NAW and sleep quality (P<0.001). Secondary: Not reported
Post Operative Nausea and Vomiting				
Schaub et al.[98] (2012) Droperidol vs placebo (or no treatment)	MA RCTs testing prophylactic droperidol in adults undergoing general anaesthesia and reporting on post operative nausea and vomiting	N=25 trails Duration varied	Primary: Prevention of nausea and vomiting; adverse events Secondary: Not reported	Primary: For the prevention of early nausea (within six hours postoperatively), the RR was 0.45 (95% CI, 0.35 to 0.58) and the number needed to treat was 7, 4, and 2 for low, medium and high baseline risk. For the prevention of early vomiting the RR was 0.65 (95% CI, 0.57 to 0.74), and the number needed to treat was 11, 6, and 4 respectively. For the prevention of late nausea (within 24 hours) the RR was 0.74 (95% CI, 0.62 to 0.87) and the number needed to treat was 15, 8, and 5 respectively. For the prevention of late vomiting the RR was 0.61 (95% CI, 0.47 to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				0.80) and the number needed to treat was 10, 5, and 3 respectively. Droperidol decreased the risk of headache but increased the risk of restlessness. There were no differences in the incidences of sedation or dizziness. Two patients receiving droperidol 0.625 mg had extrapyramidal symptoms. Cardiac toxicity data were not reported. Secondary: Not reported
Non-24-hour sleep-wake disorder				
Lockley et al.[99] (2015) SET and RESET Tasimelteon 20 mg one hour prior to bedtime vs placebo	DB, MC, PC, RCT Totally blind patients 18 to 75 years of age with non-24 hour sleep-wake disorder	*SET:* N=84 6 months *RESET:* N=20 20 weeks	*SET:* Primary: Proportion of entrained patients (patients having an internal circadian period of ≤24.1 hours and CI including 24.0 hours); proportion of patients who had a clinical response (entrainment at month one or month seven plus clinical improvement, measured by the Non-24 Clinical Response Scale) Secondary: Not reported *RESET:* Primary:	*SET:* Primary: Circadian entrainment occurred in eight (20%) of 40 patients in the tasimelteon group compared with one (3%) of 38 patients in the placebo group at month one (difference 17%; 95% CI, 3.2 to 31.6; P=0.0171). Nine (24%) of 38 patients showed a clinical response, compared with none of 34 in the placebo group (difference 24%; 95% CI, 8.4 to 39.0; P=0.0028). Secondary: Not reported *RESET:* Primary: Nine (90%) of ten patients in the tasimelteon group maintained entrainment, whereas only two (20%) of ten patients withdrawn to placebo maintained entrainment (difference 70%; 95% CI, 26.4 to 100.0; P=0.0026). Secondary: No deaths were reported in either study, and discontinuation rates due to adverse events were comparable between the tasimelteon (3 [6%] of 52 patients) and placebo (2 [4%] of 52 patients) treatment courses.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Proportion of non-entrained patients Secondary: Safety	
Sedation				
Fraser et al.[100] (2013) Dexmedetomidine or propofol vs benzodiazepine	MA RCTs consisting of critically ill, mechanically ventilated adults requiring sedation regimen	N=1,235 Duration varied	Primary: Duration of intensive care unit length of stay, duration of mechanical ventilation, delirium prevalence, and/or short-term mortality Secondary: Not reported	Primary: Compared to a benzodiazepine sedative strategy, a nonbenzodiazepine sedative strategy was associated with a shorter intensive care unit length of stay (difference, 1.62 days; 95% CI, 0.68 to 2.55; P=0.0007) and duration of mechanical ventilation (difference, 1.9 days; 95% CI, 1.70 to 2.09; P<0.00001) but a similar prevalence of delirium (risk ratio, 0.83; 95% CI, 0.61 to 1.11; P=0.19) and short-term mortality rate (risk ratio, 0.98; 95% CI, 0.76 to 1.27; P=0.88). Secondary: Not reported

Drug regimen abbreviations: ER=extended release, SL=sublingual
Study abbreviations: AC=active control, CI=confidence interval, DB=double-blind, DD=double dummy, ITT=intent to treat, LS=least square, LSM=least squares mean, MA=meta-analysis, MC=multicenter, NS=not significant, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RR=relative risk, SB=single-blind, SD=single dose, XO=crossover, WMD=weighted mean difference
Miscellaneous abbreviations: AHI=apnea hypopnea index, BAI=Beck Anxiety Inventory, CAPS=Clinician Administered PTSD Scale, CES-D=Center for Epidemiologic Studies Depression Scale, CFF=Critical Flicker Fusion, CGI=Clinical Global Impression, CGI-I=Clinical Global Impression-Improvement, CGI-S=Clinical Global Impressions-Severity, CPAP=Continuous positive airway pressure, CRT=Choice Reaction Time, CTT=Continuous Tracking Test, DLRF=Daily Living and Role Functioning, DSST=Digit-Symbol Substitution Test, ECG=electrocardiogram, ESS=Epworth Sleepiness Scale, FARD=Ferreri Anxiety Rating Diagram, FOSQ=Functional Outcomes of Sleepiness Questionnaire, FSS=Fatigue Severity Scale, HAD=Hospital Anxiety and Depression, HAMA=Hamilton Rating Scale for Anxiety, HAM-D=Hamilton Rating Scale for Depression, $HDRS_{17}$=Hamilton Depression Rating Scale 17-item, ISI=Insomnia Severity Index, LPS=latency to persistent sleep, LSAS=Liebowitz Social Anxiety Scale, LSEQ=Leeds Sleep Evaluation Questionnaire, LSO=latency to sleep onset, MADRS=Montgomery-Åsberg Depression Rating Scale, MAOI=monoamine oxidase inhibitors, MCBI=Multidimensional Caregiver Burden Inventory, MENQOL=Menopause-Related Quality of Life, MGH-CFPQ=Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire, MOTN=middle-of-the-night awakening, NAW=number of awakenings, PDQ-8=Parkinson Disease Questionnaire Short Form, PGI=Patient Global Impression, PGI-IT= Patient Global Impression of Insomnia Treatment, PMQ=Patient Morning Questionnaire, PSG=polysomnography, PSQI=Pittsburg Sleep Quality Index, PSQ-IVRS=Post-Sleep Questionnaire Interactive Voice Response System, PTSD=posttraumatic stress disorder, Q-LES-Q=Quality of Life Enjoyment and Satisfaction Questionnaire, REM=rapid eye movement, RIMA=reversible inhibitors of monoamine oxidase-A, SDS=Sheehan Disability Scale, SE=sleep efficiency, SF-36=Short Form-36, SII=Sleep Impairment Index, SIS=Sleep Impact Scale, SL=sleep latency, SOL=sleep onset latency, SOT=Sensory Organization Test, SPRINT=Short PTSD Rating Interview, SQTT=Step Quick Turn Test, SSRI=selective serotonin-reuptake inhibitor, sTSO=subjective time to sleep onset, sTST=subject reported total sleep time, sWASO=subjective wake time after sleep onset, TST=total sleep time, WASO=wake time after sleep onset, WLQ=Work Life Questionnaire, WTDS=wake time during sleep

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 12. Relative Cost of the Miscellaneous Anxiolytics, Sedatives, and Hypnotics

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Buspirone	tablet	N/A	N/A	$
Dexmedetomidine	injection	Precedex®*	$$$-$$$$$	N/A
Droperidol	injection	N/A	N/A	$
Eszopiclone	tablet	Lunesta®*	$$$$$	$
Hydroxyzine	capsule, solution, tablet	Vistaril®*	$$$-$$$$	$
Meprobamate	tablet	N/A	N/A	$$$$
Ramelteon	tablet	Rozerem®	$$$$$	N/A
Suvorexant	tablet	Belsomra®	$$$$$	N/A
Tasimelteon	capsule	Hetlioz®	$$$$$	N/A
Zaleplon	capsule	Sonata®*	$$$	$
Zolpidem	extended-release tablet, sublingual tablet, tablet	Ambien®*, Ambien CR®*, Edluar®, Intermezzo®	$$$$$	$

*Generic is available in at least one dosage form or strength.
N/A=Not available.

X. Conclusions

The miscellaneous anxiolytics, sedatives, and hypnotics are used primarily for the treatment of anxiety disorders and insomnia. In addition, some agents are approved for the treatment of acute alcohol withdrawal, management of procedural nausea/vomiting, treatment of Non-24-Hour Sleep-Wake Disorder (non-24), as well as treatment of

pruritus. All of the products are available in a generic formulation, with the exception of ramelteon, suvorexant, and tasimelteon.

The agents that are approved for the treatment of anxiety disorders include buspirone, hydroxyzine, and meprobamate.[2-5] The American Psychiatric Association recommends the initial use of either a serotonin-norepinephrine reuptake inhibitor (SNRI) or a selective serotonin reuptake inhibitor (SSRI) for the treatment of panic disorder due to their favorable safety and tolerability profiles.[21] Buspirone and sedating antihistamines are not effective as monotherapy for the treatment of panic disorder.[20-21] For the long-term treatment of generalized anxiety disorder, the National Institute for Health and Clinical Excellence recommends the use of an SSRI as first-line therapy.[20] Sedating antihistamines are one of several options for the short-term, immediate treatment of generalized anxiety disorder.[20] Buspirone is not recommended for the initial treatment of obsessive-compulsive disorder or posttraumatic stress disorder.[22-26] The available guidelines do not provide any recommendations regarding the use of meprobamate for the treatment of anxiety disorders.[20-26]

Chloral hydrate, eszopiclone, ramelteon, suvorexant, zaleplon, and zolpidem are approved for the treatment of insomnia.[1-15] The American Academy of Sleep Medicine recommends the use of a short/intermediate-acting benzodiazepine, benzodiazepine receptor agonist, or ramelteon for the initial treatment of insomnia.[27] They do not give preference to one agent over another. Chloral hydrate is not recommended for the treatment of insomnia.[27] Symptom pattern, treatment goals, past treatment responses, patient preference, comorbid conditions, contraindications, drug interactions and adverse events should be considered when selecting a specific agent.[27] The frequency and severity of adverse events may be lower with benzodiazepine receptor agonists (e.g., eszopiclone, zaleplon, and zolpidem) and ramelteon than benzodiazepines due to their shorter half-lives.[27-28] Hypnotic treatments should be combined with behavioral and cognitive therapies.[27] Patients should be followed every few weeks during the initial treatment period to assess for effectiveness, adverse events and the need for ongoing medication. Chronic use of hypnotic medications may be necessary in those individuals with severe/refractory insomnia or for those with chronic comorbid illnesses.[27] Results from clinical trials demonstrate that these agents are effective for the treatment of insomnia. Relatively few studies were found in the medical literature directly comparing the efficacy and safety of these agents. Suvorexant (Belsomra®) is a novel agent for the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance. Suvorexant is a selective antagonist of orexin receptors (OX1R and OX2R). Orexin A and orexin B are neuropeptides that promote wakefulness. Blocking the binding of orexin to the orexin receptors is thought to suppress wakefulness.[13] The use of suvorexant is not yet incorporated into the treatment guidelines.

Tasimelteon is the first FDA-approved treatment for non-24, a chronic circadian rhythm disorder which occurs almost exclusively in persons who are completely blind.[15,16] Tasimelteon was reviewed under priority review and received orphan-product designation because it is intended to treat a rare disease.[16] There are currently no guidelines incorporating the use of tasimelteon.

There is insufficient evidence to support that one brand miscellaneous anxiolytic, sedative, or hypnotic agent is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand miscellaneous anxiolytic, sedative, or hypnotic agents within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand miscellaneous anxiolytic, sedative, or hypnotic is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Genitourinary Smooth Muscle Relaxants
AHFS Class 861200 (including 861204 – Antimuscarinics and 861208 – Selective Beta-3-Adrenergic Agonists)
May 11, 2016

I. Overview

Urinary incontinence is the involuntary leakage of urine, which may be classified as urgency, stress, overflow, or mixed incontinence.[1] Urgency incontinence is accompanied by a sense of urgency, while stress incontinence generally occurs with effort, exertion, sneezing, or coughing. Overflow incontinence is associated with dribbling and/or continuous leakage due to incomplete bladder emptying.[1] Overactive bladder is a functional disorder characterized by urinary urgency, daytime frequency (>8 voids during the daytime), nocturia (>1 void at night), with or without incontinence.[2,3] Urinary incontinence and overactive bladder may be due to lower urinary tract dysfunction or secondary to non-genitourinary disorders. The most common cause of overactive bladder is overactivity of the bladder's detrusor muscle. Symptoms may be assessed by patient history, the use of validated questionnaires, and/or bladder diaries. Clinical testing (e.g., bladder stress test, postvoid residual volume testing, urine flow rate, and urodynamic testing) may help identify the pathology, but are not always necessary for diagnosis or initiation of therapy.[1,2] Urinary incontinence and overactive bladder cause both physical and psychological morbidity, as well as adversely impact quality of life.[1] Initial treatment options include lifestyle modifications (weight loss and dietary changes) and behavioral therapy (bladder training, physical therapy, and toileting assistance).[2,4] Pharmacologic therapy is typically trialed if initial treatment is ineffective.[2,4] Neurogenic lower urinary tract disorder is caused by a lesion at any level of the nervous system.[5,6] The lesion interferes with the normal nerve pathways associated with urination. Early diagnosis and treatment of neurogenic lower urinary tract disorder is essential for both congenital and acquired disorders as irreversible changes may occur.[6]

Normal voiding is dependent on acetylcholine-induced stimulation of muscarinic receptors on bladder smooth muscle. There are five muscarinic receptor subtypes, of which M1, M2, and M3 mediate bladder contractility. Muscarinic receptors are also found in the gastrointestinal tract, salivary glands, and tear ducts. Antimuscarinic drugs increase bladder capacity, decrease urgency, and are useful for the treatment of urge incontinence.[4,7-18] Darifenacin, fesoterodine, solifenacin, tolterodine, and trospium are muscarinic receptor antagonists. Flavoxate is an antispasmodic which exerts its effects directly on muscle and counteracts the smooth muscle spasm of the urinary tract. Oxybutynin has a direct antispasmodic effect on smooth muscle and inhibits the muscarinic action of acetylcholine on smooth muscle. Some antimuscarinic agents claim to have greater affinity for specific receptor subtypes that mediate bladder contractility, but the clinical significance of this is unclear. The most common adverse effects associated with the use of antimuscarinic agents include dry mouth, blurred vision, abdominal discomfort, drowsiness, nausea, and dizziness. These agents may also cause confusion or cognitive impairment in the elderly.[4]

Mirabegron is the first beta-3 adrenergic receptor agonist to be approved for the treatment of overactive bladder. Mirabegron relaxes the detrusor smooth muscle during the storage phase of the urinary bladder fill-void cycle which increases bladder capacity. Because it acts via the beta-3 adrenergic receptor rather than through muscarinic cholinergic receptors, mirabegron may have a better tolerability profile compared to other urinary antispasmodics.[18]

The genitourinary smooth muscle relaxants that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Flavoxate, oxybutynin, tolterodine, and trospium are available in a generic formulation. This class was last reviewed in May 2014.

Table 1. Genitourinary Smooth Muscle Relaxants Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Darifenacin	extended-release tablet	Enablex®	none
Fesoterodine	extended-release tablet	Toviaz®	none
Flavoxate	tablet	N/A	flavoxate

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Mirabegron	extended-release tablet	Myrbetriq®	none
Oxybutynin	extended-release tablet, syrup, tablet, transdermal gel, transdermal patch	Ditropan XL®*, Gelnique®, Oxytrol®	oxybutynin, Oxytrol®
Solifenacin	tablet	VESIcare®	none
Tolterodine	extended-release capsule, tablet	Detrol®*, Detrol LA®*	tolterodine
Trospium	extended-release capsule, tablet	N/A	trospium

*Generic is available in at least one dosage form or strength.
N/A=Not available, PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the genitourinary smooth muscle relaxants are summarized in Table 2.

Table 2. Treatment Guidelines Using the Genitourinary Smooth Muscle Relaxants

Clinical Guideline	Recommendation(s)

National Institute for Health and Clinical Excellence: **Urinary Incontinence: The Management of Urinary Incontinence in Women (2013)**[19]	Behavioral therapy
	• Bladder training should be offered as first-line treatment to women with urge or mixed urinary incontinence.
	• If women do not achieve satisfactory benefit from bladder training, the combination of an antimuscarinic agent and bladder training should be considered if frequency is a troublesome symptom.
	• In women with urinary incontinence who also have cognitive impairment, prompted and timed voiding toileting programs are recommended as strategies for reducing leakage episodes.
	• Do not offer transcutaneous sacral nerve stimulation, transcutaneous posterior tibial nerve stimulation, or percutaneous posterior tibial nerve stimulation to women with urinary incontinence.
	
	Pharmacologic therapy
	• Prescribe the lowest recommended dose when starting a new overactive bladder drug treatment and if treatment is effective do not change the drug or dose.
	• Immediate-release oxybutynin, immediate-release tolterodine or once-daily darifenacin should be offered to women with overactive bladder or mixed urinary incontinence as first-line drug treatment if bladder training has been ineffective.
	  o Do not offer oxybutynin (immediate release) to frail older women.
	• If initial therapy is not well tolerated, another alternative should be considered.
	  o Transdermal oxybutynin may be considered for patients who cannot tolerate oral medication.
	• Flavoxate, propantheline and imipramine should not be used for the treatment of urinary incontinence or overactive bladder in women.
	• The use of desmopressin may be considered to reduce nocturia in women with urinary incontinence or overactive bladder who find it a troublesome symptom.
	• Duloxetine is not recommended as a first-line treatment for women with predominant stress urinary incontinence. Duloxetine should not routinely be used as a second-line treatment for women with stress urinary incontinence, although it may be offered as second-line therapy if women prefer pharmacological to surgical treatment or are not suitable for surgical treatment.
	• Systemic hormone replacement therapy is not recommended for the treatment of urinary incontinence.
	• Intravaginal estrogens are recommended for the treatment of overactive bladder symptoms in postmenopausal women with vaginal atrophy.

Clinical Guideline	Recommendation(s)
	Complementary therapy Complementary therapies are not recommended for the treatment of urinary incontinence or overactive bladder.
European Association of Urology: **Guidelines on Urinary Incontinence (2015)**[20]	Lifestyle intervention • Weight loss (>5% in women), fluid restriction, reduction of caffeine or alcohol intake, limiting heavy activity, and smoking cessation may improve urinary incontinence. Behavioral therapy • Examples of behavioral therapy include pelvic floor muscle training, bladder training, electrical or magnetic stimulation, and posterior tibial nerve stimulation. • Pelvic floor muscle training is better than no treatment for reducing incontinence episodes and improving quality of life in women with stress or mixed incontinence. There is no evidence that pelvic floor muscle training is better than no treatment in providing a cure. Additionally, there is no consistent evidence to show superiority of drug therapy over behavioral therapy. • Pelvic floor muscle training, lasting at least three months, should be offered as a first-line therapy to women with stress or mixed urinary incontinence. In patients with mixed incontinence, pelvic floor muscle training is less satisfactory than for stress incontinence alone. Biofeedback should be considered as an adjunct in women with stress incontinence. • Pelvic floor exercises should be taught to men undergoing radical prostatectomy to speed recovery or urinary incontinence. • Bladder training is a first-line therapy to adults with urgency or mixed urinary incontinence. Antimuscarinic drugs • Antimuscarinic drugs are currently the mainstay of treatment for urgency urinary incontinence. They act by blocking muscarinic receptors in the bladder wall, which reduces detrusor contractility and alters sensation. There is no consistent evidence that one antimuscarinic drug is more efficacious to an alternative antimuscarinic drug for cure or improvement of urgency urinary incontinence. Dry mouth is the most common adverse effect, but others include constipation, blurred vision, fatigue, and cognitive dysfunction. • Offer immediate release (IR) or extended release (ER) formulations of antimuscarinic drugs for adults with urgency urinary incontinence. • If IR formulations of antimuscarinic drugs are unsuccessful for adults with urgency urinary incontinence, offer ER formulations or longer-acting antimuscarinic agents. • Consider using transdermal oxybutynin if oral antimuscarinic agents cannot be tolerated due to dry mouth. • Offer and encourage early review (of efficacy and side effects) of patients on antimuscarinic medication for urgency urinary incontinence (< 30 days). • In older people being treated for urinary incontinence, every effort should be made to employ nonpharmacological treatments first. Use antimuscarinic drugs with caution in elderly patients who are at risk of, or have, cognitive dysfunction. • Mirabegron is better than placebo for improvement of urgency urinary incontinence symptoms, but there is no evidence that mirabegron is better than placebo for curing incontinence. Mirabegron is no more effective than tolterodine with similar discontinuation rates in clinical trials. • Due to the high rate of medication nonadherence, offer and encourage early review (of efficacy and side effects) of patients on antimuscarinic medication for urgency urinary incontinence (<30 days). If oral antimuscarinic agents cannot be tolerated due to dry mouth, consider using transdermal oxybutynin. • When prescribing antimuscarinic drugs to elderly patients, be aware of the risk of

Clinical Guideline	Recommendation(s)
	cognitive side effects, especially in those receiving cholinesterase inhibitors. Solifenacin, darifenacin, and tolterodine should be used with caution in patients at risk of cognitive dysfunction, whereas oxybutynin immediate-release should be avoided. Consider use of trospium chloride in patients known to have cognitive dysfunction. An objective assessment of mental function should be assessed before and during treatment in patients whose cognitive function may be at risk. Duloxetine • Duloxetine inhibits the presynaptic reuptake of the neurotransmitters serotonin and norepinephrine leading to an increase in levels of these neurotransmitters. This increase ultimately increases the resting tone and contraction strength of the urethral striated sphincter. • Duloxetine has not been shown to cure incontinence and should not be offered to women or men who are seeking a cure for their incontinence. • Duloxetine can be offered to women or men who are seeking temporary improvement in incontinence symptoms. • Duloxetine should be initiated using dose titration because of high adverse effect rates. Estrogen • Offer post-menopausal women with urinary incontinence vaginal estrogen therapy particularly if other symptoms of vulvovaginal atrophy are present. Vaginal estrogen therapy should be long-term and in an appropriate dose. • Do not offer oral (systemic) oestrogen replacement therapy as treatment for urinary incontinence. Desmopressin • Desmopressin is a synthetic analogue of vasopressin that is most commonly used to treat diabetes insipidus and, when used at night, to treat nocturnal enuresis. • The risk of urinary incontinence is reduced within four hours of taking oral desmopressin, but not after four hours. Desmopressin should be offered to patients requiring occasional short-term relief from daytime urinary incontinence. It should not be used for long-term control of urinary incontinence and it is not licensed for this indication. Botulinum toxin • Botulinum toxin A injections into the bladder wall are being increasingly used to treat persistent or refractory urgency urinary incontinence in adult women, as well as in men despite the lack of high-quality data in males. • A single treatment session with botulinum toxin is more effective than placebo at curing and improving urgency urinary incontinence for up to 12 months. There is no evidence that repeated injections have reduced efficacy. • It is recommended to offer botulinum toxin A intravesical injections to patients with urgency urinary incontinence refractory to antimuscarinic therapy. • There is no evidence that repeated injections have reduced efficacy, but there is a high risk of increased post-voiding residual volume, which is dose dependent and may require intermittent self-catheterization. Those who require intermittent self-catheterization have a high risk of a urinary tract infection.
American Urological Association: **Diagnosis and Treatment of Overactive Bladder (Non-Neurogenic) in Adults: American**	Diagnosis • Overactive bladder is a symptom complex that is not generally life threatening. • The clinician should engage in a diagnostic process to document symptoms and signs that characterize overactive bladder and exclude other disorders that could be the cause of the patient's symptoms. • After assessment has been performed to exclude conditions requiring treatment and counseling, no treatment is an acceptable choice.

Clinical Guideline	Recommendation(s)
Urological Association/ Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction Guideline (2012); Amended (2014)[21]	First line treatment • Behavioral therapies (e.g., bladder training, bladder control strategies, pelvic floor muscle training, fluid management) should be offered as first line therapy. • Behavioral therapies can also be combined with pharmacologic management. Second line treatment • Clinicians should offer oral antimuscarinics or oral β3-adrenoceptor agonists as second line therapy. Agents include: o Darifenacin. o Fesoterodine. o Oxybutynin. o Solifenacin. o Tolterodine. o Trospium. o Mirabegron. • No agent in the group is indicated as a preferred. • If extended-release and immediate-release formulations are available the extended-release should be preferred over the immediate-release given formulation due to lower rates of adverse events. Transdermal oxybutynin is also an option. • If a patient experiences inadequate symptom control and/or unacceptable adverse drug events with one agent then a dose modification or a different antimuscarinic medication or β3-adrenoceptor agonist may be tried. • Anti-muscarinics should be avoided in patients with narrow-angle glaucoma unless approved by the treating ophthalmologist and should also be used with extreme caution in patients with impaired gastric emptying or a history of urinary retention. • Manage constipation and dry mouth before abandoning effective anti-muscarinic therapy. Management may include bowel management, fluid management, dose modification or alternative anti-muscarinics. • Use caution in prescribing anti-muscarinics in patients who are using other medications with anti-cholinergic properties. • Use caution in prescribing anti-muscarinics or β3-adrenoceptor agonists in the frail patient. Third line treatment • Clinicians may offer intradetrusor onabotulinumtoxinA as a third-line option in the carefully selected patients who has been refractory to first and second line overactive bladder treatments. • Clinicians can also offer peripheral tibial nerve stimulation as third-line treatment. • Clinicians may offer sacral neuromodulation as third line treatment in a carefully selected patient population characterized by server refractory overactive bladder symptoms or patients who are not candidates for second-line therapy and are willing to undergo a surgical procedure. • Patients should persist with new treatments for an adequate trial in order to determine whether the therapy is efficacious and tolerable.
National Institute for Health and Clinical Excellence: **Urinary Incontinence in Neurological Disease (2012)[22]**	Behavioral treatment • For patients with neurogenic lower urinary tract dysfunction, behavioral management programs should be considered (e.g., timed voiding, bladder retraining or habit retraining). • When choosing a behavioral management program, take into account that prompted voiding and habit retraining are particularly suitable for people with cognitive impairment.

Clinical Guideline	Recommendation(s)
	Antimuscarinics • Antimuscarinic drugs should be offered to patients with spinal cord disease (e.g., spinal cord injury or multiple sclerosis) who have symptoms of overactive bladder such as increased frequency, urgency and incontinence. • In patients with conditions affecting the brain (e.g., cerebral palsy, head injury or stroke) with symptoms of an overactive bladder, antimuscarinic drugs should be considered. • Antimuscarinic drug treatment should be considered in patients with urodynamic investigations showing impaired bladder storage. • Residual urine volume should be monitored in patients not using intermittent or indwelling catheterization after beginning treatment. • Antimuscarinic treatment can reduce bladder emptying, which may increase the risk of urinary tract infections and may precipitate or exacerbate constipation. Antimuscarinics known to cross the blood-brain barrier (e.g. oxybutynin) have the potential to cause central nervous system related adverse effects (e.g., confusion). Botulinum toxin A • Bladder wall injection with botulinum toxin A should be offered to adult patients with spinal cord diseases (e.g., spinal cord injury or multiple sclerosis) and symptoms of overactive bladder and an inadequate response to or poorly tolerated antimuscarinic drugs. • Bladder wall injection with botulinum toxin A may be considered for children and young people with spinal cord disease and symptoms of overactive bladder for who antimuscarinic drugs were ineffective or poorly tolerated. • Bladder wall injection with botulinum toxin A may be considered in adults with spinal cord disease with urodynamic investigations showing impaired bladder storage for whom antimuscarinic drugs were ineffective or poorly tolerated. • Consider bladder wall injection with botulinum toxin A for children and young people with spinal cord disease with urodynamic investigations showing impaired bladder storage and for whom antimuscarinic drugs were ineffective or poorly tolerated. • A catheterization regimen is needed in most people with neurogenic lower urinary tract dysfunction after botulinum toxin A treatment. The patient must be able and willing to manage such a regimen should urinary retention develop after the treatment. • Monitor residual urine volume in patients who are not using a catheterization regimen during treatment with botulinum toxin A. • Monitor upper urinary tract in patients at risk of renal complications (e.g., those with high intravesical pressures on filling cystometry) during treatment. • People should be offered repeated botulinum toxin A injections and have prompt access to repeat injections when symptoms return.

International Scientific Committee: **Evaluation and Treatment of Urinary Incontinence, Pelvic Organ Prolapse, and Fecal Incontinence (2010)**[23]	Initial management of urinary incontinence in men
	• For men with stress, urgency or mixed urgency/stress incontinence, initial treatment should include:
	  o Lifestyle interventions.
	  o Supervised pelvic floor muscle training for men with post-radical prostatectomy stress urinary incontinence.
	  o Scheduled voiding regimes for overactive bladder.
	  o Antimuscarinic drugs for overactive bladder symptoms with or without urgency incontinence and the patient has no evidence of significant post-void residual urine.
	  o Alpha adrenergic antagonists (α-blockers) can be added if it is thought that there may also be bladder outlet obstruction.
	
	Initial management of urinary incontinence in women

Clinical Guideline	Recommendation(s)

	• For women with stress, urgency or mixed urgency/stress incontinence, initial treatment should include:
	  o Advice on caffeine reduction and weight reduction.
	  o Supervised pelvic floor muscle training and vaginal cones for women with stress incontinence.
	  o Supervised bladder training for overactive bladder.
	  o If estrogen deficiency and/or urinary tract infection is found, the patient should be treated at initial assessment and then reassessed after a suitable interval.
	  o Antimuscarinics for overactive bladder symptoms with or without urgency incontinence.
	  o Duloxetine may be considered for stress urinary incontinence.
	
	<u>Initial management of neurogenic urinary incontinence</u>
	• Conservative treatment modalities (often in combination):
	  o Intermittent catheterization.
	  o Behavioral treatment.
	  o Timed voiding.
	  o External appliances.
	  o Antimuscarinics.
	  o Alpha-blockers.
	  o Intravesical ES.
	  o Bladder expression.
	  o Triggered voiding.
	  o Indwelling catheter.
	
	<u>Management of urinary incontinence in frail older persons</u>
	• Initial treatment should be individualized and influenced by goals of care, treatment preferences, and estimated remaining life expectancy, as well as the most likely clinical diagnosis.
	• In some frail elders the only possible outcome may be contained urinary incontinence (managed with pads), especially for persons with minimal mobility (require assistance of >2 persons to transfer), advanced dementia (unable to state their name), and/or nocturnal urinary incontinence.
	• Conservative and behavioral therapy for urinary incontinence include lifestyle changes, bladder training for more fit alert patients, and prompted voiding for frailer, more impaired patients.
	• For select cognitively intact patients, pelvic muscle exercises may be considered. Antimuscarinics may be added to conservative therapy of urgency urinary incontinence.
	• Alpha-blockers may be cautiously considered in frail men with suspected prostatic outlet obstruction.
	• DDAVP (vasopressin) has a high risk of severe hyponatremia in frail persons and should not be used.

Neurogenic Bladder Society: **Clinical Guidelines for Overactive Bladder (2009)**[2]	<u>Behavioral therapy</u> • Behavioral therapy can include lifestyle guidance, bladder training, physical therapy and toileting assistance. • Behavioral therapy is minimally invasive with no adverse reactions and combination therapy with other forms of treatment is also possible. • Behavioral therapy should be considered as the first-line choice for initial treatment of overactive bladder. • The efficacy of combined behavioral therapy and drug therapy over monotherapy has yet to be determined, but it is the recommended treatment approach. <u>Drug therapy</u>

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	• Drug therapy forms the basis of treatment for overactive bladder. • The drugs for which efficacy and safety have been investigated are the antimuscarinic agents. These are most commonly used for the treatment of overactive bladder. • When using antimuscarinic drugs, it is necessary to consider adverse reactions due to blockade of the systemic muscarine receptors <u>Antimuscarinic drugs</u> • Oxybutynin has a direct relaxing effect and paralyzing effect on smooth muscle in addition to its antimuscarinic activity. It has been extensively evaluated and its efficacy has been well demonstrated. The incidence of adverse reactions associated with its antimuscarinic activity is higher than that of other antimuscarinic drugs. It is recommended that treatment is started from a low dose and titrated gradually to determine the optimal dose. Oxybutynin can pass through the blood-brain barrier potentially causing central nervous system adverse events (cognitive impairment, etc.). Caution is required in elderly patients. • Tolterodine has no selectivity for muscarinic receptor subtypes, is well distributed to and has a high binding affinity for the bladder, and as compared to the salivary glands, is highly selective for the bladder. It has been extensively evaluated and there is substantial evidence for efficacy and safety in overactive bladder patients, including the elderly and patients with severe overactive bladder. • Solifenacin is highly selective for the muscarinic receptor M3, and is more highly selective for the bladder than for the salivary glands. It has been shown to be effective for urgency, frequency, and urge urinary incontinence in overactive bladder. • Flavoxate has no antimuscarinic activity, but appears to have a moderate calcium antagonistic action, inhibitory effect on phosphodiesterase, and a local relaxant effect on smooth muscle. Flavoxate has been observed to have almost no adverse reactions, but its efficacy has not been adequately evaluated. • Darifenacin is high selectivity for the M3 receptor subtype, and it has shown a higher selectivity for the bladder than the salivary glands in animal studies. Concern has been raised about adverse reactions involving the salivary glands and gastrointestinal tract, in which M3 receptors are numerous. <u>Antidepressants</u> • Several types of tricyclic antidepressants are indicated for enuresis or nocturnal enuresis, with imipramine being the most commonly used drug. Imipramine appears to be useful for nocturnal enuresis in children, but its usefulness as a therapeutic agent for overactive bladder is yet to be adequately evaluated. <u>Botulinum Toxin</u> • Botulinum toxin is believed to inhibit bladder contraction by blocking the release of acetylcholine from cholinergic nerves, primarily by causing chemical denervation. • Injection of botulinum toxin into the bladder wall is believed to be a promising therapeutic method for overactive bladder, but its usefulness is yet to be adequately explored. <u>Efficacy of drug therapy for overactive bladder symptoms in benign prostatic hyperplasia patients</u> • α_1-blockers are first-line drug therapy for overactive bladder symptoms in benign prostatic hyperplasia patients, but their long-term efficacy in patients without lower urinary tract obstruction has yet to be proven. • Randomized controlled studies to demonstrate the efficacy and safety of antimuscarinic drugs for overactive bladder symptoms associated with benign

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	prostatic hyperplasia have yet to be performed.
	• Despite the fact that antimuscarinic drugs may be effective in some benign prostatic hyperplasia patients with overactive bladder symptoms, there is ample risk of causing acute urinary retention or chronic urinary retention.
	• The therapeutic positioning of antimuscarinic drugs for men with lower urinary tract symptoms is uncertain, and they are contraindicated in patients with severe lower urinary tract obstruction or urinary retention.
	• It remains uncertain whether combination therapy with an α_1-blocker and an antimuscarinic drug is superior to α_1-blocker monotherapy in benign prostatic hyperplasia patients with overactive bladder symptoms.
	
	<u>Practical guidelines for drug therapy for overactive bladder: Rules for treatment with anticholinergic drugs, classified by sex and age</u>
	• Overactive bladder in women:
	  o Antimuscarinic drugs can be administered immediately.
	  o If voiding symptoms, as well as overactive bladder symptoms, are present, antimuscarinic drugs should be administered with caution.
	  o Since overactive bladder and impaired detrusor contractility may both be present in elderly women (80 years or older) in particular, patients should be referred to a urological specialist if voiding symptoms are severe or if residual urine is copious (50 mL or more).
	• Overactive bladder in men under 50 years of age:
	  o For overactive bladder in relatively young men, it is recommended that patients be evaluated by a urological specialist at least once, as there may be an underlying comorbid neurological disease or urological disease.
	• Overactive bladder in men aged 50 years or older:
	  o Because there is a high probability of overactive bladder as a complication of benign prostatic hyperplasia, give top priority to starting an α_1-blocker if voiding symptoms are confirmed.
	  o If there is no improvement in overactive bladder symptoms, an antimuscarinic drug can be coadministered. However, since there is not adequate evidence regarding this combination, the patient should also be referred to a urological specialist.

American College of Obstetricians and Gynecologists: **Practice Bulletin: Urinary Incontinence in Women (2015)**[24]	• Behavioral therapy (e.g., bladder training and prompted voiding) and pelvic floor muscle exercises improve symptoms of stress, urgency, and mixed urinary incontinence and may be recommended as an initial, noninvasive treatment in many women. • Moderate weight loss can improve urinary incontinence symptoms in overweight and obese women. • Pelvic floor muscle exercises appear to be an effective treatment for adult women with stress, urgency, or mixed incontinence and can be recommended as a noninvasive treatment for many women. • Current evidenced-based medical treatments typically are reserved for urgency urinary incontinence. Medical therapies for treatment of stress urinary incontinence are less effective and generally are not recommended. Available medical treatments for urgency urinary incontinence include antimuscarinic agents (also known as anticholinergic agents), β-agonists, onabotulinumtoxinA, and estrogen. • The antimuscarinic medications have been shown to have a small beneficial effect as therapy for urgency incontinence. Numerous antimuscarinic agents are available, including darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, and trospium, that have similar efficacy and safety profiles; however, conclusions regarding comparative effectiveness and safety are limited by the lack of high-quality evidence from head-to-head trials between specific agents. • Antimuscarinic medications also were associated with significant discontinuation

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	rates because of bothersome adverse effects, with dry mouth as the most frequently reported adverse event. • Compared with antimuscarinic treatment, intravesical onabotulinumtoxinA results in similar reduction of incontinence episodes, and more patients report complete resolution of incontinence. Thus, intradetrusor onabotulinumtoxinA may be a treatment option for overactive bladder in appropriate patients, and consideration of its use requires shared decision making between the patient and physician. • Systemic estrogen therapy, with or without progesterone, does not appear to be effective in the prevention or treatment of urinary incontinence; several large trials of hormone therapy have found an increased occurrence of stress incontinence in users of hormone therapy (estrogen alone or combined with progesterone). Locally administered (vaginal) estrogen, however, may be of some benefit in decreasing urinary incontinence.
European Association of Urology/European Society for Pediatric Urology: **Guidelines on Pediatric Urology: Management of Neurogenic Bladder in Children (2015)**[5]	Early management with clean intermittent catheterization • Management of neurogenic bladder in infants has demonstrated that children do not have upper tract deterioration when managed early with clean intermittent catheterization and antimuscarinic medication. • Clean intermittent catheterization should be started soon after birth in all babies, especially in those with signs of possible outlet obstruction. Early intermittent catheterization results in fewer upper tract changes, but also better bladder protection and lower incontinence rates. Medical therapy • Oxybutynin, tolterodine, trospium, and propiverine are the most frequently used drugs for the treatment of neurogenic bladder. Most of the studies have been conducted with oxybutynin. • Two different forms of tolterodine have been investigated in children with neurogenic bladder. The extended-release formulation has been found to be as effective as the immediate-release formulation, while being less expensive and only being administered once daily. Despite encouraging clinical outcomes, the level of evidence remains low for antimuscarinic medications due to a lack of controlled studies. • The use of medication to facilitate emptying in children with neurogenic bladder has not been well studied. • The use of α-adrenergic blockade in children with neurogenic bladder has resulted in a good response rate, but the studies lacked controls and long-term followup is warranted. Botulinum toxin injections • Injection of botulinum toxin into the detrusor is an alternative treatment option for neurogenic bladders, which are refractory to antimuscarinics. The use of botulinum toxin in adults prompted its use in children and even though it has been shown to have beneficial effects on clinical and urodynamic variables, the findings are limited by the lack of prospective controlled trials in children. • Injection of botulinum toxin in therapy-resistant bladders appears to be an effective and safe treatment alternative. Botulinum toxin seems to be more effective in patients who have bladders with obvious detrusor muscle over activity. Stiff bladders without an active component are unlikely to respond to botulinum toxin. No evidence regarding the optimal dose exists and it is unclear how many times this treatment can be repeated in children. • Although the evidence is too low to recommend its routine use in decreasing outlet resistance, injection of botulinum toxin in the urethral sphincter has been shown to be effective in decreasing urethral resistance and improving voiding.
European Association of Urology:	Treatment goals • The primary goals for the treatment of neurogenic lower urinary tract dysfunction

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Guidelines on Neuro-Urology (2015)[6]	are: o Protection of the upper urinary tract. o Improvement of urinary continence. o Improvement of the patient's quality of life. o Restoration of (parts of) normal lower urinary tract function. • Other considerations include the patient's disability, cost-effectiveness, technical complexity, and possible complications. <u>Assisted bladder emptying</u> • Incomplete bladder emptying is a risk factor for urinary tract infections, for developing high intravesical pressure during the filling phase, and for incontinence. • Methods to improve the voiding process should be practiced in patients with neurogenic lower urinary tract dysfunction and include the following: third party bladder expression (Credé), voiding by abdominal straining (Valsalva), triggered reflex voiding, behavioral modification techniques (bladder training, lifestyle modifications), pelvic floor muscle training, and biofeedback <u>Lower urinary tract rehabilitation</u> • Bladder rehabilitation aims to re-establish bladder function in patients with neurogenic lower urinary tract dysfunction. While improving voluntary control of lower urinary tract dysfunction has been described in non-neurogenic patients, evidence for bladder rehabilitation using electrical stimulation in neurogenic patients is lacking and is based on pilot studies with small patient numbers. • Peripheral temporary electrostimulation suppresses neurogenic detrusor over activity during acute stimulation and it has demonstrated sustained effects in patients with neurogenic bladder due to multiple sclerosis. In multiple sclerosis patients, a combined approach of pelvic floor muscle training with neuromuscular electrostimulation and biofeedback was more efficacious to electrostimulation alone in achieving a substantial reduction in lower urinary tract dysfunction. • Biofeedback can be used for supporting the alleviation of neuro-urological symptoms. • Intravesical electrostimulation may increase bladder capacity; improve bladder compliance as well as the sensation of bladder filling in patients with incomplete spinal cord injuries or meningomyelocele. • Chronic peripheral pudendal stimulation may produce neuromodulatory effects in the brain, which are correlated with clinical improvement. <u>Drug treatment</u> • An optimal medical treatment for neurogenic lower urinary tract dysfunction is not available, and currently a combination of treatment modalities is the best therapeutic approach. Most drugs only resolve part of the problem or are adjunct to other measures. • Antimuscarinic drugs are first-line in the treatment of neurogenic detrusor overactivity (NDO). They increase bladder capacity and reduce episodes of urinary incontinence secondary to NDO by the inhibition of parasympathetic pathways. • Outcomes for neurogenic detrusor overactivity can be maximized by considering a combination or using higher doses of antimuscarinic agents. However, antimuscarinics have a high incidence of adverse events which may lead to discontinuation of therapy. • Alternative routes of administration (i.e., transdermal or intravesical) of antimuscarinic agents may be used to help reduce adverse effects. • Oxybutynin, tolterodine, trospium, and propiverine are established, effective, and well-tolerated treatment choices. These agents have different tolerability profiles

Clinical Guideline	Recommendation(s)
	and an alternative antimuscarinic agent may be prescribed if the patient experiences adverse effects with one. • Darifenacin and solifenacin have been evaluated in NDO secondary to spinal cord injury and multiple sclerosis and had results similar to other antimuscarinic drugs. • In pilot studies, phosphodiesterase-5 inhibitors have shown promising effects for treatment of NDO. • β-3 adrenergic agonists are currently being studied and may become a treatment option. • In patients with detrusor underactivity, cholinergic drugs (bethanechol chloride and distigmine bromide) may enhance detrusor contractility and promote bladder emptying, but are not used in clinical practice due to a lack of clinical evidence. • Alpha-blockers have been used successfully on occasion for decreasing bladder outlet resistance, postvoid residual and autonomic dysreflexia. Combination therapy with a cholinergic drug and an alpha-blocker appears to be more useful than monotherapy with either agent. • Several drugs have been shown to be effective for the treatment of mild stress incontinence, but there are few studies in patients with neurogenic lower urinary tract dysfunction. <u>External appliances</u> • Social continence may be achieved by collecting the urine when incontinence cannot be resolved by any other methods. • Condom catheters with urine collection devices are a practical method for men. Incontinence pads may also offer a reliable solution. • With both incontinence pads and condom catheters, the patient must be closely observed for a urinary tract infection. <u>Minimal invasive treatment</u> • Intermittent catheterization is the standard treatment of neurogenic lower urinary tract dysfunction and it is effective in patients with: detrusor underactivity or acontractility, detrusor over activity (provided the over activity can be controlled. • Botulinum toxin injection in the detrusor is the most effective minimally invasive treatment to reduce neurogenic detrusor over activity. Therapy causes a long-lasting chemical denervation that lasts approximately nine months. • Antimuscarinics can be administered intravesically to reduce detrusor over activity. This route of administration may decrease adverse effects and a greater amount is sequestered in the bladder.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the genitourinary smooth muscle relaxants are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Genitourinary Smooth Muscle Relaxants[7-18]

Indication	Darifenacin	Fesoterodine	Flavoxate	Mirabegron	Oxybutynin	Solifenacin	Tolterodine	Trospium
Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency	✔	✔		✔	✔ *†	✔	✔	✔
For symptomatic relief of dysuria, urgency, nocturia, suprapubic pain, frequency and incontinence as may occur in cystitis, prostatitis, urethritis, urethrocystitis and urethrotrigonitis			✔					
Relief of symptoms of bladder instability associated with voiding in patients with uninhibited neurogenic or reflex neurogenic bladder (i.e., urgency, frequency, urinary leakage, urge incontinence, dysuria)					✔ ‡			
Treatment of pediatric patients aged six years and older with symptoms of detrusor overactivity associated with a neurological condition (e.g., spina bifida)					✔ †			

*Transdermal formulations.
† Extended-release oral formulation.
‡Immediate-release oral formulation.

IV. Pharmacokinetics

The pharmacokinetic parameters of the genitourinary smooth muscle relaxants are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Genitourinary Smooth Muscle Relaxants[8]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Darifenacin	15 to 25	98	Liver; Intestinal wall	Renal (60) Feces (40)	13 to 19
Fesoterodine	52	50	Liver	Renal (70) Feces (7)	4 to 7
Flavoxate	Not reported	Not reported	Not reported	Renal (57)	Not reported
Mirabegron	29 to 35	71	Liver	Renal (6 to 12)	50
Oxybutynin	IR: 6 ER: 156 to 187 (compared to IR)	>99	Liver; Intestinal wall	Renal (<0.1)	Gel: 30 ER: 13.2 IR: 2.0 to 3.0 Patch: 7 to 8
Solifenacin	90	98	Liver	Renal (3 to 6) Feces (22.5)	40 to 68
Tolterodine	IR: 77	Not reported	Liver	Renal (77) Feces (17)	1.9 to 3.7
Trospium	IR: 9.6	IR: 50 to 85 ER:48 to 78	Liver	Renal (5.8) Feces (85.2)	IR: 18.3 ER: 35

ER=extended-release formulation, IR=immediate-release formulation

V. Drug Interactions

Major drug interactions with the genitourinary smooth muscle relaxants are listed in Table 5.

Table 5. Major Drug Interactions with the Genitourinary Smooth Muscle Relaxants[8]

Generic Name(s)	Interaction	Mechanism
Genitourinary smooth muscle relaxants (mirabegron, solifenacin)	Thioridazine	Coadministration may have additive effects on the prolongation of the QT interval.
Genitourinary smooth muscle relaxants (darifenacin, fesoterodine, flavoxate, oxybutynin, solifenacin, tolterodine, trospium)	Potassium preparations	Antimuscarinic agents may slow gastrointestinal motility and cause delay in tablet passage through the gastrointestinal tract.
Genitourinary smooth muscle relaxants (fesoterodine, solifenacin, tolterodine)	Imidazoles	Inhibition of cytochrome P450 3A4 by imidazoles may decrease the metabolic elimination of genitourinary smooth muscle relaxants. Plasma concentrations and pharmacologic effects of genitourinary smooth muscle relaxants may be increased.
Genitourinary smooth muscle relaxants (solifenacin, tolterodine)	Macrolides	Inhibition of cytochrome P450 3A4 by macrolides may decrease the metabolic elimination of genitourinary smooth muscle relaxants. Plasma concentrations and pharmacologic effects of genitourinary smooth muscle relaxants may be increased.
Genitourinary smooth muscle relaxants (solifenacin, tolterodine)	Protease inhibitors	Inhibition of cytochrome P450 3A4 by protease inhibitors may decrease the metabolic elimination of genitourinary smooth muscle relaxants. Plasma concentrations and pharmacologic effects of genitourinary smooth muscle relaxants may be

Generic Name(s)	Interaction	Mechanism
		increased.
Genitourinary smooth muscle relaxants (solifenacin, tolterodine)	Nefazodone	Inhibition of cytochrome P450 3A4 by nefazodone may decrease the metabolic elimination of genitourinary smooth muscle relaxants. Plasma concentrations and pharmacologic effects of genitourinary smooth muscle relaxants may be increased.

VI. Adverse Drug Events

The most common adverse drug events reported with the genitourinary smooth muscle relaxants are listed in Table 6.

Table 6. Adverse Drug Events (%) Reported with the Genitourinary Smooth Muscle Relaxants[7-18]

Adverse Events	Darifenacin	Fesoterodine	Flavoxate	Mirabegron	Oxybutynin (Oral)	Oxybutynin (Transdermal)	Solifenacin	Tolterodine	Trospium
Cardiovascular									
Arrhythmia	-	-	-	-	1 to 5		-	-	<1
Atrial fibrillation	✔	-	-	-	-	-	-	-	-
Chest pain	-	✔	-	-	1 to 5	✔ §	-	2	✔
Hypertension	≥1	-	-	7.5 to 11.3	1 to 5	-	≤1	-	✔
Hypotension	-	-	-	-	1 to 5	-	-	-	-
Myocarditis	-	-	-	-	-	✔ §	-	-	-
Palpitations	✔	✔	✔	-	1 to 5	-	-	✔	✔
Peripheral edema	≥1	1	-	-	1 to 5	-	-	✔	-
QT_c prolongation	-	✔	-	-	1 to 5	-	✔	-	-
Supraventricular tachycardia	-	-	-	-	-	-	-	-	✔
Syncope	-	-	-	-	-	-	-	-	✔
T-wave inversion	-	-	-	-	-	-	-	-	✔
Tachycardia	✔	✔	✔	-	1 to 5	✔ §	-	✔	1 to 2
Torsade de pointes	-	-	-	-	-	-	✔	-	-
Central Nervous System									
Agitation	-	-	-	-	1 to 5	-	-	-	-
Anxiety	-	-	-	-	-	-	-	1†	-
Confusion	✔	-	✔	-	-	-	✔	✔	-
Delirium	✔	-	-	-	-	-	-	-	✔
Depression	-	-	-	-	1 to 5	-	≤1	-	-
Disorientation	-	-	-	-	-	-	-	✔	-
Dizziness	1 to 2	-	-	-	4 to17	2 to 3‡	≤1	2†, 5γ	-
Drowsiness	-	-	✔	-	-	-	-	-	-
Dysphonia	✔	-	-	-	✔	-	-	-	-
Fatigue	-	-	✔	-	1 to 5	2‡	1 to 2	2†, 4γ	2
Hallucinations	✔	-	-	-	1 to 5	✔ §	✔	✔	✔
Headache	7	-	✔	-	6 to 10	2‡	3 to 6	7†, 6γ	4 to 7
Heat prostration	-	✔	-	-	-	-	-	-	-
Hyperpyrexia	-	-	✔	-	-	-	-	-	-

Adverse Events	Darifenacin	Fesoterodine	Flavoxate	Mirabegron	Oxybutynin (Oral)	Oxybutynin (Transdermal)	Solifenacin	Tolterodine	Trospium
Insomnia	-	1	-	-	1 to 6	-	-	-	-
Memory impairment	-	-	-	-	1 to 5	-	-	✔	-
Nervousness	-	-	✔	-	1 to 7	-	-	-	-
Psychotic disorder	-	-	-	-	1 to 5	-	-	-	-
Seizure	-	-	-	-	1 to 5	-	-	-	-
Somnolence	✔	-	✔	-	2 to 14	-	-	3	✔
Vertigo	-	-	✔	-	-	-	-	5γ	-
Dermatological									
Application site reaction	-	-	-	-	-	5‡, 17§	-	-	-
Dermatitis	-	-	-	-	-	5‡	-	-	-
Dry skin	≥1	-	-	-	1 to 5	-	-	1γ	✔
Erythema	-	-	-	-	✔	5‡, 6 to 8§	✔	-	-
Flushing	-	-	-	-	1 to 5	-	-	-	-
Irritation	-	-	-	-	-	5‡	-	-	-
Papules	-	-	-	-	-	5‡	-	-	-
Pruritus	≥1	-	-	-	1 to 5	1 to 5‡, 14§	✔	-	-
Rash	≥1	≤1	✔	-	1 to 5	3§	✔	-	✔
Stevens-Johnson syndrome	-	-	-	-	-	-	-	✔	✔
Sweating decreased	-	-	-	-	1 to 5	✔ §	-	-	-
Urticaria	-	-	✔	-	-	-	✔	-	-
Vesicles	-	-	-	-	-	3§	-	-	-
Gastrointestinal									
Abdominal pain	2 to 4	1	-	-	1 to 5	-	1 to 2	4†, 5γ	1 to 3
Anorexia	-	-	-	-	✔	-	-	-	-
Aptyalism	-	-	-	-	1 to 5	-	-	-	-
Constipation	15 to 21	4 to 6	✔	-	7 to 15	1‡, 3§	5 to 13	6†, 7γ	9 to 10
Diarrhea	1 to 2	-	-	-	1 to 9	3§	-	✔	-
Diverticulitis	-	<1	-	-	-	-	-	-	-
Dysgeusia	-	-	-	-	1 to 5	-	-	-	-
Dyspepsia	3 to 8	2	-	-	5 to 7	-	1 to 4	3†, 4γ	1 to 2
Dysphagia	-	-	-	-	1 to 5	-	-	-	-
Eructation	-	-	-	-	1 to 5	-	-	-	-
Fecal impaction	-	-	-	-	-	-	✔	-	-
Feces hard	-	-	-	-	-	-	-	-	✔
Flatulence	-	-	-	-	1 to 5	-	-	-	1 to 2

Adverse Events	Darifenacin	Fesoterodine	Flavoxate	Mirabegron	Oxybutynin (Oral)	Oxybutynin (Transdermal)	Solifenacin	Tolterodine	Trospium
Gastritis	-	-	-	-	-	-	-	-	✔
Gastroenteritis	-	<1	-	-	-	2‡	-	-	-
Gastrointestinal obstruction	-	-	-	-	-	-	✔	-	-
Gastroesophageal reflux disease	✔	-	-	-	1 to 5	-	-	-	-
Gastrointestinal motility decreased	-	-	-	-	1 to 5	-	-	-	-
Hoarseness	-	-	-	-	1 to 5	-	-	-	-
Irritable bowel syndrome	-	<1	-	-	-	-	-	-	-
Loose stools	-	-	-	-	1 to 5	-	-	-	-
Nausea	2 to 4	1 to 2	✔	-	2 to 12	-	2 to 3	-	≤1
Taste abnormality	-	-	-	-	1 to 5	-	-	-	✔
Thirst	-	-	-	-	1 to 5	-	-	-	-
Tongue coated	-	-	-	-	1 to 5	-	-	-	-
Vomiting	≥1	-	✔	-	1 to 5	-	≤1	-	✔
Weight gain	≥1	-	-	-	-	-	-	1	-
Xerostomia	19 to 35	19 to 35	✔	-	29 to 71	7 to 8‡, 4 to 10§	11 to 28	23†, 35γ	10 to 22
Genitourinary									
Cystitis	-	-	-	-	1 to 5	-	-	-	-
Dysuria	-	1 to 2	✔	-	1 to 5	2§	-	1†, 2γ	-
Impotence	-	-	-	-	1 to 5	✔ §	-	-	-
Pollakiuria	-	-	-	-	1 to 5	-	-	-	-
Urinary retention	✔	1 to 2	-	-	6	-	≤1	-	≤1
Urinary tract infection	4 to 5	2 to 4	-	5.9	5 to 7	7‡	3 to 5	-	1 to 7
Vaginitis	≥1	-	-	-	-	-	-	-	-
Hepatic									
Alanine transaminase increased	✔	≤1	-	-	-	-	-	-	-
Gamma-glutamyl transferase increased	-	≤1	-	-	-	-	-	-	-
Musculoskeletal									
Arthralgia	≥1	-	-	-	1 to 5	-	-	2	-
Back pain	≥1	1 to 2	-	-	1 to 5	-	-	-	✔
Rhabdomyolysis	-	-	-	-	-	-	-	-	✔
Weakness	<3	-	-	-	3 to 7	-	-	-	-

Adverse Events	Darifenacin	Fesoterodine	Flavoxate	Mirabegron	Oxybutynin (Oral)	Oxybutynin (Transdermal)	Solifenacin	Tolterodine	Trospium
Respiratory									
Asthma	-	-	-	-	1 to 5	-	-	-	-
Bronchitis	≥1	-	-	-	1 to 5	-	-	-	-
Cough	-	1 to 2	-	-	1 to 5	-	≤1	-	-
Dry throat	-	1 to 2	✔	-	1 to 5	-	-	-	-
Nasal congestion	-	-	-	-	1 to 5	-	-	-	-
Nasal dryness	-	-	-	-	1 to 5	-	-	-	1
Nasopharyngitis	-	-	-	-	1 to 5	3‡	-	-	3
Pharyngitis	≥1	-	-	-	-	-	-	-	-
Rhinitis	≥1	-	-	-	2 to 6	-	-	-	-
Sinus congestion	-	-	-	-	1 to 5	-	-	-	-
Sinus headache	-	-	-	-	1 to 5	-	-	-	-
Sinusitis	≥1	-	-	-	1 to 5	-	-	2†	-
Upper respiratory tract infection	-	2 to 3	-	-	1 to 5	-	-	-	-
Special Senses									
Abnormal vision	≥1	-	-	-	-	-	-	1†, 2γ	-
Blurred vision	-	✔	✔	-	1 to 10	-	4 to 5	-	1
Cycloplegia	-	-	-	-	1 to 5	✔ §	-	-	-
Dry eyes	1.5 to 2.0	1 to 4	-	-	3 to 6	-	≤2	3	1 to 2
Eye irritation	-	-	-	-	1 to 5	-	-	-	-
Intraocular pressure increased	✔	-	✔	-	-	-	-	-	-
Keratoconjunctivitis sicca	-	-	-	-	1 to 5	-	-	-	-
Mydriasis	-	-	-	-	1 to 5	-	-	-	-
Vision changes	-	-	✔	-	-	3§	-	-	-
Other									
Anaphylactoid reactions	-	-	-	-	-	-	-	✔	-
Anaphylaxis	-	-	-	-	-	-	✔	-	✔
Angioedema	✔	-	-	-	✔	-	-	✔	-
Angioneurotic edema	-	-	-	-	✔	-	✔	-	✔
Edema	-	-	-	-	1 to 5	-	≤1	-	-
Extremity pain	-	-	-	-	1 to 5	-	-	-	-
Flank pain	-	-	-	-	1 to 5	-	-	-	-
Flu-like syndrome	1 to 3	-	-	-	-	-	-	3	-

Adverse Events	Darifenacin	Fesoterodine	Flavoxate	Mirabegron	Oxybutynin (Oral)	Oxybutynin (Transdermal)	Solifenacin	Tolterodine	Trospium
Fungal infection	-	-	-	-	1 to 5	-	-	-	-
Hyperglycemia	-	-	-	-	1 to 5	-	-	-	-
Hyperkalemia	✔	-	-	-	-	-	-	-	-
Hypersensitivity	✔	-	-	-	-	-	✔	✔	-
Infection	-	-	-	-	-	-	-	1	-
Influenza	-	-	-	-	-	-	≤2	-	2
Lactation suppression	-	-	-	-	1 to 5	✔ §	-	-	-
Leukopenia	-	-	✔	-	-	-	-	-	-
Pain	≥1	-	-	-	1 to 7	-	-	-	-
Pharyngolaryngeal pain	-	-	-	-	1 to 5	-	-	-	-
Renal impairment	✔	-	-	-	-	-	-	-	-

✔ Percent not specified.
- Event not reported or incidence <1%.
†Extended-release formulation.
‡Transdermal gel formulation.
§Transdermal patch formulation.
γ Immediate-release formulation.

VII. Dosing and Administration

The usual dosing regimens for the genitourinary smooth muscle relaxants are listed in Table 7.

Table 7. Usual Dosing Regimens for the Genitourinary Smooth Muscle Relaxants[7-18]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Darifenacin	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency: Tablet (ER): 7.5 to 15 mg once daily	Safety and efficacy in children have not been established.	Tablet (ER): 7.5 mg 15 mg
Fesoterodine	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency: Tablet (ER): 4 to 8 mg once daily	Safety and efficacy in children have not been established.	Tablet (ER): 4 mg 8 mg
Flavoxate	For symptomatic relief of dysuria, urgency, nocturia, suprapubic pain, frequency and incontinence as may occur in cystitis, prostatitis, urethritis, urethrocystitis and urethrotrigonitis: Tablet: 100 to 200 mg three or four times/day	For symptomatic relief of dysuria, urgency, nocturia, suprapubic pain, frequency and incontinence as may occur in cystitis, prostatitis, urethritis, urethrocystitis and urethrotrigonitis in patients ≥12 years of age: Tablet: 100 to 200 mg three or four times/day	Tablet: 100 mg
Mirabegron	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency: Tablet (ER): 25 to 50 mg once daily	Safety and efficacy in children have not been established.	Tablet (ER): 25 mg 50 mg
Oxybutynin	Relief of symptoms of bladder instability associated with voiding in patients with uninhibited neurogenic or reflex neurogenic bladder (i.e., urgency, frequency, urinary leakage, urge incontinence, dysuria): Tablet/syrup (IR): 5 mg two to three times/day; maximum, 5 mg four times/day Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency: Tablet (ER): 5 to 10 mg once daily; maximum, 30 mg/day Transdermal gel in 3% pump container: three pumps should be applied daily Transdermal gel in 10% packets: the contents of one sachet should be applied once daily Transdermal patch: one 3.9 mg/day system applied twice weekly (every	Relief of symptoms of bladder instability associated with voiding in patients with uninhibited neurogenic or reflex neurogenic bladder (i.e., urgency, frequency, urinary leakage, urge incontinence, dysuria) in patients ≥5 years of age: Tablet/syrup (IR): 5 mg twice daily; maximum, 5 mg three times daily Treatment of pediatric patients aged six years and older with symptoms of detrusor overactivity associated with a neurological condition (e.g., spina bifida): Tablet (ER): 5 mg once daily; maximum, 20 mg/day	Syrup: 5 mg/5 mL Tablet (ER): 5 mg 10 mg 15 mg Tablet (IR): 5 mg Transdermal gel: 3% 10% Transdermal patch: 3.9 mg/24 hours

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	three to four days)		
Solifenacin	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency: Tablet: 5 to 10 mg once daily	Safety and efficacy in children have not been established.	Tablet: 5 mg 10 mg
Tolterodine	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency: Capsule (ER): 4 mg once daily Tablet (IR): 2 mg twice daily	Safety and efficacy in children have not been established.	Capsule (ER): 2 mg 4 mg Tablet (IR): 1 mg 2 mg
Trospium	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency: Capsule (ER): 60 mg once daily Tablet (IR): 20 mg twice daily	Safety and efficacy in children have not been established.	Capsule (ER): 60 mg Tablet (IR): 20 mg

ER=extended-release, IR=immediate-release

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the genitourinary smooth muscle relaxants are summarized in Table 8.

Table 8. Comparative Clinical Trials with the Genitourinary Smooth Muscle Relaxants

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Buser et al.[25] (2008) Available antimuscarinic drugs at the time of the analysis, excluding drugs with less direct antimuscarinic effects (e.g., flavoxate)	MA Trials evaluating safety and efficacy in patients being treated for OAB	Efficacy comparison: N=38,662 (76 trials) Safety comparison: N=39,919 (90 trials)	Primary: Perception of cure or improvement, urgency episodes per 24 hours, leakage episodes per 24 hours, urgency incontinence episodes per 24 hours, micturitions per 24 hours, and nocturia episodes per 24 hours and safety outcomes Secondary: Not reported	Primary: 40 mg/day trospium chloride, 100 mg/g per day oxybutynin topical gel and 4 mg/day fesoterodine had the best efficacy, while higher dosages of orally administered oxybutynin and propiverine had the least favorable relationship of efficacy and adverse events. Secondary: Not reported
Chapple et al.[26] (2005) Darifenacin ER 7.5 to 15 mg once daily vs placebo	DB, PG, MC, RCT (Pooled analysis) Men and women ≥18 years of age with symptoms of OAB for ≥6 months, 5 to 50 episodes of incontinence/week, and a high voiding frequency (a mean of ≥8 voids/24 hours) and urgency	N=1,059 (3 trials) 12 weeks	Primary: Median change in the number of incontinence episodes/week Secondary: Number of significant leaks/week, voiding frequency, bladder capacity, frequency and severity of	Primary: The median change in weekly incontinence episodes from baseline was -8.8 (-68.4%) for darifenacin 7.5 mg and -10.6 (-76.8%) for darifenacin 15 mg compared to placebo (-53.8 and -58.3%; P=0.004 and P<0.001 vs placebo, respectively). Secondary: There was a decrease in the number of significant leaks (P<0.001), voiding frequency (P<0.001), number/severity of urgency episodes (P<0.001), and an increase in bladder capacity (P<0.001) with both doses of darifenacin compared to placebo. There was no difference in the number of nocturnal awakenings/week caused by OAB between the darifenacin and placebo groups (P=0.13 and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	(a mean of ≥1 episode/24 hours)		urgency, number of nocturnal awakenings caused by OAB, responder rates, proportion of patients experiencing three or more dry days/week, or at least seven consecutive dry days, in the last two weeks of study treatment, adverse events	P=0.06 for darifenacin 7.5 and 15 mg, respectively). The proportion of patients who achieved a ≥70% reduction from baseline in the number of incontinent episodes/week was 48% for 7.5 mg and 57% for 15 mg darifenacin, compared to 33 and 39% of patients in the placebo group (P<0.001). The proportion of patients who achieved a ≥90% reduction from baseline was 27 and 28% of patients in each of these groups, respectively, compared to 17% of patients in the placebo group (P<0.005). The OR for improvement compared to placebo were consistent for both doses across all responder rates analyzed (OR, 1.8 to 1.9 for 7.5 mg and 1.8 to 2.2 for 15 mg darifenacin; P<0.005). Responder rates for the reduction in urgency episodes also showed significant differences from placebo (P<0.05) for both doses of darifenacin at all levels of response (≥30%, ≥50%, ≥70%, ≥90%). The proportion of patients who attained a normal voiding frequency (<8 voids/day) after 12 weeks of treatment was significantly greater with both doses of darifenacin (7.5 mg, 34%; P=0.029 vs placebo; and 15 mg, 35%; P=0.007 vs placebo) than in the corresponding placebo groups (27 and 28%, respectively). Twenty-four percent of patients treated with darifenacin 15 mg were 'dry' for at least seven days, compared to 16% in the corresponding placebo group (P=0.011). More patients (55 and 61%) had ≥3 dry days/week in the darifenacin 7.5 and 15 mg groups, respectively, than in those taking placebo (43 and 48%, respectively; both P<0.001). The overall incidence of any cause was 54% with darifenacin 7.5 mg and 65.6% with 15 mg darifenacin compared to 48.7% with placebo. The most common all-cause adverse events were dry mouth and constipation, most of which were mild to moderate. The incidence of nervous system adverse events reported by patients taking 7.5 or 15 mg of darifenacin was comparable to placebo. The most common nervous system adverse events were central nervous system-related: dizziness (darifenacin 7.5 mg, 0.9%; 15 mg, 2.1%; vs placebo 1.3%) and somnolence (0.3 and 0.9% vs 0.8%, respectively). The incidence of all-cause cardiovascular adverse events

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				with darifenacin 7.5 mg (6.2%) or 15 mg (3.6%) was also comparable with that of placebo (2.3%).
Foote et al.[27] (2005) Darifenacin ER 7.5 to 15 mg once daily vs placebo	DB, MC, RCT (Pooled analysis) Men and women ≥65 years of age with symptoms of OAB for ≥6 months, 5 to 50 episodes of incontinence/week, and a high voiding frequency (a mean of ≥8 voids/24 hours) and urgency (a mean of ≥1 episode/24 hours)	N=317 (3 trials) 12 weeks	Primary: Median change in the number of incontinence episodes/week Secondary: Number of micturitions/24 hours, bladder capacity, number of urgency episodes per 24 hours, and adverse events	Primary: At week 12, the median reduction in the number of incontinence episodes/week was significantly greater for darifenacin 7.5 mg (-11.2; -66.7%) and darifenacin 15 mg (-10.8; 75.9%) compared to placebo (-4.8; -34.8 and -6.8; 44.8%, respectively; P<0.001). Secondary: There was a significant decrease in the frequency of micturition/24 hours (P<0.001) and urgency episodes (P<0.001), and increased bladder capacity (P<0.001) with both doses of darifenacin compared to placebo. Adverse events were reported by 53.6, 69.1 and 50.9% of patients treated with 7.5 mg darifenacin, 15 mg darifenacin or placebo. The most common treatment-related adverse events, dry mouth, constipation and dyspepsia. The incidence of nervous system and cardiovascular adverse events during darifenacin therapy was similar to that with placebo, and did not increase with increasing dose of darifenacin.
Haab et al.[28] (2006) Darifenacin ER 7.5 to 15 mg once daily	ES, MC, OL Men and women ≥65 years of age who had completed one of two RCTs (feeder studies) who had previously had symptoms of OAB for ≥6 months, 5 to 50 episodes of incontinence/week, and a high voiding frequency (a mean of ≥8 voids/24 hours) and urgency (a mean of ≥1 episode/24 hours)	N=716 2 years	Primary: Safety, tolerability and efficacy Secondary: Not reported	Primary: All-causality adverse events were reported by 80% of patients at some time during the two-year extension and resulted in discontinuation in 8.9% of patients. The most commonly reported adverse events were dry mouth and constipation (23.3 and 20.9%, respectively). There were no relevant changes in any bowel-habit variables from feeder-study end to ES end in the overall group. There were few treatment-related cardiovascular and nervous system adverse events; 0.4, 0.3 and 0.3% of patients reported hypertension, arrhythmias and tachycardia, respectively, while 0.4% of patients each reported hypertonia, somnolence and paresthesia. Abnormal vision was reported in 0.6% of patients. No patient developed treatment-related glaucoma or reported worsening of a pre-existing glaucomatous condition.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				After 24 months of treatment with darifenacin, the median change from baseline of the feeder studies in incontinence episodes/week was -11.0 (84.4%), voids/24 hours was -1.4 (-13.9%), urgency episodes/24 hours was -3.9 (-56.4%), severity of urgency was -15.4 (-28.8%), nocturnal awakenings for OAB/week was -1.5 (-14.3%), and significant leaks/week was -4.7 (-100%). All variables were P<0.001 vs feeder study baseline. Overall, 62.3% of patients achieved a ≥70% reduction in incontinence episodes and 43.8% achieved a ≥90% reduction at two years. Secondary: Not reported
Hill et al.[29] (2007) Darifenacin ER 7.5 to 15 mg once daily	ES, MC, OL Men and women ≥18 years of age who had completed one of two RCTs (feeder studies) who had previously had symptoms of OAB for ≥6 months, 5 to 50 episodes of incontinence/week, and a high voiding frequency (a mean of ≥8 voids/24 hours) and urgency (a mean of ≥1 episode/24 hours)	N=214 2 years	Primary: Safety, tolerability and efficacy Secondary: Not reported	Primary: Dry mouth and constipation were the most common treatment-related (adverse events) adverse events in this older patient population (23.4 and 22.4%, respectively) and were associated with low discontinuation rates (2.3 and 4.2%, respectively). Treatment-related cardiovascular and peripheral/central nervous system adverse events were infrequently reported (1.4 and 3.3%, respectively). After 24 months of treatment with darifenacin, the median change from baseline of the feeder studies in incontinence episodes/week was -11.0 (83.7%), voids/24 hours was -1.2 (-12.4%), urgency episodes/24 hours was -3.7 (-52.0%), severity of urgency was -12.6 (-23.3%), nocturnal awakenings for OAB/week was -1.4 (-10.9%), and significant leaks/week was -4.9 (-100%). All variables were P<0.001 vs feeder study baseline. There were high proportions of responders by all definitions (≥50, ≥70 or ≥90% reductions in incontinence episodes/week), with 74.1%, 60.0% and 44.4%, patients age ≥65 years of age achieving these response levels at 24 months, respectively. Thirty-four percent of older patients experienced normalization of micturition (<8 micturitions/day) after three months of darifenacin treatment and this effect was maintained in approximately the same number of patients at the end of the two-year study (33.8%). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
But et al.[30] (2012) Darifenacin 7.5 mg once daily vs solifenacin 5 mg once daily	MC, OL, RCT Female patients with idiopathic OAB, defined as urgency intensity and urgency urinary incontinence of ≥3 on the UPS and frequency of ≥1 urgency episodes per day who have not received any anticholinergic drugs for at least 6 months	N=100 3 months	Primary: OAB symptoms Secondary: Changes in dose throughout the study, QOL scores, objective assessment of treatment improvement and safety evaluations.	Primary: Analyses of OAB symptoms at baseline were generally similar between the two treatment groups, although urgency (bothersome) scores were higher in the darifenacin group, and frequency scores were higher in the solifenacin group. Following one and three months of treatment, all measured OAB symptoms decreased, with no statistically significant treatment differences being seen between the groups. Nocturia decreased to a greater extent in the solifenacin group at one month and this group also used less incontinence pads than those in the darifenacin group at three months. Secondary: The majority of patients in the solifenacin group who completed the study maintained the same dose post-study (21/25 patients). However, in the darifenacin group only 11 patients who completed then maintained the same dose (11/24 patients). Patients treated with solifenacin indicated a greater improvement in QOL compared to patients treated with darifenacin. Overall patient subjective and objective assessment of treatment improvement was higher for solifenacin compared to darifenacin, with the difference again being statistically significant in favor of solifenacin (P=0.01). Adverse events of dry mouth, constipation, blurred vision, headache, dizziness, concentration problems, memory problems, and insomnia were solicited at the one month and three month assessments, as well as at baseline. Solifenacin showed statistically a decreased incidence of dry mouth after three months of treatment compared to the darifenacin group.
Zinner et al.[31] (2005) Darifenacin ER 15 to 30 mg once daily	DB, PC, RCT, XO Patients 18 to 85 years of age with urge incontinence with ≥4 significant	N=76 2 weeks	Primary: Incontinence episodes/week, urgency episodes/day, severity of urgency	Primary: The mean number of incontinence episodes/week decreased from 20.4 to 10.93 with solifenacin 15 mg (P<0.05 vs placebo), 8.82 with solifenacin 30 mg (P<0.05 vs placebo), 9.45 with oxybutynin (P<0.05 vs placebo), and 14.64 with placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs oxybutynin IR 5 mg three times daily vs placebo	incontinent episodes/week (defined as leakage that would normally require a change of clothing or absorbent pad) and urinary frequency ≥8 voids/24 hours		episodes, and micturitions/day Secondary: Not reported	The mean number of urgency episodes/day decreased from 9.3 to 7.95 with solifenacin 15 mg (P<0.05 vs placebo), 7.59 with solifenacin 30 mg (P<0.05 vs placebo), 8.12 with oxybutynin (P<0.05 vs placebo), and 8.71 with placebo. The mean severity of urgency episodes decreased from 2.00 to 1.93 with solifenacin 15 mg (P<0.05 vs placebo), 1.84 with solifenacin 30 mg (P<0.05 vs placebo), 1.89 with oxybutynin (P<0.05 vs placebo), and 2.03 with placebo. The number of micturitions/day decreased from 10.4 to 9.93 with solifenacin 15 mg (P=NS vs placebo), 8.85 with solifenacin 30 mg (P<0.05 vs placebo), 9.24 with oxybutynin (P=NS vs placebo), and 9.62 with placebo. Dry mouth occurred in a similar percentage of patients receiving darifenacin 30 mg and oxybutynin, which was significantly higher than treatment with placebo or darifenacin 15 mg (P<0.05). There was no significant difference between darifenacin 15 mg and placebo. Constipation occurred more frequently with darifenacin and oxybutynin than placebo. There was no significant difference between darifenacin 15 mg and oxybutynin. Blurred vision and dizziness occurred in 3.3 and 1.6% of patients receiving oxybutynin, respectively. Secondary: Not reported
Chapple et al.[32] (2005) <u>Cohort 1</u> Darifenacin IR 2.5 mg three times daily for 7 days vs oxybutynin 2.5 mg	DB, RCT, XO Patients 18 to 75 years of age with detrusor overactivity within the previous 6 months (either idiopathic or neurogenic with ≥2 associated	N=65 7 days	Primary: Urodynamic parameters, salivary flow, tolerability and safety Secondary: Not reported	Primary: All urodynamic pressure parameters significantly decreased from baseline after seven days' therapy with each treatment. No significant differences between treatments were observed for any dose of darifenacin vs oxybutynin. There were no differences between treatments in responder rates for any of the ambulatory urodynamic parameters. Reduction in salivary flow was significantly less with darifenacin ER (15 and 30 mg) than with oxybutynin (5 mg three times daily). Salivary flow

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
three times daily for 7 days Cohort 2 Darifenacin ER 15 mg once daily for 7 days vs oxybutynin 5 mg three times daily for 7 days Cohort 3 Darifenacin ER 30 mg once daily for 7 days vs oxybutynin 5 mg three times daily for 7 days	symptoms (average of ≥7 micturitions per day, ≥7 episodes of urgency/week, ≥1 urge incontinence episode/week necessitating change of clothing or pads)			was comparable for darifenacin IR (2.5 mg three times daily) and oxybutynin (2.5 mg three times daily). The mean maximum decrease in salivary flow from baseline to day seven was significantly greater with oxybutynin 5 mg three times daily than with darifenacin ER 15 mg (P<0.01). There were no differences in mean heart rate for darifenacin and oxybutynin on day seven. There were no significant differences with darifenacin and oxybutynin for visual nearpoint. The most common adverse events were dry mouth and constipation, which were generally mild or moderate in severity. Dry mouth was reported more frequently in oxybutynin-treated patients than in darifenacin-treated patients. Secondary: Not reported
Wyndaele et al.[33] (2009) Fesoterodine ER 4 to 8 mg once daily	MC, OL Men and women ≥18 years of age with self-reported OAB symptoms for ≥3 months, mean micturition frequency of ≥8 micturitions/24 hours, mean number of urgency episodes ≥3/24 hours, and	N=516 12 weeks	Primary: Number of micturitions, number of UUI episodes, number of micturition-related urgency episodes/24 hours, and the percentage of patients reporting treatment satisfaction at week 12 (‘very	Primary: The change from baseline to week 12 in the number of micturitions was -3.0 (-22%; P<0.0001), -1.7 for the number of UUI episodes (-100%; P<0.0001), and -5.0 for urgency episodes (-57%; P<0.0001). At 12 weeks, 80% of patients who responded to the TSQ reported being satisfied with fesoterodine treatment, with 38.4% of patients being ‘very satisfied’ and 41.4% of patients being ‘somewhat satisfied’. Secondary: The change from baseline to week 12 in the number of nocturnal micturitions was -0.8 (-31%; P<0.0001), -3.5 for severe urgency episodes (-94%; P<0.0001), and -15.2 for frequency-urgency sum/24 hours

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	treated with tolterodine or tolterodine ER for OAB within 2 years who reported being 'somewhat dissatisfied' or 'very dissatisfied' with tolterodine treatment on the TSQ		satisfied' or 'somewhat satisfied' on the TSQ) Secondary: Change from baseline to week 12 in nocturnal micturitions, severe micturition-related urgency episodes, frequency-urgency sum/24 hours, change from baseline in PPBC, UPS and OAB-q scores at week 12	(P<0.0001). Mean PPBC scores improved from 4.9 at baseline to 3.1 at week 12 (P<0.0001). Mean UPS scores improved from 1.8 at baseline to 2.4 at week 12 (P<0.0001). The mean change in OAB-q Symptom Bother score (29-point improvement) from baseline to week 12 was statistically significant (P<0.0001). Mean changes in total HRQOL (26-point improvement) and all four HRQOL domain (Concern, 29-point improvement; Coping, 31-point improvement; Sleep, 25-point improvement; Social Interaction, 17-point improvement) scores were also significant at 12 weeks, compared to baseline (P<0.0001). The improvements for all scales and domains were above the minimally important difference of 10 points, indicating that these changes were clinically meaningful. Dry mouth (23%) and constipation (5%) were the most frequently reported adverse events.
Nitti et al.[34] (2007) Fesoterodine ER 4 to 8 mg once daily vs placebo	DB, MC, PC, RCT Men and women ≥18 years of age with OAB syndrome for ≥6 months, urinary frequency (≥8 micturitions/24 hours) and urinary urgency (≥6 episodes during the 3-day diary period) or UUI	N=836 12 weeks	Primary: Number of micturitions/24 hours, number of UUI episodes/24 hours and treatment response Secondary: Mean volume voided/micturition, daytime micturitions, nocturnal micturitions,	Primary: The mean change from baseline in the number of micturitions/24 hours was significantly improved with fesoterodine 4 mg (-1.61, -14.9%; P<0.001) and fesoterodine 8 mg (-2.09, -16%; P<0.001) compared to placebo (-1.08, -6.9%). The mean change from baseline in the number of UUI episodes/24 hours was significantly improved with fesoterodine 4 mg (-1.65, -67.4%; P<0.001) and fesoterodine 8 mg (-2.28, -81.8%; P<0.001) compared to placebo (-0.96, -40%). Subject-reported treatment response rates with fesoterodine 4 mg (64%) and fesoterodine 8 mg (74%) were significantly higher than those with placebo (45%) at study end point (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			urgency episodes/24 hours and continent days/week	Secondary: Fesoterodine 4 mg showed significant improvements in the mean change from baseline compared to placebo for the number of nocturnal micturitions (P<0.05), urgency episodes (P<0.001) and continent days/week (P<0.001). Fesoterodine 8 mg was significantly better than placebo for MVV/micturition, number of urgency episodes, number of daytime micturitions and continent days/week (each P<0.001). Treatment-emergent adverse events occurred in 55, 61 and 69% of patients receiving placebo, and 4 and 8 mg fesoterodine, respectively. Dry mouth was the most commonly reported adverse event. It was usually mild to moderate in severity and it occurred in 7, 16 and 36% of patients receiving placebo, and 4 and 8 mg fesoterodine, respectively.
Chapple et al.[35] (2014) EIGHT Fesoterodine 4 mg once daily vs fesoterodine 8 mg once daily vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with OAB symptoms including UUI	N=1955 12 weeks	Primary: Change from baseline to week 12 in UUI episodes per 24 hours Secondary: Changes in micturitions and urgency episodes per 24 hours, patient reported outcomes	Primary: Fesoterodine 8 mg treatment resulted in significantly greater improvements in the change from baseline in UUI episodes/24 hours at week 12 compared with placebo (P<0.001) and compared with fesoterodine 4 mg (P=0.011). Secondary: Patients receiving fesoterodine 8 mg also had significantly greater improvements in micturition frequency and urgency episodes/24 h than patients receiving placebo (both P<0.001) or fesoterodine 4 mg (both P<0.001). Improvements in scores on the PPBC, UPS, and all OAB-q scales and domains at week 12 were significantly greater with fesoterodine 8 mg compared with placebo (all P<0.001) and fesoterodine 4 mg (all P<0.01).
Chapple et al.[36] (2007) Fesoterodine ER 4 to 8 mg once daily	AC, DB, PC, RCT Men and women ≥18 years of age with a medical history of OAB symptoms with	N=1,135 12 weeks	Primary: Micturitions/24 hours and treatment response Secondary: Mean volume	Primary: The mean number of micturitions/24 hours was significantly reduced from baseline in patients receiving tolterodine (-1.73, -13.8%; P=0.001 vs placebo), fesoterodine 4 mg (-1.76, -16.7%; P<0.001 vs placebo), and fesoterodine 8 mg (-1.88, -18.6%; P<0.001 vs placebo). Treatment with tolterodine resulted in significantly greater proportion of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs tolterodine ER 4 mg once daily vs placebo	urinary urgency for ≥6 months, ≥8 micturitions/24 hours, and either ≥6 urgency episodes or ≥3 UUI/24 hours, and self-reported perception of moderate problems using a Likert scale		voided/micturition, daytime micturitions/24 hours, nocturnal micturitions/24 hours, urgency episodes/24 hours, continent days/week, adverse events	patients who responded to treatment compared to placebo (P<0.001). The proportion of patients reporting a positive treatment response was significantly greater among patients receiving tolterodine (72%; P<0.001) fesoterodine 4 mg (75%; P<0.001) and fesoterodine 8 mg (79%; P<0.001) compared to placebo (53%). The mean reduction from baseline in UUI episodes/24 hours was significantly greater for patients receiving tolterodine (-1.74, -70%; P=0.008 vs placebo), fesoterodine 4 mg (-1.95, -80%; P=0.001 vs placebo), and fesoterodine 8 mg (-2.22, -87.5%; P<0.001 vs placebo). Secondary: Active treatment significantly increased MVV from baseline (P≤0.002) compared to placebo. The increases in MVV were 2.5, 3.0, and 3.6 times greater than placebo in the patients receiving tolterodine, fesoterodine 4 mg, or fesoterodine 8 mg, respectively. The mean number of daytime micturitions/24 hours was significantly reduced from baseline in patients receiving tolterodine (-1.35, -13.6%; P=0.003), fesoterodine 4 mg (-1.37, -14.3%; P=0.001), and fesoterodine 8 mg (-1.48, -16.9%; P<0.001) compared to placebo (-0.60, -9.5%). The mean number of nocturnal micturitions/24 hours did not differ significantly from placebo in patients receiving tolterodine (-0.40, -25%; P=0.815), fesoterodine 4 mg (-0.39, -28.6%; P=0.982), and fesoterodine 8 mg (-0.39, -23.1%; P<0.896). The mean number of urgency episodes/24 hours was significantly reduced from baseline in patients receiving tolterodine (-2.03, -16%; P=0.004), fesoterodine 4 mg (-1.88, -17.6%; P=0.002), and fesoterodine 8 mg (-2.36, -19.1%; P<0.001) compared to placebo (-1.07, -11.1%). Significant improvements in change from baseline compared to placebo in number of continent days/week were observed in patients receiving fesoterodine 4 or 8 mg. The most frequent adverse event was dry mouth, which was mild to

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				moderate in most patients; however, 3% of patients receiving fesoterodine 8 mg reported severe dry mouth.
Chapple et al.[37] (2008) Fesoterodine ER 4 to 8 mg once daily vs tolterodine ER 4 mg once daily vs placebo Only the results of fesoterodine ER 8 mg vs tolterodine ER 4 mg are reported.	AC, DB, PC, RCT (Post-hoc analysis) Men and women ≥18 years of age with a medical history of OAB symptoms with urinary urgency for ≥6 months, ≥8 micturitions/24 hours, and either ≥6 urgency episodes or ≥3 UUI/24 hours, and self-reported perception of moderate problems using a Likert scale	N=1,135 12 weeks	Primary: Number of micturitions/24 hours and treatment response Secondary: Mean volume voided/micturition, urgency episodes/24 hours, continent days/week, HRQOL (KHQ and ICIQ-SF), adverse events	Primary: There was no significant difference in the number of micturitions/24 hours or rate of treatment response reported with tolterodine 4 or fesoterodine 8 mg. Fesoterodine 8 mg led to a significant improvement in UUI episodes/24 hours compared to tolterodine 4 mg in 'incontinent patients' (P<0.001). Secondary: Fesoterodine 8 mg led to a significant improvement in MVV/void in 'all patients' and 'incontinent patients' compared to tolterodine (P<0.05). Fesoterodine 8 mg led to a significant improvement in continent days/week (P<0.05) and severe urgency episodes/24 hours (P<0.05) in 'incontinent patients' compared to tolterodine 4 mg. There was no significant difference in the median percent change in number of urgency episodes/24 hours reported in 'all patients' and 'incontinent patients' with fesoterodine 8 mg or tolterodine 4 mg. Scores from the KHQ and ICIQ-SF showed a significant improvement in HRQOL for the groups treated with fesoterodine 8 mg and tolterodine 4 vs placebo. The fesoterodine 8 mg dose produced significant improvements on eight of the nine domains assessed compared to placebo. Tolterodine-treated patients reported significant improvements in six of nine KHQ domains compared to placebo. Both fesoterodine 8 mg and tolterodine 4 mg treatment resulted in a ≥5-point improvement from baseline (which constitutes a meaningful change for the patient) for all domains except General Health. A major improvement in the severity of bladder-related problems from baseline to the end of treatment was reported by 39% of fesoterodine 8 mg and 34% of tolterodine 4 patients (P=0.01 for both groups vs placebo), compared to 25% on placebo. Adverse events reported in ≥2% of patients in the active-treatment groups and occurring more frequently than placebo included dry mouth,

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				constipation, dry eye, dry throat, and elevated levels of alanine aminotransferase. More patients treated with fesoterodine 8 mg had dry mouth than those receiving tolterodine 4 mg or placebo. Most cases of dry mouth were mild or moderate; 3% of patients on fesoterodine 8 mg reported severe dry mouth. More patients on fesoterodine 8 mg reported constipation than those receiving tolterodine 4 or placebo; most cases were mild to moderate. Overall, 3.2% of patients discontinued the study prematurely because of an adverse event: placebo, 2%; tolterodine 4 mg, 3%; fesoterodine 8 mg, 5%.
Ginsberg et al.[38] (2013) Fesoterodine ER 4 mg once daily for 1 week, then 8 mg once daily vs tolterodine ER 4 mg once daily vs placebo	DB, DD, RCT Men and women ≥18 years of age with a medical history of OAB symptoms with self-reported symptoms ≥3 months in 3-day baseline diaries and had ≥8 micturitions and ≥1 UUI episode per 24 hours	N=4,129 Two 12-week studies	Primary: Change from baseline to week 12 in UUI episodes Secondary: Changes from baseline in three-day bladder diary variables, scores from the PPBC, UPS, and OAB-q, diary-dry rate, proportion of subjects with >0 UUI episodes according to baseline diary and no UUI episodes according to post-baseline diary and safety evaluations	Primary: At week 12, women showed significantly greater improvement with fesoterodine than with ER tolterodine (-1.9 vs -1.7; P≤0.007) and placebo (-1.9 vs -1.6; P≤0.001) in UUI episodes. In men, there were no significant differences in improvement in UUI episodes between any treatment groups at week 12 (-1.4 for all groups; P>0.05 for both comparisons). Secondary: At week 12, women showed significantly greater improvement with fesoterodine 8 mg than with ER tolterodine 4 mg and placebo in micturition frequency, urgency episodes, and all other diary endpoints (except nocturnal micturitions vs ER tolterodine), and also in scores on the PPBC, UPS, and all OAB-q scales and domains (all P<0.005). Improvements in men were significantly greater with fesoterodine than with ER tolterodine for severe urgency and the OAB-q Symptom Bother domain and were also significantly greater with fesoterodine than with placebo for micturition frequency, urgency episodes, severe urgency episodes, PPBC responses and scores on all OAB-q scales and domains at week 12 (all P<0.04). The most frequently reported treatment-emergent adverse events in both genders were dry mouth (women: fesoterodine, 29%; ER tolterodine, 15%; placebo, 6%; men: fesoterodine, 21%; ER tolterodine, 13%; placebo, 5%) and constipation (women: fesoterodine, 5%; ER tolterodine, 4%; placebo, 2%; men: fesoterodine, 5%; ER tolterodine, 3%; placebo, 1%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Van Kerrebroeck et al.[39] (2010) Fesoterodine ER 4 to 8 mg once daily	ES, OL Men and women ≥18 years of age with a medical history of OAB symptoms with urinary urgency for ≥6 months, ≥8 micturitions/24 hours, and either ≥6 urgency episodes or ≥3 UUI/24 hours, and self-reported perception of moderate problems using a Likert scale	N=417 24 to 32 months	Primary: Safety and tolerability Secondary: Bladder diary variables and PROs	Primary: A total of 161 patients (39%) discontinued treatment before or at the 24-month study visit. Primary reasons for discontinuation were adverse events (n=47), withdrawal of consent (n=46), and insufficient clinical response (n=36). A total of 264 patients (63%) received fesoterodine for ≥24 months during the DB and the OL extension phases. Patients received the higher fesoterodine 8 mg dose for an average of 80% of their respective treatment days during OL extension. A total of 315 patients (76%) experienced at least one treatment emergent adverse event, of which 219 cases were related to fesoterodine. The most common treatment emergent adverse events were dry mouth (34%), constipation (7%), and UTI (15%). Overall, ≥88% of patients rated treatment tolerance with fesoterodine "good" or "excellent" at months four, 12, and 24. Secondary: Compared to OL baseline, there were significant mean improvements in all diary variables throughout the 24-month extension (all P<0.001). Diary variables included UUI episodes per 24 hours, micturitions per 24 hours, urgency episodes per 24 hours, and MVV per micturition. There were significant improvements in all KHQ domains (P≤0.002), except for general health perception at months 12 and 24. Changes in mean scores typically exceeded the minimally important difference of 5. There were significant mean improvements in ICIQ-SF scores at months four, 12, and 24 (P<0.0001 for all). In the overall population, patient-reported treatment satisfaction was 97% at month 24.
Scarpero et al.[40] (2011)	ES, OL (Pooled analysis)	N=890 (2 trials)	Primary: Safety and tolerability	Primary: Overall, 55% of men (n=102) and 50% of women (n=349) discontinued treatment within the first 24 months of the OL extension. The most

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Fesoterodine ER 4 to 8 mg once daily	Men and women ≥18 years of age with OAB syndrome for ≥6 months, urinary frequency (≥8 micturitions/24 hours) and urinary urgency (≥6 episodes during the 3-day diary period) or UUI	24 to 36 months	Secondary: Bladder diary entries (number of UUI episodes, micturitions, and urgency episodes	common reasons for discontinuation in men and women were insufficient clinical response (16 and 13%), adverse events (16 and 12%), and withdrawal of consent (14 and 13%). Both men and women were treated with the higher 8 mg dose for the majority of days on OL fesoterodine (89 and 83%). A total of 539 women (77%) and 140 men (76%) experienced ≥1 treatment emergent adverse event. A total of 351 women (50%) and 86 men (47%) experienced ≥1 treatment emergent adverse event that were determined to be related to fesoterodine. The most commonly reported treatment emergent adverse events in men were dry mouth (24%) and constipation (6%), compared to dry mouth (32%) and UTI (18%) in women. The majority of men and women (≥92 and ≥91%, respectively) reported "good" or "excellent" treatment tolerance at months four, 12, and 24. Secondary: Among women, improvements in all diary variables (mean UUI episodes per 24 hours, micturitions per 24 hours, urgency episodes per 24 hours, and MVV per micturition) were significant at each time point during OL treatment compared to both DB baseline (P<0.0001) and OL baseline (P<0.0001). Among men, improvements in all diary variables were significant at each time point during OL treatment compared to DB baseline (P<0.05). Improvements in micturitions and urgency episodes per 24 hours were significant at months one, four, eight, and 12 compared to OL baseline (P<0.05). At month 24, there were no statistically significant differences from OL baseline for any diary variable.
Kelleher et al.[41] (2008) Fesoterodine ER 4 to 8 mg once daily	DB, MC, PC, RCT (Pooled analysis) Men and women ≥18 years of age with OAB	N=1,971 (2 trials) 12 weeks	Primary: Treatment-related effects on HRQOL using the KHQ (disease-specific questionnaire to	Primary: The fesoterodine 8 mg group had statistically significant improvements over placebo in eight of nine KHQ domains. Fesoterodine 4 mg and tolterodine showed statistically significant improvements over placebo in seven of nine domains of the KHQ. Fesoterodine 8 mg led to better results than 4 mg in two domains (Emotions and Severity/Coping; P<0.05). There

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs tolterodine ER 4 mg once daily vs placebo	syndrome for ≥6 months		assess LUTS), ICIQ-SF (questionnaire to evaluate patients with UI including urinary frequency, urine leakage and perceived impact of these symptoms on patients' daily lives) and a six-point Likert Scale used by patients to rate the severity of problems related to their bladder condition, and treatment response Secondary: Not reported	were no significant differences between fesoterodine 8 mg and tolterodine 4 mg. In all treatment groups, all but one KHQ domain (General Health) showed improvements meaningful to the patient (i.e., changes of ≥5 points from baseline). All active-treatment groups reported a significant improvement in the ICIQ-SF score vs placebo (P<0.001). There were no significant differences between active treatment groups. Baseline scores for the six-point Likert scale were 3.6, which indicates moderate to severe problems. At the end of the study, the scores were 2.3 to 2.8, which indicate minor problems. The percentage of patients reporting scores of 1 to 3 was <1% at baseline and increased after 12 weeks. There was also a similar change in scores with placebo. A major improvement in bladder condition (i.e., ≥2-point change) was reported by 33% of patients on fesoterodine 4 mg, 38% on fesoterodine 8 mg, and 34% on tolterodine compared to 21% on placebo (P<0.001). The percentage of patients reporting a positive treatment response was significantly higher in those receiving fesoterodine than those receiving placebo. There were significant differences between the doses in favor of fesoterodine 8 mg at two weeks and 12 weeks. Secondary: Not reported
Herschorn et al.[42] (2010) Fesoterodine ER 4 to 8 mg once daily vs tolterodine ER 4 mg once daily	DB, MC, PC, RCT Men and women ≥18 years of age with symptoms of OAB for ≥3 months	N=1,697 12 weeks	Primary: Changes from baseline to week 12 in UUI episodes Secondary: Total and nocturnal voids, urgency episodes, severe urgency episodes, frequency-urgency sum per 24 hours,	Primary: The mean reduction in the number of UUI episodes/24 hours was significantly greater in the fesoterodine group than in the tolterodine group (P=0.017) and placebo group (P<0.001). The median percentage reduction in UUI episodes was 100% for fesoterodine. Tolterodine ER also produced a significantly greater improvement in UUI episodes than placebo (P=0.011). The diary-dry rate at week 12 was significantly greater for patients receiving fesoterodine than for those receiving tolterodine ER (64 vs 57.2%; P=0.015) or placebo (45%; P<0.001). The difference between tolterodine ER and placebo in diary-dry rate was also significant

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo			and MVV per void, UPS, OAB-q, and PPBC	(P<0.001). Secondary: Fesoterodine produced a significantly greater increase in MVV per void than tolterodine ER (P=0.005) or placebo (P<0.001). Compared to placebo, fesoterodine also significantly reduced voids, urgency episodes, severe urgency episodes, and frequency-urgency sum per 24 hour (all P<0.001 vs placebo). Fesoterodine did not significantly improve nocturnal voids (P=0.327). Compared to tolterodine ER, total voiding, urgency episodes, severe urgency episodes, and frequency-urgency sum per 24 hours were not statistically different. Compared to placebo, tolterodine ER significantly improved total voids, urgency episodes, severe urgency episodes, and frequency-sum per 24 hours (all P<0.001). The categorical change in PPBC score was significantly more favorable in the fesoterodine group than in patients on placebo (P<0.001) and tolterodine ER (P<0.001). The change between tolterodine ER and placebo was also significant (P<0.001). The categorical change in UPS was significantly more favorable for fesoterodine than placebo (P<0.001) and tolterodine (P=0.014). The difference between tolterodine ER and placebo was NS. Improvements in the OAB-q scores were significantly greater in the fesoterodine than the placebo group on the Symptom Brother scale, total HRQOL scale, and all four HRQOL domains (all P<0.001). In a post-hoc analysis, improvements with fesoterodine were also significantly greater than tolterodine ER on the Symptom Bother (P<0.001) and total HRQOL (P=0.006) scales and the Concern (P=0.008), Coping (P=0.002), and Social Interaction (P=0.019) domains. Six patients (2%) receiving placebo, 28 (4%) receiving tolterodine ER, and 42 (6%) receiving fesoterodine discontinued treatment due to treatment-emergent adverse effects. The most frequent treatment emergent adverse event in the fesoterodine and tolterodine groups were dry mouth (28 vs 16%), headache (6 vs 3%), and constipation (5 vs 4%). Sixteen (2%) of patients in the fesoterodine group had a non-fatal serious adverse events during treatment, two of which were considered related to fesoterodine. One patient with BPH developed urinary retention requiring catheterization.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Kaplan et al.[43] (2011) Fesoterodine ER 4 to 8 mg once daily vs tolterodine ER 4 mg once daily vs placebo	DB, PC, PG, RCT Men and women ≥18 years of age who have self-reported OAB symptoms for ≥3 months and had a mean of at least one UUI episode and ≥8 micturitions per 24 hours in 3-day bladder diary	N=2,417 12 weeks	Primary: Change in UUI episodes from baseline to week 12 Secondary: Change from baseline in micturitions, nocturnal micturitions, urgency episodes, severe urgency episodes, frequency-urgency sum per 24 hours, three-day diary-dry rate, and MVV per micturition	Primary: The median percentage reduction in UUI episodes at week 12 was 100% in all groups; however, the treatment differences between the fesoterodine group and the tolterodine ER group (P=0.0093) and placebo (P=0.0001) were significant. Additionally, the difference between groups was shown as early as week four. Secondary: At week 12, fesoterodine 8 mg had significantly greater mean improvements than patients receiving tolterodine ER for micturitions (P=0.0016), urgency episodes (P<0.0001), severe urgency episodes (P<0.0001), and frequency-urgency sum (P<0.0001). Compared to tolterodine, fesoterodine did not improve nocturnal micturition or MVV. Fesoterodine also significantly improved all diary endpoints compared to placebo at week 12 (all P<0.02). Tolterodine ER significantly improved UUI episodes (P=0.0228), MVV (P=0.0021), and micturitions (P=0.0407) compared to placebo at week 12. The three-day diary-dry rate at week 12 was significantly better in the fesoterodine group vs tolterodine ER and placebo (P=0.0169 and P=0.0003). PPBC, UPS, and OAB-q scores were better at week 12 with fesoterodine compared to both tolterodine ER and placebo. These changes were also better for tolterodine ER compared to placebo. The most frequent treatment emergent adverse events in all groups were dry mouth, constipation, and headache.
Nitti et al.[44] (2013) Mirabegron 100 mg once daily vs	DB, MC, PC, PG, RCT Patients ≥18 years of age, with OAB symptoms for ≥3 months and with an average baseline	N=1,328 12 weeks	Primary: Change from baseline to end of treatment in the mean number of incontinence episodes per 24 hours, change from	Primary: Change from baseline to end of treatment in the mean number of incontinence episodes per 24 hours was -1.63 in the mirabegron 100 mg group, -1.47 in the mirabegron 50 mg group and -1.13 in the placebo group. When compared to placebo the change from baseline was statistically significant in both the mirabegron 100 mg (P<0.05) and 50 group (P<0.05).

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mirabegron 50 mg once daily vs placebo	micturition frequency of ≥8 micturitions/24 hours and ≥3 urgency episodes with or without incontinence during the 3-day micturition diary period		baseline to end of treatment in the mean number of micturitions per 24 hours Secondary: Change from baseline to end of treatment in the mean VVPM, change from baseline to week four in the mean number of incontinence episodes per 24 hours, change from baseline to week four in the mean number of micturitions per 24 hours, change from baseline to final visit in mean level of urgency, change from baseline to final visit in mean number of urgency incontinence episodes per 24 hours, change from baseline to final visit in grade 3 or 4 urgency episodes per 24 hours,	Change from baseline to end of treatment in the mean number of micturitions per 24 hours was -1.75 in the mirabegron 100 mg group, -1.66 in the mirabegron 50 mg group, and -1.05 in the placebo group. When compared to placebo the change from baseline was statistically significant in both the mirabegron 100 mg (P<0.05) and 50 group (P<0.05). Secondary: Change from baseline to end of treatment in the mean VVPM was 18.0 mL in the mirabegron 100 mg group, 18.2 mL in the mirabegron 50 mg group, and 7 mL in the placebo group. When compared to placebo the change from baseline was statistically significant in the mirabegron 100 mg (P<0.05) and 50 group (P<0.05). Change from baseline to week 4 in the mean number of incontinence episodes per 24 hours was -1.18 in the mirabegron 100 mg group, -1.20 in the mirabegron 50 mg group, and -0.72 in the placebo group. When compared to placebo the change from baseline was statistically significant in the mirabegron 100 mg (P<0.05) and 50 group (P<0.05). Change from baseline to week 4 in the mean number of micturitions per 24 hours was -1.37 in the mirabegron 100 mg group, -1.19 in the mirabegron 50 mg group, and -0.77 in the placebo group. When compared to placebo the change from baseline was statistically significant in the mirabegron 100 mg (P<0.05) and 50 group (P<0.05). Change from baseline to final visit in mean level of urgency was -0.21 in the mirabegron 100 mg group, -0.19 in the mirabegron 50 mg group, and -0.08 in the placebo group. When compared to placebo the change from baseline was statistically significant in the mirabegron 100 mg (P<0.05) and 50 group (P<0.05). Change from baseline to final visit in mean number of urgency incontinence episodes per 24 hours was -1.45 in the mirabegron 100 mg group, -1.32 in the mirabegron 50 mg group and -0.89 in the placebo group. When compared to placebo the change from baseline was statistically significant in the mirabegron 100 mg (P<0.05) and 50 group (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			change from baseline to final visit in mean number of nocturia episodes, safety	Change from baseline to final visit in grade 3 or 4 urgency episodes per 24 hours was -1.76 in the mirabegron 100 mg group, -1.57 in the mirabegron 50 mg group, and -0.82 in the placebo group. When compared to placebo the change from baseline was statistically significant in the mirabegron 100 mg (P<0.05) and 50 group (P<0.05). Change from baseline to final visit in mean number of nocturia episodes was -0.57 in the mirabegron 100 mg and mirabegron 50 mg group compared to -0.38 in the placebo group. When compared to placebo the change from baseline was statistically significant in the mirabegron 100 mg (P<0.05) and 50 group (P<0.05). Mirabegron was well tolerated and the incidence of adverse events was similar across all groups. Adverse events reported in the placebo group, mirabegron 50 mg group and mirabegron 100 mg respectively were hypertension (6.6 vs 6.1 vs 4.9%), UTI (1.8 vs 2.7 vs 3.7), headache (2.0 vs 3.2 vs 3.0%), nasopharyngitis (2.9 vs 3.4 vs 2.5%), URI (2.6 vs 2.7 vs 2.1%), diarrhea (1.3 vs 2.3 vs 2.3%), sinusitis (2.2 vs 2.0 vs 2.1%), dry mouth (1.5 vs 0.5 vs 2.1%), constipation (1.8 vs 1.4 vs 1.6%). Serious adverse events were reported in 2.0, 2.5 and 3.2% of patients in the placebo group, mirabegron 50 mg group and mirabegron 100 mg respectively. Treatment discontinuation due to adverse events was reported in 3.8, 4.1 and 4.4% of patients in the placebo group, mirabegron 50 mg group and mirabegron 100 mg respectively.
Chapple et al.[45] (2013) Mirabegron 100 mg once daily vs mirabegron 50 mg once daily vs	DB, MC, RCT Patients ≥18 years of age with OAB symptoms for ≥3 months and with an average baseline micturition frequency of ≥8 micturitions/24 hours and ≥3 urgency episodes	N=2,444 12 months	Primary: Incidence and severity of treatment-emergent adverse events, vital signs and laboratory tests Secondary: Change from baseline in micturition	Primary: The incidence of treatment-emergent adverse events was similar among patients treated with mirabegron 50 mg (59.7%), 100 mg (61.3%) or tolterodine ER (62.6%). Most events were categorized as mild or moderate in severity. The most frequent treatment-related adverse events included hypertension, dry mouth, constipation, and headache, occurring at a similar incidence across all treatment groups, except for dry mouth, which was highest in the tolterodine group. Discontinuations resulting from adverse events were similar between treatment groups, with 6.4, 5.9 and 6.0% of patients treated with mirabegron 50 mg, 100 mg and tolterodine ER 4 mg, discontinuing

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tolterodine ER 4 mg once daily	with or without incontinence during the 3-day micturition diary period		frequency and urgency frequency at one, three, six, nine and 12 months; OAB-q, PPBC and VAS scores, proportion of treatment responders (≥50% decrease from baseline in the incontinence episodes/24 hours or those with zero incontinence episodes at final visit)	treatment, respectively. Urinary retention occurred in one patient each in the mirabegron 50 mg and 100 mg group compared to three patients treated with tolterodine ER. Urinary retention requiring catheterization was reported in one patient receiving mirabegron 100 mg and tolterodine ER. There was a higher incidence of cardiac arrhythmias with tolterodine ER 4 mg (6.0%) compared to mirabegron 50 mg (3.9%) and 100 mg (4.1%). Mean changes from baseline in systolic blood pressure with mirabegron 50 mg, 100 mg and tolterodine were 0.2, 0.4 and -0.5 mm Hg for morning measurements and -0.3, 0.1 and 0.0 mm Hg for evening measurements, respectively. The mean changes in diastolic blood pressure were -0.3, 0.4, and 0.1 mm Hg, respectively for morning measurements and 0.0, 0.1 and 0.6 mm Hg, respectively for evening measurements. There was a higher incidence of neoplasm (benign, malignant and unspecified including cysts and polyps) in the mirabegron 100 mg group (1.3%) compared to the 50 mg group (0.1%) and tolterodine ER 4 mg (0.5%). Secondary: There were similar improvements between treatments with regard to the mean number of micturitions/24 hours (-1.27 for mirabegron 50 mg, -1.41 for mirabegron 100 mg and -1.39 for tolterodine ER 4 mg; P values not reported). Improvements in the mean number of incontinence episodes/24 hours (-1.01 for mirabegron 50 mg, -1.24 for mirabegron 100 mg and -1.26 for tolterodine ER 4 mg) and MVV (17.5 mL for mirabegron 50 mg, 21.5 mL for mirabegron 100 mg and 18.1 mL for tolterodine ER 4 mg) were similar among treatment groups (P values not reported). At the final visit, the proportion of treatment responders (≥50% reduction from baseline in the mean number of incontinence episodes/24 hours was 63.7, 66.3 and 66.8% for patients treated with mirabegron 50 mg, 100 mg and tolterodine ER, respectively; P values not reported). The proportion of patients who reported zero incontinence episodes at the final visit was 43.4, 45.8 and 45.1%, respectively; P values not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Both doses of mirabegron showed numerical improvements on the other secondary efficacy variables including OAB-q symptom bother and QOL, treatment satisfaction, number of nocturia episodes and PPBC.
Khullar et al.[46] (2013) Mirabegron 100 mg once daily vs mirabegron 50 mg once daily vs tolterodine SR 4 mg once daily vs placebo	AC, DB, MC, PC, PG, RCT Patients ≥18 years of age, with OAB symptoms for ≥3 months and an average baseline micturition frequency of ≥8 micturitions/24 hours and ≥3 urgency episodes with or without incontinence during the 3-day micturition diary period	N=1,978 12 weeks	Primary: Change from baseline to end of treatment in the mean number of incontinence episodes per 24 hours, change from baseline to end of treatment in the mean number of micturitions per 24 hours Secondary: Change from baseline to end of treatment in the mean VVPM, change from baseline to week four in the mean number of incontinence episodes per 24 hours, change from baseline to week 4 in the mean number of micturitions per 24 hours, change from baseline to final visit in mean level	Primary: Change from baseline to end of treatment in the mean number of incontinence episodes per 24 hours was -1.46 in the mirabegron 100 mg group, -1.57 in the mirabegron 50 mg group, -1.27 in the tolterodine SR group and -1.17 in the placebo group. When compared to placebo the change from baseline was statistically significant in the mirabegron 100 mg (P<0.05) and 50 group (P<0.05) but not in the tolterodine SR group (P value not reported). Change from baseline to end of treatment in the mean number of micturitions per 24 hours was -1.77 in the mirabegron 100 mg group, -1.93 in the mirabegron 50 mg group, -1.59 in the tolterodine SR group and -1.34 in the placebo group. When compared to placebo the change from baseline was statistically significant in the mirabegron 100 mg (P<0.05) and 50 group (P<0.05) but not in the tolterodine SR group (P value not reported). Secondary: Change from baseline to end of treatment in the mean VVPM was 25.6 mL in the mirabegron 100 mg group, 24.2 mL in the mirabegron 50 mg group, 25.0 mL in the tolterodine SR group and 12.3 mL in the placebo group. When compared to placebo the change from baseline was statistically significant in the mirabegron 100 mg (P<0.05) and 50 group (P<0.05) and tolterodine SR group (P<0.05). Change from baseline to week four in the mean number of incontinence episodes per 24 hours was -1.03 in the mirabegron 100 mg group, -1.04 in the mirabegron 50 mg group, -1.00 in the tolterodine SR group and -0.65 in the placebo group. When compared to placebo the change from baseline was statistically significant in the mirabegron 100 mg (P<0.05) and 50 group (P<0.05) and tolterodine SR group (P<0.05). Change from baseline to week four in the mean number of micturitions per

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			of urgency, change from baseline to final visit in mean number of urgency incontinence episodes per 24 hours, change from baseline to final visit in grade 3 or 4 urgency episodes per 24 hours, change from baseline to final visit in mean number of nocturia episodes, safety	24 hours was -1.29 in the mirabegron 100 mg group, -1.16 in the mirabegron 50 mg group, -1.10 in the tolterodine SR group and -0.77 in the placebo group. When compared to placebo the change from baseline was statistically significant in the mirabegron 100 mg (P<0.05) and 50 group (P<0.05) and tolterodine SR group (P<0.05). Change from baseline to final visit in mean level of urgency was -0.30 in the mirabegron 100 mg group, -0.31 in the mirabegron 50 mg group, -0.29 in the tolterodine SR group and -0.22 in the placebo group (P values not reported). Change from baseline to final visit in mean number of urgency incontinence episodes per 24 hours was -1.33 in the mirabegron 100 mg group, -1.46 in the mirabegron 50 mg group, -1.18 in the tolterodine SR group and -1.11 in the placebo group (P values not reported). Change from baseline to final visit in grade 3 or 4 urgency episodes per 24 hours was -1.96 in the mirabegron 100 mg group, -2.25 in the mirabegron 50 mg group, -2.07 in the tolterodine SR group and -1.65 in the placebo group (P values not reported). Change from baseline to final visit in mean number of nocturia episodes was -0.56 in the mirabegron 100 mg group, -0.41 in the mirabegron 50 mg group, -0.50 in the tolterodine SR group and -0.45 in the placebo group (P values not reported). Mirabegron and tolterodine SR were well tolerated and the incidence of adverse events was similar across all groups. Adverse events reported in ≥2% of the placebo, mirabegron 50 mg group, mirabegron 100 mg and tolterodine SR group respectively included hypertension (7.7 vs 5.9 vs 5.4 vs 8.1%), nasopharyngitis (1.6 vs 2.8 vs 2.8 vs 2.8%), dry mouth (2.6 vs 2.8 vs 2.8 vs 10.1%), headache (2.8 vs 3.7 vs 1.8 vs 3.6%), influenza (1.6 vs 2.2 vs 2.0 vs 1.4%), UTI (1.4 vs 1.4 vs 1.8 vs 2.0%), constipation (1.4 vs 1.6 vs 1.6 vs 2.0%).
Yamaguchi et al.[47] (2014)	AC, DB, PC, RCT Patients ≥20 years	N=1139 12 weeks	Primary: Change in the mean number of	Primary: Mirabegron 50 mg was associated with a significantly greater change from baseline in the mean number of micturitions/24 h compared with placebo

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mirabegron 50 mg once daily vs placebo once daily vs tolterodine 4 mg once daily (as an active comparator)	of age experiencing OAB symptoms for ≥24 weeks		micturitions/24 h from baseline Secondary: Micturition variables related to urgency and/or incontinence and quality-of-life domain scores on KHQ, adverse events	(P<0.001). Secondary: The mean [SD] change from baseline to final assessment for the secondary efficacy variables showed significant improvements for mirabegron vs placebo for number of urgency episodes/24 h (–1.85 [2.555] vs –1.37 [3.191]; P=0.025); number of incontinence episodes/24 h (–1.12 [1.475] vs –0.66 [1.861]; P=0.003); number of urgency incontinence episodes/24 h (–1.01 [1.338] vs –0.60 [1.745]; P=0.008); and volume voided/micturition (24.300 [35.4767] vs 9.715 [29.0864] mL; P<0.001); but not for number of nocturia episodes (–0.44 [0.933] vs –0.36 [1.062]; P=0.277). The percentage of subjects with zero incontinence episodes at the final assessment in the placebo, mirabegron, and tolterodine groups was 39.4, 50.8, and 48.8%, respectively. Treatment with mirabegron for 12 weeks was associated with significant improvements compared with placebo in seven of the nine quality-of-life domain scores in the KHQ. The overall incidence of treatment-related AEs was similar in the mirabegron (24.5%) and placebo (24.0%) groups, but higher in the tolterodine group (34.9%).
Chapple et al.[48] (2015) Mirabegron 50 mg once daily vs placebo	Pooled post hoc analysis Patients with OAB and incontinent at baseline	N=1740 (3 trials) 12 weeks	Primary: Mean change from baseline to final visit (end of treatment) in mean number of incontinence episodes per 24 h and mean number of micturitions per 24 h Secondary: Mean number of urgency incontinence episodes per 24 h, mean number of urgency episodes	Primary: Mirabegron 50 mg resulted in statistically significant improvements from baseline to final visit relative to placebo in mean number of incontinence episodes per 24 h and mean number of micturitions per 24 h (P<0.001). Secondary: Mirabegron 50 mg resulted in statistically significant improvements from baseline to final visit relative to placebo in mean number of urgency episodes per 24 h and mean volume voided per micturition (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			per 24 h, and level of urgency	
Staskin et al.[49] (2009) Oxybutynin 10% topical gel 1 g applied once daily vs placebo	DB, MC, PC, PG, RCT Patients ≥18 years of age with OAB, urge or mixed urinary incontinence with predominance of UUI episodes as well as ≥8 daily urinary voids and ≥4 daily UUI episodes	N=789 12 weeks	Primary: Change in mean number of daily incontinence episodes Secondary: Mean change in urinary frequency, urinary volume per void, number of nocturia episodes, proportion of patients achieving complete urinary continence and safety	Primary: Patients receiving oxybutynin topical gel reported a significantly greater decrease in the mean number of daily incontinence episodes compared to patients receiving placebo (-3.0 vs -2.5; P<0.0001). Secondary: Oxybutynin topical gel was associated with a significant improvement in the mean number of episodes of urinary frequency (-2.7 vs -2.0; P=0.0017) and voided urinary volume compared to placebo (21.0 vs 3.8 mL; P=0.0018). The difference between groups in the number of nocturia episodes did not reach statistical significance (-0.75 daily for oxybutynin topical gel compared to -0.65 daily for placebo; P=0.1372). Complete urinary continence was demonstrated in 27.8% patients receiving oxybutynin topical gel patients compared to 17.3% of patients randomized to placebo (P value not reported). Compared to placebo, oxybutynin topical gel was associated with a higher incidence of dry mouth (6.9 vs 2.8%; P=0.0060) and application site dermatitis (1.8 vs 0.3%; P=0.0358).
Goldfischer et al.[50] (2013) Oxybutynin 3% topical gel 84 g applied once daily vs Oxybutynin 3% topical gel 56 g applied once daily vs	DB, MC, PC, RCT Patients ≥18 years of age with symptoms of urgency and/or mixed UI and a predominance of urgency incontinence for ≥3 months and who had a history of at least 1 to 2 urinary urgency episodes and ≥8 voids per	N=626 12 weeks	Primary: Change from baseline to week 12 in mean number of weekly UI episodes Secondary: Change from baseline to week 12 in daily urinary frequency, average urinary void volume per void, daily UI episodes	Primary: At 12 weeks, the 84 and 56 mg/day arms achieved significantly greater improvement vs placebo in weekly UI episodes (mean change from baseline: -20.4 and -16.4 vs -18.1; P<0.05 and P=0.04, respectively). Secondary: At 12 weeks, the 84 mg/day arm achieved significantly greater improvement vs placebo in daily urinary frequency (-2.6 vs -1.9; P=0.001) and urinary void volume (32.7 vs 9.8; P<0.0001). For oxybutynin gel 56 mg/day, the changes from baseline in these secondary endpoints were not significantly different from placebo. The 84-mg/day arm also reduced the number of daily UI episodes from baseline by a mean of 2.9 episodes, and significant changes from baseline in weekly and daily UI episodes, daily urinary frequency, and urinary void

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo	day; were treatment-naive or had a previous beneficial response to anticholinergic treatment; and, if on anticholinergic medication or any pharmacologic treatment for OAB at screening, were willing to undergo a 2-week washout period.		and change from baseline to week one in these analyses and safety endpoints	volume were achieved within one week after the start of treatment. The most common treatment-emergent adverse events (>2% of patients) that occurred significantly more often in patients receiving oxybutynin gel than in those receiving placebo, were dry mouth and application site erythema.
Anderson et al.[51] (1999) Oxybutynin ER 5 to 30 mg daily vs oxybutynin IR 5 mg 1 to 4 times/day	AC, DB, MC, RCT Community dwelling men and women with urge incontinence or mixed incontinence with a primary urge component who had at least 6 urge incontinence episodes a week when not taking medication (who had previously responded to oxybutynin)	N=97 Not specified	Primary: Urge incontinence episodes/week Secondary: Proportion of participants achieving elimination of urge incontinence episodes, number of incontinence episodes, proportion of those achieving continence, adverse events	Primary: The mean number of weekly urge incontinence episodes decreased from 27.4 to 4.8 in the ER group and from 23.4 to 3.1 in the IR group (P=0.6). The percentage reduction in weekly urge incontinence episodes was 84% in the ER group and 88% in the IR group (P=0.71). Secondary: Of the participants, 52% in the ER group and 51% in the IR group had no urge incontinence episodes at the end of treatment (P=0.7). Total incontinence (urge, stress and other) episodes decreased from 29.3 to 6.0 in the ER group and from 26.3 to 3.8 in the IR group from baseline to the end of the study (P=0.6). The percentage reduction in any incontinence episodes was 82% in the ER group and 88% in the IR group (P=0.5). The proportions of patients who were totally continent was 41% in the ER group and 40% in the IR group (P=0.9). Normal void frequency increased 54% in the ER group and 17% in the IR group (P<0.001). At least one anticholinergic event occurred in 87% of patients in the ER group and 94% of patients in the IR group. The most common

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				anticholinergic event in both groups was dry mouth (68% of the ER group and 87% of the IR group; P=0.04). Fewer participants reported moderate or severe dry mouth with ER oxybutynin (25 vs 46%; P=0.03). There was no significant difference among the treatment groups for other anticholinergic adverse events. There were few reports of moderate to severe dry mouth at the 5 mg dose, and there was a trend in both groups toward increasing frequency of dry mouth as doses increased.
Barkin et al.[52] (2004) Oxybutynin ER 15 mg daily vs oxybutynin IR 5 mg three times daily	DB, MC, PG, RCT Men and women >18 years of age with UUI who demonstrated >7 UI episodes/week and >8 voids/day	N=123 9 weeks	Primary: Void frequency, UI episodes, treatment-related changes in QOL as assessed by the IIQ and UDI, and adverse events Secondary: Not reported	Primary: The mean number of incontinence episodes/week decreased from 24.3 to 10.4 in the ER group (P<0.001 vs baseline) and from 23.0 to 6.1 in the IR group (P<0.001 vs baseline). There was no significant difference among the treatment groups (P=0.404). The mean voluntary micturition episodes/day decreased from 11.4 to 9.6 in the ER group (P<0.001 vs baseline) and from 11.0 to 8.6 in the IR group (P<0.001 vs baseline). There was no significant difference among the treatment groups (P=0.286). There was no significant difference among the treatment groups in mean urine voided/micturition (P=0.533), incidence of urgency (P=0.116), or severity of urgency (P=0.255). There was a significant reduction from baseline in the mean number of pads/day in the ER group (2.3. to 1.7; P<0.001); however, there was no change from baseline in the IR group (2.4 to 1.9; P=NS). Patients in both treatment groups demonstrated significant improvements from baseline in mean IIQ scores (ER; P<0.001, IR; P<0.001) and mean UDI scores (ER; P<0.001, IR; P<0.001). There were no significant differences among the treatment groups. The most frequently reported adverse events in the ER and IR oxybutynin groups were dry mouth (68 and 72%, respectively) and dry throat (31 and 37%, respectively). There was no significant difference in the incidence of moderate and severe dry mouth among the treatment groups (ER, 26% and IR, 42%). More patients in the ER group rated their medication tolerable compared to the IR group (P=0.020). More patients discontinued treatment

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				in the IR oxybutynin group than in the ER oxybutynin group (P=0.047), primarily due to adverse events. Secondary: Not reported
Birns et al.[53] (2000) Oxybutynin ER 10 mg once daily vs oxybutynin IR 5 mg twice daily	DB, MC, PC, RCT Patients 18 to 76 years of age with detrusor instability or detrusor hyperreflexia whose symptoms were stabilized on conventional oral oxybutynin tablets (5 mg twice daily) for 2 weeks	N=130 6 weeks	Primary: Proportion of patients with daytime continence at completion of the study Secondary: Percentage of patients with nighttime continence, median change in the number of voluntary daytime voids, voluntary nighttime voids, daytime episodes of incontinence and nighttime episodes of incontinence from the week preceding treatment to the completion of the study, adverse events	Primary: At the completion of the study, 53% of patients receiving oxybutynin ER were continent during the day compared to 58% of patients receiving oxybutynin IR (P=0.62). Secondary: There was no significant difference between the treatment groups in the percentage of patients with nighttime continence at the completion of the study or the median change in the number of voluntary daytime voids, voluntary nighttime voids, daytime episodes of incontinence and nighttime episodes of incontinence from the week preceding treatment to the completion of the study. Dry mouth and vision abnormalities were more common in patients receiving oxybutynin ER than in those receiving oxybutynin IR; however, this was NS (P=NS).
Versi et al.[54] (2000) Oxybutynin ER	DB, MC, PG, RCT Patients with 7 to 45 urge incontinence	N=226 Duration not specified	Primary: Number of incontinence episodes and total	Primary: Urge incontinence episodes decreased from 18.6 to 2.9/week with oxybutynin ER (83% reduction; P<0.001) and from 19.8 to 4.4/week with oxybutynin IR from baseline (76% reduction; P<0.001). There was no

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
5 to 20 mg/day vs oxybutynin IR 5 to 20 mg/day	episodes/week and ≥4 days of incontinence/week who had previously responded to treatment with antimuscarinic drugs		incontinence episodes Secondary: Not reported	significant difference between the treatment groups (P=0.36). Total incontinence episodes decreased from 20.2 to 3.5/week with oxybutynin ER (81% reduction; P<0.001) and from 22.4 to 5.4/week with oxybutynin IR from baseline (75% reduction; P<0.001). There was no significant difference between the treatment groups (P=0.41). There was no significant difference in anticholinergic adverse events among the treatment groups. Dry mouth occurred in 47.7% and 59.1% of patients receiving oxybutynin ER and IR, respectively. Secondary: Not reported
Nilsson et al.[55] (1997) Oxybutynin ER 10 mg daily for 60 days vs oxybutynin IR 5 mg twice daily for 60 days	XO Female patients 37 to 65 years of age with symptoms of urge incontinence and detrusor instability	N=17 120 days	Primary: Frequency of voluntary voiding, the maximal volume of urine/single void, and the total volume of voluntarily voided urine/24 hour Secondary: Not reported	Primary: The frequency of voids/24 hour was reduced by 23% with oxybutynin ER and by 24% with oxybutynin IR (P=0.51). Treatment with oxybutynin ER resulted in a 28% reduction in the total weight of pads compared to a 21% reduction with oxybutynin IR (P=0.80). The total volume of voluntary voided urine/day increased by 15% with both treatments (P=0.75), and the maximal volume of urine/void increased by 26% and 34% with oxybutynin ER and oxybutynin IR, respectively (P=0.95). There were no significant differences in adverse events among the treatment groups, including dry mouth (P=0.41), headache (P=1.00), dyspepsia (P=0.26), or vision abnormality (P=0.32). Secondary: Not reported
Appell et al.[56] (2001) Oxybutynin ER 10 mg daily	DB, PG, MC, RCT Participants with OAB who had between 7 and 50	N=378 12 weeks	Primary: Number of urge incontinence episodes/week, number of total	Primary: The number of urge incontinence episodes/week decreased from 25.6 to 6.1 in the oxybutynin group and from 24.1 to 7.8 in the tolterodine group (P=0.03).

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vs tolterodine IR 2 mg twice daily	episodes of urge incontinence/week and 10 or more voids/24 hours		incontinence episodes/week and micturition frequency episodes/week Secondary: Not reported	The number of total incontinence episodes/week decreased from 28.6 to 7.1 in the oxybutynin group and from 27.0 to 9.3 in the tolterodine group (P=0.02). Micturition frequency episodes/week decreased from 91.8 to 67.1 in the oxybutynin group and from 91.6 to 71.5 in the tolterodine group (P=0.02). Both drugs improved symptoms of OAB significantly from baseline to the end of the study as assessed by the three main outcome measures (P<0.001). Overall, 92.6 and 95.3% of the patients in the oxybutynin and tolterodine groups, respectively, had fewer incontinence episodes at the end of the study period compared to baseline. The incidence of dry mouth was similar among the treatment groups (28.1% for oxybutynin and 33.2% for tolterodine; P=0.32). Moderate to severe dry mouth was also similar among the treatment groups (10.2% for oxybutynin and 10.9% for tolterodine; P=0.87). Other adverse events were similar among the treatment groups. Overall, the discontinuation rates for adverse events were 7.6% in the oxybutynin group and 7.8% in the tolterodine group (P=0.99). Secondary: Not reported
Sand et al.[57] (2004) Oxybutynin ER 10 mg once daily vs tolterodine IR 2 mg twice daily	DB, RCT Women with urge or mixed incontinence (≥7 and ≤50 urge incontinence episodes/week and ≥10 voids/24 hours)	N=315 12 weeks	Primary: Number of urge incontinence episodes, total incontinence, micturition frequency, tolerability Secondary: Not reported	Primary: The number of urge incontinence episodes decreased from 28.1 to 6.2/week in the oxybutynin ER group compared to a reduction from 28.9 to 8.5/week in the tolterodine IR group (P=0.038). Total incontinence episodes decreased from 25.2 to 7.3/week in the oxybutynin ER group compared to a reduction from 25.1 to 10.1/week in the tolterodine IR group (P=0.030). Micturition frequency decreased from 91.7 to 68.0/week in the oxybutynin ER group compared to a reduction from 91.6 to 71.2/week in the tolterodine IR group (P=0.272).

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				There was no significant difference in dry mouth, central nervous system events or other adverse events among the treatment groups. Secondary: Not reported
Diokno et al.[58] (2003) Oxybutynin ER 10 mg daily vs tolterodine ER 4 mg daily	AC, DB, MC, RCT Women ≥18 years of age with OAB who documented 21-60 UUI episodes/week and ≥10 voids/day	N=790 12 weeks	Primary: Mean weekly UUI episodes, weekly total incontinence episodes and weekly micturition frequency, adverse events Secondary: Not reported	Primary: The mean weekly episodes of UUI decreased from 37.1 to 10.8 in the oxybutynin group and from 36.7 to 11.2 in the tolterodine group (P=0.28). The mean number of total incontinence episodes decreased from 43.4 to 12.3 in the oxybutynin group and from 42.4 to 13.8 in the tolterodine group (P=0.08). Patients receiving oxybutynin had a greater decrease in the mean weekly micturition frequency compared to tolterodine participants (P=0.003). The proportion of participants who reported total dryness (no incontinence episodes) in their last seven-day 24-hour voiding diary was 23.0% in the oxybutynin group compared to 16.8% in the tolterodine group (P=0.03). The proportion of participants who reported no UUI episodes at the last assessment was 26.7% in the oxybutynin group compared to 20.9% in the tolterodine group (P=0.06). Dry mouth was more common in the oxybutynin group than in the tolterodine group (29.7 vs 22.3%, respectively; P=0.02). Most reports of dry mouth events were mild. Other anticholinergic adverse events (constipation, impaired urination-retention, and blurred vision) and central nervous system adverse effects (dizziness, somnolence, depression, and confusion) occurred at similar frequencies in each group. Adverse events led to discontinuation of study medication by 20 patients receiving oxybutynin and 19 receiving tolterodine. Secondary: Not reported
Reinberg et al.[59]	OL	N=132	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2003) Oxybutynin ER 5 mg/day vs tolterodine ER 2 mg/day vs tolterodine IR 2 mg/day	Pediatric patients with a history of non-neurogenic diurnal urinary incontinence and symptoms of OAB	Duration not specified	Urinary frequency, incontinence and safety Secondary: Not reported	Oxybutynin ER led to a greater reduction in urinary frequency compared to tolterodine IR (P<0.01). Both oxybutynin ER and tolterodine ER were significantly better than tolterodine IR in improving symptoms of diurnal incontinence and urinary frequency (P<0.01 and P<0.05, respectively). Oxybutynin ER was significantly more effective than tolterodine ER in completely resolving diurnal incontinence (P<0.05). There were no significant differences in the peripheral or central nervous system anticholinergic side effects among the treatment groups. Secondary: Not reported
Nelken et al.[60] (2011) Oxybutynin IR 5 mg twice daily vs estradiol vaginal ring 7.5 µg/day	PRO, RCT Women who had ≥10 voids in a 24 hour period, as recorded in a 72 hour voiding diary, and were postmenopausal	N=59 12 weeks	Primary: Change from baseline in number of daily voiding episodes Secondary: Change in vaginal pH levels, vaginal maturation index, and QOL scores, as assessed by the UDI-6 and the IIQ-7	Primary: After 12 weeks, both groups had a significant decrease in the number of daily voids (14.7 to 11.7 for oxybutynin [P=0.003] and 14.9 to 10.4 for estradiol ring [P<0.001]). The difference between groups was not statistically significant. Secondary: There was a significant decrease in UDI-6 (12.1 to 9.4 for oxybutynin [P=0.003] and 11.4 to 7.8 for estradiol [P<0.001]) and IIQ-7 (14.7 to 11.3 for oxybutynin [P=0.02] and 13.2 to 8.1 for estradiol [P<0.001]) scores in both treatment groups. Mean vaginal pH levels in the oxybutynin group remained unchanged after 12 weeks of treatment, but those who received the estradiol ring had a significant decrease in mean pH (6 to 4.9; P=0.002). Mean maturation index did not significantly change in the oxybutynin group, whereas mean maturation index increased significantly after 12 weeks of therapy with an estradiol ring (24.3 to 70.1; P<0.001). Dry mouth, constipation, and blurry vision occurred significantly more in patients who received oxybutynin, whereas more women in the estradiol

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				group reported vaginal discharge.
Davila et al.[61] (2001) Oxybutynin transdermal 2 to 4 patches applied twice weekly vs oxybutynin IR 5 to 7.5 mg orally two or three times daily	DB, MC, PC, RCT Patients ≥18 years of age with a history of urge or mixed urinary incontinence with a predominance of urge symptoms who had symptomatic improvement during a minimum of 6 weeks of oral oxybutynin	N=76 6 weeks	Primary: Average number of daily incontinence episodes, patient-completed VAS for efficacy, dry mouth on an anticholinergic symptoms questionnaire, cystometric comparisons Secondary: Not reported	Primary: The average daily incontinence episodes were reduced by approximately five episodes in both groups (P<0.0001), with no significant difference between transdermal and oral therapy. The change in the mean VAS score for each group was 5.8 vs 6.0 cm for the transdermal and oral groups, respectively (P<0.0001). The difference in mean VAS score between transdermal and oral therapy was 0.1 cm (P=0.9). Dry mouth occurred in 38% of patients in the transdermal group compared to 94% of patients in the oral group (P<0.001). Blurred vision, dizziness, drowsiness, palpitations, nausea and impotence were comparable between the groups. Average bladder volume at first detrusor contraction increased by 66 mL in the transdermal (P<0.0055) and 45 mL in the oral groups (P=0.1428). There was no significant difference among the transdermal and oral groups (P=0.57). Average maximum cystometric capacity increased 53 and 51 mL in the transdermal (P<0.0011) and the oral (P<0.0538) groups, respectively. Post-void residual volume increased by an average of 13 and 16 mL in the oral and transdermal groups, respectively (P=NS). The most frequent treatment related adverse events were dry mouth, constipation, somnolence, dizziness, blurred vision and impaired urination, which occurred more frequently in the oral group. Secondary: Not reported
Dmochowski et al.[62] (2003)	DB, RCT Patients ≥18 years of age who were	N=361 12 weeks	Primary: Change from baseline in the number of	Primary: There was a significant reduction in the number of urinary incontinence episodes/day in patients treated with OXY-TDS compared to placebo (median change -3 vs -2, respectively; P=0.0137). There was a significant

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Oxybutynin transdermal delivery system (OXY-TDS) 3.9 mg/day applied twice weekly vs tolterodine ER (TOL-LA) 4 mg daily vs placebo	receiving pharmacologic treatment for OAB and who had a beneficial response to the pre-study treatment		incontinence episodes/day, average daily urinary frequency, average urinary volume/void, and changes in the QOL instruments Secondary: Not reported	reduction in the number of urinary incontinence episodes/day in patients treated with TOL-LA compared to placebo (median change -3 vs -2, respectively; P=0.0011). There was no significant difference between OXY-TDS and TOL-LA in the reduction of incontinent episodes (P=0.2167). The reduction in incontinence episodes corresponded to a 75% improvement in the OXY-TDS group, 75% in the TOL-LA group, and 50% in the placebo group. Complete continence was achieved by 39% of patients in the OXY-TDS group, 38% of patients in the TOL-LA group, and 22% of patients in the placebo group (both, P=0.014 vs placebo). The mean decrease in average daily urinary frequency was -1.9 micturitions/day with OXY-TDS (P=0.1010 vs placebo) -2.2 micturitions/day with TOL-LA (P=0.0025 vs placebo), and -1.4 micturitions/day with placebo. There was no significant difference between OXY-TDS and TOL-LA (P=0.2761). The median increases in average urinary volume/void was 24 mL with OXY-TDS (P=0.0010 vs placebo), 29 mL with TOL-LA (P=0.0017 vs placebo) and 5.5 mL in the placebo group. There was no significant difference between OXY-TDS and TOL-LA (P=0.7690). The patients' Global Assessment of Disease State scores were significantly improved with OXY-TDS (P=0.0106) and TOL-LA (P=0.0001) compared to placebo. There was no significant difference between OXY-TDS and TOL-LA (P=0.1861). The total IIQ scores improved significantly with OXY-TDS (P=0.0018) and TOL-LA (P=0.0045) compared to placebo. Significant improvements in irritative symptoms of the UDI questionnaire were also observed with OXY-TDS (P=0.0156) and TOL-LA (P=0.0010) compared to placebo. The most common treatment-related adverse events in the OXY-TDS group were application site reactions, including erythema (8.3%) and pruritus (14.0%). Dry mouth (4.1 vs 1.7% with placebo; P=0.2678) and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				constipation (3.3%) were also reported. Adverse events led to treatment discontinuation in 10.7% of patients receiving OXY-TDS. Anticholinergic adverse events were the most common treatment-related events in the TOL-LA group (13.0%). Dry mouth occurred at a greater rate with TOL-LA (7.3%) than placebo (1.7%; P=0.0379). Constipation occurred in 5.7% of TOL-LA patients. Adverse events led to treatment discontinuation in 1.6% of patients receiving TOL-LA. Secondary: Not reported
Metello et al.[63] (2007) Solifenacin 5 mg once daily	OL Women ≥18 years of age with OAB symptoms (≥8 voids/24 hours and ≥1 incontinence episode/24 hours) for ≥3 months who had either not received any previous medication or who had been previously unsuccessfully treated with trospium	N=40 30 days	Primary: Patient self-assessment of improvement after 30 days using the USS in both treatment groups Secondary: Reduction of the daily number of voids and urgency or involuntary leakage episodes	Primary: After 30 days of therapy, treatment with solifenacin led to a significant improvement in USS scores when assessed in all patients (P<0.001). There was no significant difference in USS scores among patients who were drug naïve compared to those who had previously failed trospium. Overall 16% of patients experienced no improvement, 13.5% had mild improvement and 69.5% had great improvement. Secondary: Treatment with solifenacin resulted in a significant reduction in urgency episodes, involuntary leakage episodes, and number of voids/24 hours when assessed in all patients (P<0.001). There was no significant difference in these endpoints among patients who were drug naïve compared to those who had previously failed trospium. Overall, 16% of patients had no improvement in the number of involuntary leakage episodes, 11% of patients had mild improvement and 73% of patients had great improvement. For daily urgency episodes, 13.5% of patients had no improvement, 27.0% had a mild reduction, and 59.0% had a great reduction.
Chancellor et al.[64] (2008) Solifenacin 5 to 10 mg once daily	MC, OL Patients ≥18 years of age with symptoms of OAB	N=441 12 weeks	Primary: Change in urgency episodes compared to pre-washout (when patients	Primary: The mean change in the number of urgency episodes/24 hours was −3.4 from pre-washout to study end (P<0.001). The median percent change was -75%.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	for ≥3 months who had been treated with tolterodine ER 4 mg for ≥4 weeks, and wished to switch therapy because of a lack of sufficient subjective improvement in urgency (≥3 urgency episodes/24 hours)		were receiving tolterodine ER 4 mg) Secondary: Change in micturitions, incontinence episodes, nocturia episodes, and nocturnal voids compared to pre-washout and post-washout; PRO using the PPBC and the OAB-q was also assessed	Secondary: The mean change in micturitions, incontinence episodes, nocturia episodes, and nocturnal voids from pre-washout to study end was –1.6, –1.9, –0.7, and –0.8, respectively (all, P<0.001). The median percent change from pre-washout was –15.0% for the number of micturitions, –96.4% for incontinence episodes, –40.8% for nocturia episodes, and –40.0% for nocturnal voids. The median change in micturitions, incontinence episodes, nocturia episodes, and nocturnal voids from post-washout to study end was –2.0 (-19.5%), –2.0 (-100%), –0.7 (-43.7%), and –0.7 (-40.0%), respectively (all, P<0.001). The mean PPBC score decreased from pre-washout by 1.2 points (95% CI, –1.3 to –1.1; P<0.001) and from post-washout by 1.2 points (95% CI, –1.3 to –1.0; P<0.001). Patients had significant improvements on the OAB-q at study end compared to both pre-washout and post-washout (all, P<0.001). The mean changes in OAB-q scores at study end relative to pre-washout and post-washout were –27.4 and –29.5, respectively, for symptom bother; 23.1 and 27.9 for coping; 25.2 and 29.7 for concern; 21.9 and 24.5 for sleep; 11.1 and 15.0 for social interaction; and 21.1 and 25.2 for total HRQOL. The most common adverse events were dry mouth (17.5%), constipation (11.6%), and blurred vision (2.3%).
Zinner et al.[65] (2008) Solifenacin 5 to 10 mg once daily	MC, OL Patients ≥18 years of age with OAB symptoms for ≥3 months who were previously treated with tolterodine ER 4 mg/day for ≥4 weeks, and who wished to switch to	N=441 12 weeks	Primary: WPAI-SHP, HUI, and a resource utilization questionnaire administered at pre-washout and week 12 Secondary: Not reported	Primary: Patients reported significantly fewer physician office visits (0.2 vs 1.2; P<0.0001), UTIs (0.1 vs 0.2; P<0.0001), and pads/diapers (7.9 vs 10.7/week; P=0.0009) with solifenacin compared to the pre-washout period. There were no significant differences in the numbers of skin rashes or falls reported at end of the study compared to pre-washout. Patients reported using fluid management as a behavioral management strategy on fewer days with solifenacin compared to when they were

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	solifenacin due to lack of sufficient improvement in urgency episodes while receiving tolterodine (≥3 urgency episodes/24 hours)			taking tolterodine ER 4 mg/day (14.2 vs 18.0 days; P=0.0381). There were no significant differences in other behavioral management strategies. Based on the WPAI-SHP, patients who were working reported a reduction in percent of work time missed (0.2 vs 2.1%; P=0.0017), a reduction in percent of impairment while working (11.3 vs 22.9%; P<0.0001), a reduction in percent of overall work impairment (11.9 vs 24.0%; P<0.0001), and a reduction in percent of activity impairment (18.4 vs 31.6%; P<0.0001) after 12 weeks of therapy with solifenacin. There was no significant difference in the health utility score between pre-washout and end of study based on the HUI 2/3. Secondary: Not reported
Wong et al.[66] (2009) Solifenacin 5 to 10 mg once daily	OL Women with OAB who had previously taken oxybutynin IR without benefit or developed intolerable adverse effects	N=9 12 weeks	Primary: Daytime frequency, nocturia, number of incontinence episodes, average urinary voided volume, and quality-of-life (OAB-q short form symptom bother) Secondary: Not reported	Primary: The mean number of daytime micturitions was reduced from 11.4 to 7.3 with solifenacin (P=0.0002). The mean number of nocturia episodes was reduced from 2.8 to 0.9 with solifenacin (P=0.0004). The total number of incontinence episodes/day was reduced from 4.9 to 1.9 with solifenacin (P=0.02). The mean micturition volumes were increased from 160 to 280 ml with solifenacin (P=0.002). The symptom severity domain of the OAB-q showed a value of 60.8% at baseline and 32.0% at 12 weeks with solifenacin (P=0.001). The HRQOL domain of the OAB-q showed a value of 45.5% at baseline and 73.3% at 12 weeks with solifenacin (P=0.0006). Secondary: Not reported
Garely et al.[67] (2006)	MC, OL	N=2,225	Primary: PPBC scale, OAB-	Primary: The mean PPBC scale score decreased significantly to 2.9 (mean change,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Solifenacin 5 to 10 mg once daily	Patients ≥18 years of age with OAB (urgency, urge urinary incontinence, frequency, and/or nocturia for ≥3 months)	12 weeks	q, and a VAS for the degree of bother caused by individual OAB symptoms Secondary: Not reported	-1.4; 95% CI, -1.49 to -1.38; P<0.001), which corresponded to a perception of "some minor problems" associated with their bladder condition. There were significant improvements in all of the OAB-q scoring domains (symptom severity, coping, concern, sleep, social interaction, and overall HRQoL) with solifenacin (all subscales, P<0.001). Significant improvements in urinary urgency, urge urinary incontinence, frequency, or nocturia were observed with solifenacin on the VAS. For urinary urgency, 88.2% of patients indicated less bothersome symptoms; for urge urinary incontinence, 89.4% of patients indicated less bothersome symptoms; for frequency, 88.3% of patients indicated frequency was less bothersome; for nocturia, 87.5% of patients indicated that nocturia was less bothersome. Anticholinergic adverse events occurred as follows: dry mouth (21.4%), constipation (13.3%), headache (3.4%), blurred vision (2.6%), nausea (1.8%), dyspepsia (1.5%), and dry eyes (1.3%). A total of 9.7% of patients discontinued treatment due to an adverse event. The most frequently reported treatment-emergent adverse events that resulted in discontinuation were dry mouth (1.9%) and constipation (1.9%). Secondary: Not reported
Haab et al.[68] (2005) Solifenacin 5 to 10 mg once daily	ES, OL Patients ≥18 years of age with symptoms of OAB (≥8 micturitions/24 hours and either ≥1 urgency episode/24 hours or ≥1 incontinence episode/24 hours) for >3 months	N=1,633 40 weeks	Primary: Safety and tolerability Secondary: Efficacy	Primary: Dry mouth occurred in 10% of patients receiving solifenacin 5 mg and 17% of patients receiving solifenacin 10 mg. The discontinuation rate due to dry mouth was 0.4%. After 40 weeks, 85% of patients indicated satisfaction with solifenacin tolerability, and 99% of patients rated solifenacin tolerability as either ‘‘satisfactory’’ or ‘‘acceptable.’’ Secondary: The mean number of urgency episodes/24 hours decreased by 63%. For patients with ≥1 episode of urgency/24 hours at baseline, 40% had no

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				symptomatic urgency at end point. The mean number of incontinence episodes/24 hours decreased by 66%. For patients with ≥1 episode of incontinence at baseline, 58% were continent at end point. The mean number of micturitions/24 hours decreased by 2.97 (23%) with solifenacin. A total of 39% of patients had <8 micturitions/24 hours by study end. The mean number of nocturia episodes/24 hours decreased by 32% and the mean volume voided/micturition increased by 31%.
Bolduc et al.[69] (2010) Solifenacin 0.15 to 0.25 mg/kg once daily	OL, PRO Children with OAB (neurogenic and non-neurogenic) who failed intensive medical and behavioral therapy	N=72 ≥3 months	Primary: Efficacy for continence, safety and tolerability Secondary: Not reported	Primary: Subjective continence improved in all cases. Patients/parents rated improvement as 100% (complete dryness in 24 patients, >90% improvement in 42 patients, and a 50 to 89% decrease in six patients). MVV and cystometric bladder capacity improved without deterioration in compliance (P<0.001). Maximum detrusor contraction pressure decreased overall as well (P<0.0001). There were no significant differences in response in neurogenic vs non-neurogenic cases. The mean PPBC score at baseline was 4.9 (mod-severe problems), which significantly improved to 1.8 (minor problems) at study end (P<0.0001). No adverse events were reported in 50 patients (70%). The most common adverse event was dry mouth (n=14). Secondary: Not reported
Chapple et al.[70] (2006) Solifenacin 5 to 10 mg once daily vs	DB, MC, PC, RCT (Pooled analysis) Patients ≥18 years of age with OAB (≥8 micturitions/24 hours, and either a	N=2,848 (4 trials) 12 weeks	Primary: Urgency episodes (mean absolute values and median percentage values), incontinence episodes,	Primary: Treatment with solifenacin 5 and 10 mg resulted in a -2.9 (-66.1%) and -3.4 (-70.0%) reduction in urgency episodes, respectively, compared to a -2.0 (-40.0%) reduction with placebo (P<0.001). Treatment with solifenacin 5 and 10 mg resulted in a -1.5 (-100%) and -1.8 (-100%) reduction in incontinence episodes, respectively compared to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo	mean of ≥1 incontinence episode/24 hours or a mean of ≥1 urgency episode/24 hours)		micturition frequency, nocturia episodes/24 hours, and volume voided/micturition Secondary: Not reported	a -1.1 (-63.6%) reduction with placebo (P<0.001). The frequency of micturition was significantly reduced with solifenacin 5 mg (-2.3; -19.4%) and 10 mg (-2.7; -22.5%) compared to placebo (-1.4; -12.0%; P<0.001). The number of nocturia episodes were significantly reduced with solifenacin 5 mg (-0.6; -35.5%) and 10 mg (-0.6; -36.4%) compared to placebo (-0.4; -25.0%; P<0.05 and P<0.001 for solifenacin 5 and 10 mg, respectively). The volume voided/micturition increased significantly with solifenacin 5 mg (32.3 mL; 19.0%) and 10 mg (42.5 mL; 25.7%) compared to placebo (8.5 mL; 3.1%; P<0.001). The most common adverse events were dry mouth, constipation, and blurred vision. The incidence of dry mouth was higher in the 10 mg solifenacin group compared to the 5 mg group. The numbers of patients discontinuing treatment due to adverse events were as follows: 4.4, 2.8, and 6.8% with placebo, solifenacin 5 mg and solifenacin 10 mg. Secondary: Not reported
Abrams et al.[71] (2005) Solifenacin 5 to 10 mg once daily vs placebo	DB, MC, PC, RCT (Pooled analysis) Subgroup of patients >18 years of age with symptoms of OAB (≥8 micturitions/24 hours or ≥1 urgency episode/24 hours) who did not experience incontinence episodes at baseline	N=975 (4 trials) 12 weeks	Primary: Urgency episodes, micturition frequency, and nocturia episodes/24 hours, and volume voided/micturition Secondary: Not reported	Primary: The mean change from baseline in urgency episodes/24 hours (-3.2, -3.2, -2.1), micturition frequency/24 hours (-2.6, -2.8, -1.6), and volume voided/micturition (24.9 mL, 33.9 mL, 7.0 mL) were significantly greater with solifenacin 5 and 10 mg than placebo, respectively (all P<0.001). The mean change from baseline in nocturia episodes/24 hours was significantly greater for solifenacin 10 mg than placebo (P<0.01). The percentage of patients with resolution of urgency (36.6, 32.9, 24.6%) and normalization of micturitions (29, 34.7, 18.5%) was significantly greater with solifenacin 5 mg and solifenacin 10 mg compared to placebo, respectively (P<0.05 to P<0.001). The percentage of patients with resolution of nocturia (14.1, 20.9, 12.8%) was significantly greater with solifenacin 10 mg compared to placebo (P<0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Dry mouth was reported in 3.6, 10.8, and 24.4% of patients receiving placebo, 5 mg solifenacin, and 10 mg solifenacin, respectively. The incidence of constipation was 1.3, 4.0, and 12.2% with placebo, 5 mg, and 10 mg, respectively. Discontinuations due to adverse events for the solifenacin 5 mg group (2.8%) and solifenacin 10 mg group (7.8%) were comparable with or less than that of the placebo group (6.2%). Secondary: Not reported
Millard et al.[72] (2006) Solifenacin 5 to 10 mg once daily vs placebo	DB, MC, PC, RCT (Pooled analysis) Subgroup of patients ≥18 years of age with severe OAB (>3 incontinence episodes/24 hour, >8 urgency episodes/24 hours, or >13 micturition episodes/24 hours)	N=2,848 (4 trials) 12 weeks	Primary: Responder rates, urgency episodes, incontinence episodes, micturition, frequency, nocturia episodes/24 hours, and volume voided/micturition Secondary: Not reported	Primary: For those with >3 incontinence episodes/24 hours, the percentage of patients who were continent at study end point was significantly higher with solifenacin 5 mg (28.4%; P<0.01) and 10 mg (30.5%; P<0.001) compared to placebo (15.3%). The mean change in the number of episodes of incontinence and urgency, the frequency of micturitions and volume voided/micturition was significantly greater with solifenacin 5 mg (P<0.01) and 10 mg (P<0.001) than with placebo. For those with >8 urgency episodes/24 hours, the percentage of patients with resolution of urgency at study end point was significantly higher with solifenacin 5 mg (12.4%; P<0.01) and 10 mg (13.9%; P<0.001) compared to placebo (4.6%). The mean change in the number of episodes of incontinence and urgency, the frequency of micturitions and volume voided/micturition was significantly greater with solifenacin 10 mg compared to placebo (P<0.001). For solifenacin 5 mg, the mean change for all efficacy parameters was significantly greater than placebo (P<0.05; except micturition frequency/24 hours). For those with >13 micturitions/24 hours, the percentage of patients who achieved normalization of micturition frequency (<8 micturitions/24 hours) at study end point was significantly higher with solifenacin 10 mg (13.3%; P<0.001) compared to placebo (4.0%). There was no significant difference between solifenacin 5 mg and placebo. The mean change in the number of episodes of incontinence and urgency, the frequency of micturitions and volume voided/micturition was significantly greater with solifenacin 5 mg (P<0.05) and 10 mg (P<0.001) compared to placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The incidence of adverse events was comparable among the treatment groups. Dry mouth, constipation, UTI, blurred vision, and nausea occurred at a higher incidence with solifenacin 5 or 10 mg than with placebo. Discontinuations due to adverse events occurred in 4.1, 7.5, and 4.8% of patients in the solifenacin 5 and 10 mg and placebo groups, respectively. Secondary: Not reported
Wagg et al.[73] (2006) Solifenacin 5 to 10 mg once daily vs placebo	DB, MC, PC, RCT (Pooled analysis) Subgroup of patients ≥65years of age with OAB (≥8 micturitions/24 hours, and either a mean of ≥1 incontinence episode/24 hours or a mean of ≥1 urgency episode/24 hours)	N=1,554 (5 trials) 12 to 40 weeks	Primary: Urgency episodes (mean absolute values and median percentage values), incontinence episodes, micturition frequency, nocturia episodes/24 hours, and volume voided/micturition Secondary: Not reported	Primary: In the 12-weeks studies, elderly patients had significantly greater decreases in the mean number of incontinence episodes/24 hours with solifenacin 5 and 10 mg compared to placebo (P=0.013 and P<0.001, respectively). The median change in the number of incontinence episodes/24 hours was -1.0 (-92.4%) and -1.5 (-91.9%) with solifenacin 5 and 10 mg, respectively, and -0.7 (-50%) with placebo (P<0.001 for 10 mg dose). There was no significant difference between solifenacin 5 mg and placebo. A greater percentage of elderly patients who were incontinent at baseline were continent with solifenacin 5 and 10 mg (49.1 and 47.3%, respectively) compared to placebo (28.9%; P<0.001). In 12-week studies, elderly patients had significantly greater decreases in the mean number of urgency episodes/24 hours with solifenacin 5 and 10 mg compared to placebo (P<0.001). The median change in the number of urgency episodes was -2.3 (-76.1%) and -2.7 (-66.7%) with solifenacin 5 and 10 mg, respectively, and -1.5 (-33.3%) with placebo (P<0.001 for 10 mg dose). A greater percentage of elderly patients with urgency at baseline had resolution of urgency with solifenacin 5 and 10 mg (34.6 and 24.9%, respectively) compared to placebo (16.9%; P<0.001 for 5 mg and P<0.01 for 10 mg). In 12-week studies, elderly patients had significantly greater decreases in the mean number of micturitions/24 hours with solifenacin 5 and 10 mg compared to placebo (P<0.001). The median change in the number of micturitions was -2.0 (-18.3%) and -2.3 (-22%) with solifenacin 5 and 10 mg, respectively, and -1.0 (-10.3%) with placebo (P=0.008 for the 5 mg dose and P<0.001 for the 10 mg dose.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				In 12-week studies, elderly patients had a significantly greater increase in the mean volume voided/micturition with solifenacin 5 and 10 mg compared to placebo (P<0.001).The median change in volume voided/micturition was 27.2 (17.8%) and 40.1 (28.5%) with solifenacin 5 and 10 mg, respectively, and 6.2 (3.7%) with placebo (P<0.001). During the 40-week extension trial, elderly patients maintained improvements in the number of incontinence episodes/24 hours, urgency episodes/24 hours, and number of micturitions/24 hours, and experienced an increase in the volume voided/micturition compared to baseline. A total of 59.5% of elderly patients were continent and 37.8% reported resolution of urgency at the end of the study period. During the 12-week trials, the most commonly reported adverse events were dry mouth, constipation, and UTI. Rates of discontinuation were 5.5% in the placebo group, 4.7% in the solifenacin 5 mg group, and 9.3% in the solifenacin 10 mg group. During the 40-week extension, the most common adverse events were dry mouth, constipation, and UTI. A total of 9.2% of patients discontinued therapy due to any type of adverse event. Secondary: Not reported
Kelleher et al.[74] (2005) Solifenacin 5 to 10 mg once daily vs placebo	DB, MC, PC, RCT (Pooled analysis) Patients ≥18 years of age with symptoms of OAB (≥8 micturitions/24 hours and either ≥1 urgency episode/24 hours or ≥1 incontinence episode/24 hours)	N=3,237 (3 trials) 12 to 40 weeks	Primary: QOL data using the KHQ Secondary: Not reported	Primary: In the 12-weeks studies, there was a significant improvement in all QOL domains (except personal relationships) with solifenacin compared to placebo (P<0.05 to P<0.001). In the 40-week ES, there was a significant improvement in all QOL domains with solifenacin (17% for the general health perception and 35 to 48% for all the other domains). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	for >3 months			
Herschorn et al.[75] (2010) Solifenacin 5 mg once daily vs oxybutynin IR 5 mg three times daily	DB, MC, RCT Patients ≥18 years of age with OAB symptoms (>1 urgency episode per 24 hours and ≥8 micturitions per 24 hours for ≥3 months)	N=132 8 weeks	Primary: Incidence and severity of dry mouth reported after direct questioning Secondary: Three-day diary changes in urgency, frequency, incontinence, nocturia, voided volume, PPBC, and the OAB-q	Primary: Significantly fewer patients on solifenacin reported dry mouth after direct questioning compared to oxybutynin IR (35 vs 83%; 95% CI, 33 to 62; P<0.0001). Additionally, in those reporting dry mouth, solifenacin was associated with significantly lower severity than that of oxybutynin IR (P=0.001). Secondary: Patients in both groups showed improvement in bladder diary documented urgency, incontinence, frequency, nocturia, and VVPM from baseline to end of treatment. PPBC and OAB-q scores also significantly improved with both groups. Overall adverse events were significantly fewer with solifenacin than with oxybutynin IR (72 vs 92%; P=0.003). Besides dry mouth, the incidence of other adverse events was 59% for solifenacin and 70% for oxybutynin (P=0.17). Fewer patients that received solifenacin withdrew from the study due to dry mouth compared to oxybutynin IR (3 vs 19%; P=0.003).
Herschorn et al.[76] (2011) Solifenacin 5 mg once daily vs oxybutynin IR 5 mg three times daily	DB, MC, RCT (Subgroup analysis) Patients ≥18 years of age with OAB symptoms (>1 urgency episode per 24 hours and ≥8 micturitions per 24 hours for ≥3 months)	N=132 8 weeks	Primary: Adverse events in patients ≤ 65 years of age and in those >65 years of age Secondary: Not reported	Primary: In both age groups, solifenacin 5 mg/day was associated with numerically fewer episodes of dry mouth compared to oxybutynin IR. Patients receiving oxybutynin IR were >8 times more likely to have dry mouth than those receiving solifenacin, regardless of age (OR, 8.88; 95% CI, 3.91 to 20.17). Additionally, oxybutynin IR caused more severe dry mouth compared to solifenacin. The incidence and severity of other adverse events with solifenacin were similar between age groups. Discontinuation of oxybutynin IR treatment occurred more often than solifenacin, irrespective of age. Although the numbers were low, there was a higher incidence of constipation and fatigue in patients >65 years who received solifenacin compared to oxybutynin IR. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Hsiao et al.[77] (2011) Solifenacin 5 mg once daily vs tolterodine ER 4 mg once daily	OL, RCT Women ≥18 years who had ≥3 month history of OAB symptoms (including urgency, urinary frequency, nocturia or urge incontinence) and a mean of ≥8 micturitions per 24 hours	N=48 12 weeks	Primary: Changes in total voided volume, VVPM, and the episodes of micturition, urgency, incontinence and nocturia in 24 hours Secondary: Not reported	Primary: In the solifenacin group, there was a decrease in the PPBC and the micturition, urgency and incontinence episodes per 24 hours and the VVPM increased at most follow-up visits. In the tolterodine group, there was a decrease in the PPBC and the nocturia episodes per 24 hours, but the heart rate increased at most follow-up visits. There were no between- or within-group differences in the changes of the number of episodes of micturition, urgency, incontinence, nocturia or total voided volume per 24 hours or VVPM at weeks four, eight or 12. Compared to baseline, the volume voided was significantly increased after solifenacin treatment (P=0.04). The strong desire to void and pad test result improved after tolterodine treatment (P=0.02 and P=0.03, respectively). At 12 weeks, there were no between-group differences in changes of urodynamic data and pad test results. Changes in the heart rate differed significantly between these two groups at visit two (solifenacin vs tolterodine ER, -4.3; 95% CI, -7.2 to -1.3 vs 3.8; 95% CI, 0.3 to 7.3; P=0.02 and visit three (-3.2; 95% CI, -7.4 to 1.0 vs 4.8; 95% CI, 1.2 to 8.3; P=0.03). There was no difference in the number of patients who experienced adverse events between groups (P=0.23). Ten patients in the solifenacin group experienced adverse events, including dry mouth (n=7), constipation (n=3), palpitations (n=1), dizziness (n=1) and fatigue (n=1). Five patients in the tolterodine group experienced adverse events, including dry mouth (n=3), constipation (n=1), and palpitations (n=1). Secondary: Not reported
Armstrong et al.[78] (2007) Oxybutynin XL 10 mg once daily	MA of 2 studies Present study is a MA of the OPERA and OBJECT	N=1,168 12 weeks	Primary: Adverse events Secondary: Not reported	Primary: Gastrointestinal adverse events occurred in 41.8, 36.3 and 45.1% of patients receiving oxybutynin XL, tolterodine LA and tolterodine IR therapy, respectively (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs tolterodine LA 4 mg once daily vs tolterodine IR 2 mg twice daily	studies (Appell et al and Diokno et al)			The most common adverse event was dry mouth, occurring in 29.3, 22.3 and 33.2% of patients receiving oxybutynin XL, tolterodine LA and tolterodine IR therapy, respectively (P value not reported). The incidence of nervous system adverse events in the oxybutynin XL, tolterodine LA, and tolterodine IR groups was comparable (10.2 vs 8.3 vs 10.9%, respectively; P value not reported). Most adverse events were mild or moderate in intensity. Severe drug-related adverse events occurred in 4.3, 1.5 and 2.6% of patients in the oxybutynin XL, tolterodine LA and tolterodine IR groups, respectively. The most common adverse event resulting in early discontinuation from the study was dry mouth, with 1.2, 1.0 and 1.6% of patients discontinuing treatment with oxybutynin XL, tolterodine LA and tolterodine IR, respectively (P value not reported). Secondary: Not reported
Madhuvrata et al.[79] (2012) Fesoterodine 4 to 8 mg once daily vs oxybutynin IR 2.5 to 5 mg twice daily to four times daily vs oxybutynin XL 5 to 20 mg once daily	MA of 86 studies Patients with a symptomatic diagnosis of OAB syndrome with or without a urodynamic diagnosis of detrusor overactivity	N=31,249 Up to 52 weeks	Primary: Condition-specific QOL and psychosocial measures Secondary: Patient observations, quantification of symptoms, clinician's measures, socioeconomics	Primary: There was no significant difference between tolterodine and oxybutynin with regard to QOL (SMD, -0.00; 95% CI, -0.18 to 0.18). The results from three studies reported a statistically significant improvement in QOL for patients treated with solifenacin compared to tolterodine (SMD, -0.12; 95% CI, -0.23 to -0.01). Treatment with fesoterodine was associated with a significant improvement in QOL compared to tolterodine LA (SMD, -0.20; 95% CI, -0.27 to -0.14). Secondary: There was no statistically significant difference between tolterodine and oxybutynin with regard to the proportion of patients reporting a symptomatic cure or improvement (RR, 1.01; 95% CI, 0.93 to 1.11), fewer leakage episodes or voids over 24 hours (WMD, 0.33; 95% CI, -0.08 to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs tolterodine IR 1 to 2 mg twice daily vs tolterodine LA 2 to 4 mg once daily vs trospium IR 20 mg twice daily vs solifenacin 5 to 10 mg once daily vs placebo				0.73). There was no difference in patient reported cure or improvement between patients receiving oxybutynin or trospium (RR, 1.00; 95% CI, 0.90 to 1.11). Moreover, there was no significant difference between the treatments with regard to cystometric capacity or residual bladder volume. Trospium was associated with fewer treatment withdrawals (RR, 0.66; 95% CI, 0.48 to 0.91) and a lower risk of dry mouth compared to oxybutynin (RR, 0.64; 95% CI, 0. 52 to 0.77). Compared to oxybutynin, tolterodine was associated with significantly lower rates of withdrawal due to adverse events (RR, 0.52; 95% CI, 0.40 to 0.66) and a lower incidence of dry mouth (RR, 0.65; 95% CI, 0.60 to 0.71). Treatment with solifenacin was associated with a higher patient report of cure or improvement compared to tolterodine (RR, 1.25; 95% CI, 1.13 to 1.39). There was a statistically significant reduction in the number of leakage episodes/24 hours (WMD, -0.30; 95% CI, -0.53 to -0.08 and urgency episodes/24 hours with solifenacin compared to tolterodine (WMD, -0.43; 95% CI, -0.74 to -0.13). Withdrawal rates due to adverse events and the incidence of dry mouth were similar between solifenacin and tolterodine; however, following the exclusion of one study with tolterodine LA, dry mouth rates were significantly lower with solifenacin compared to tolterodine LA (RR, 0.69; 95% CI, 0.51 to 0.94). Fesoterodine treatment was associated with a higher rate of patient reported cure or improvement compared to tolterodine LA (RR, 1.11; 95% CI, 1.06 to 1.16). Compared to tolterodine LA, patients taking fesoterodine reported significant reductions in leakage episodes (WMD, -0.19; 95% CI, -0.30 to -0.09), frequency (WMD, -0.27; 95% CI, -0.47 to -0.06) and urgency

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				episodes/24 hours (WMD, -0.44; 95%CI, -0.72 to -0.16). Patients receiving treatment with fesoterodine had a higher risk of withdrawal due to adverse event compared to tolterodine LA treatment (RR, 1.45; 95% CI, 1.07 to 1.98) and higher risk of dry mouth (RR, 1.80; 95% CI, 1.58 to 2.05). Similar improvements in leakage episodes and micturitions/24 hours were reported for 1, 2 and 4 mg doses of tolterodine IR administered twice daily. There was a higher incidence of dry mouth with both the 2 and 4 mg doses relative to the lower doses of tolterodine IR. Fesoterodine 8 mg was associated with a greater clinical efficacy (patient reported cure, leakage episodes, micturition/24 hours) compared to the 4 mg fesoterodine. There was no difference in efficacy between the 4 mg and 12 mg doses, although higher dose was associated with a greater incidence of dry mouth. The 8 mg strength was also associated with a higher risk of dry mouth compared to fesoterodine 4 mg. Both tolterodine LA and oxybutynin XL were associated with a lower risk of dry mouth compared to their respective IR formulations; however, no significant differences in cure, improvement, leakage episodes, micturitions/24 hours, or withdrawal events were reported between. There was a lower risk of dry mouth with tolterodine LA compared to oxybutynin XL (RR, 0.75; 95% CI, 0.59 to 0.95). There was no difference in the incidence of dry mouth between transdermal oxybutynin and tolterodine LA, although there was a higher withdrawal rate with transdermal oxybutynin due to a skin reaction at the transdermal patch site at 12 weeks.
Ho et al.[80] (2010) Solifenacin 5 mg once daily vs	OL, PRO, RCT Male or female patients ≥18 years of age with OAB symptoms (urinary frequency, urgency,	N=75 12 weeks	Primary: Change from baseline to endpoint for the mean number of micturitions per 24 hours	Primary: Compared to baseline, both treatment groups showed significant improvements in reducing mean micturition numbers per 24 hours from week four. At week 12, the mean changes were not significantly different between solifenacin and tolterodine (-2.56 vs -2.44; P=0.58). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
tolterodine ER 4 mg once daily	or urge incontinence) ≥3 months, who experienced frequency (defined as ≥8 micturitions per 24 hours)		Secondary: Change from baseline to endpoint for MVV per micturition, mean urgency episode per 24 hours, mean incontinence per 24 hours, PPBC, patient and physician assessment of treatment benefit	Both groups significantly improved urgency and incontinence episodes per 24 hours. At week 12, the mean changes from baseline were not significant for urgency episodes between solifenacin and tolterodine (-1.7 vs -1.15; P=0.37), nor were the mean changes for incontinence episodes (-2.79 vs -4.67; P=0.28). A significant increase in MVV per micturition was only observed in the solifenacin group (27.61±51.74 mL). PPBC was significantly improved with both groups compared to baseline. At week 12, the mean changes from baseline were -1.4 and -1.4 in the solifenacin and tolterodine groups, respectively. The difference between solifenacin and tolterodine was not statistically significant. Patient and physician assessment of treatment benefit showed that improvements were made in both groups compared to baseline, but not between each other. The most common adverse events for solifenacin and tolterodine were dry mouth (18.0 vs 8.3%; P=0.31) and constipation (12.8 vs 2.8%; P=0.2).
Chapple et al.[81] (2005) Solifenacin 5 to 10 mg once daily vs tolterodine ER 4 mg once daily	DB, MC, RCT Patients ≥18 years of age with OAB symptoms (≥8 micturitions/24 hours, ≥1 incontinence episode/24 hours, or ≥1 urgency episode/24 hours) for ≥3 months	N=1,200 12 weeks	Primary: Micturition frequency Secondary: Urgency episodes, urge incontinence, total incontinence, nocturia, proportion of patients who experienced a 50% reduction in incontinence episodes, pad usage, and QOL using a six-point	Primary: The mean number of micturitions was reduced with solifenacin (-2.45) compared to treatment with tolterodine (-2.24; P=0.004 for non inferiority). Secondary: Treatment with solifenacin led to a reduction in the number of urgency episodes/24 hours (-2.85) compared to treatment with tolterodine (-2.42; P<0.05). Treatment with solifenacin led to a reduction in the number of urge incontinence episodes/24 hours (-1.42) compared to treatment with tolterodine (-0.83; P<0.01). Treatment with solifenacin led to a reduction in the number of total incontinence episodes/24 hours (-1.60) compared to treatment with tolterodine (-1.11; P<0.01). There was no significant difference in nocturia

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			categorical scale to assess perception of bladder condition	among the treatment groups (P=0.730). Approximately 74% of patients receiving solifenacin who were incontinent at baseline experienced ≥50% reduction in incontinence episodes compared to 67% of patients receiving tolterodine (P=0.021). The percentage of patients who were incontinent at baseline who became continent at study end point was 59% (solifenacin) and 49% (tolterodine; P=0.006). The mean volume voided/micturition increased with solifenacin (38 mL) compared to tolterodine (31 mL; P=0.010). Solifenacin decreased the number of incontinence pads used compared to tolterodine (P=0.0023). Patient-reported perception of bladder condition was significantly improved with solifenacin compared to tolterodine (P=0.006). Approximately 5.9% of patients receiving solifenacin and 7.3% of patients receiving tolterodine discontinued treatment (for any reason); 1.2% and 2.0% discontinued therapy due to insufficient therapeutic response with solifenacin and tolterodine, respectively. The most common adverse events were dry mouth, constipation and blurred vision. The percentage of patients discontinuing treatment due to adverse events was similar between the treatment groups (3.5% of patients receiving solifenacin and 3.0% of patients receiving tolterodine). A total of 1.2 and 2.0% of patients discontinued therapy due to an insufficient therapeutic response with solifenacin and tolterodine, respectively.
Chapple et al.[82] (2004) Solifenacin 2.5 to 20 mg once daily vs	DB, PC, RCT Patients 18 to 80 years of age with OAB and urodynamic evidence of detrusor	N=225 6 weeks	Primary: Number of voids/24 hours Secondary: Volume voided/ void; incontinence	Primary: The mean change in number of voids/24 hours was significantly lower with solifenacin 5 mg (-2.21), 10 mg (-2.47) and 20 mg (-2.75) compared to placebo (-1.03; all P<0.05). There was no significant difference with tolterodine (-1.79) compared to placebo (P=NS). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
tolterodine IR 2 mg twice daily vs placebo	overactivity (>8 voids/24 hours and >3 episodes of incontinence or urgency)		episodes/24 hours; urgency episodes/24 hours; and total sum score of Contilife items 1 to 27, sum scores of the five Contilife domains (i.e., daily activities, effort, self-image, emotional consequences, and sexuality), and overall Contilife QOL score	The mean volume voided/void was significantly greater for solifenacin 5 mg, 10 and 20 mg than for placebo (all P<0.01). There was no significant difference with tolterodine compared to placebo. There was no significant difference in the mean number of incontinence episodes/24 hours with solifenacin or tolterodine compared to placebo. There was no significant difference in the number of urgency episodes/24 hours with solifenacin or tolterodine compared to placebo. Treatment with solifenacin led to significant improvements over baseline based on the results of the Contilife sum score QOL analysis compared to placebo. There was no significant difference with tolterodine compared to placebo. Treatment with solifenacin led to significant improvements in the daily life activities (all groups; P<0.01), self-image (10 and 20 mg; P<0.05), emotional consequences (5, 10 and 20 mg; P<0.05) and sexuality (10 and 20 mg; P<0.05) compared to placebo. Tolterodine resulted in significant improvements in the daily life activities domain only compared to placebo (P<0.05). Solifenacin 10 and 20 mg and tolterodine produced significant improvements over placebo in the Contilife overall QOL score (P<0.05). The most frequently reported adverse event was dry mouth, followed by constipation and blurred vision. The frequency of dry mouth was highest among patients receiving solifenacin 20 mg (38%), tolterodine 2 mg (24%) and solifenacin 5 and 10 mg (14% each). Constipation was reported in 19% of patients taking solifenacin 20 mg.
Chapple et al.[83] (2004) Solifenacin 5 to 10 mg once daily vs	DB, MC, RCT Patients ≥18 years of age with symptoms of OAB (including urgency, urge incontinence,	N=1,081 12 weeks	Primary: Urgency episodes, all incontinence episodes, urge incontinence episodes, voids/24 hours and voided	Primary: There was a significant decrease in the mean number of urgency episodes/24 hours with solifenacin 5 and 10 mg (-52% and -55%, respectively) compared to placebo (-33%; both P<0.001). There was no significant difference in urgency episodes/24 hours between tolterodine (-38%) and placebo (P=0.0511). Direct comparison of solifenacin 5 and 10 mg with tolterodine resulted in estimated differences

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
tolterodine IR 2 mg twice daily vs placebo	or frequency) for ≥3 months (≥8 voids/24 hours, ≥3 episodes of urgency and/or ≥3 episodes of incontinence)		volume/void Secondary: Not reported	of - 0.791 and - 1.015 (95% CI, -1.434 to -0.148, and -1.659 to -0.370), respectively. There was a significant decrease in urge incontinence episodes/24 hours with solifenacin 5 mg (-1.41; P=0.002) and 10 mg (-1.36; P=0.0028) compared to placebo (-0.62). There was no significant difference in urge incontinence episodes/24 hours between tolterodine (-0.91) and placebo (P=0.2390). There was no significant difference in urge incontinence episodes/24 hours between solifenacin and tolterodine (5 mg, -0.487; 95% CI, -0.988 to 0.014 and 10 mg, -0.436; 95% CI, -0.921 to 0.048). There was a significant decrease in all incontinence episodes/24 hours with solifenacin 5 mg (-1.42; P=0.008) and 10 mg (-1.45; P=0.0038) compared to placebo (-0.76). There was no significant difference in all incontinence episodes/24 hours between tolterodine (-1.14) and placebo (P=0.1122). There was no significant difference in all incontinence episodes/24 hours between solifenacin and tolterodine (5 mg, -0.276; 95% CI, -0.761 to 0.208 and 10 mg, -0.316; 95% CI, -0.786 to 0.164). There was a significant decrease in mean number of voids/24 hours with solifenacin 5 mg (-2.19, -17%; P<0.001), solifenacin 10 mg (-2.61, -20%; P<0.001) and tolterodine (- 1.88, -15%; P=0.0145) compared to placebo (-1.20, - 8%). Direct comparison of solifenacin 5 and 10 mg with tolterodine resulted in estimated differences of -0.312 and -0.737 (95% CI -0.844 to 0.219, and -1.269 to -0.204). There was a significant increase in mean volume voided/void with solifenacin 5 mg (32.9 mL, +25.1%), solifenacin 10 mg (39.2 mL, +29.0%), and tolterodine (24.4 mL, +20.3%) compared to placebo (7.4 mL; all, P<0.001). There was no significant difference in mean volume voided/void between solifenacin and tolterodine (5 mg, 8.4 mL; 95% CI, 0.496 to 16.34 and 10 mg, 14.8 mL; 95% CI, 6.855 to 22.72). The percentages of patients discontinuing treatment for an adverse event were 3.7% in the placebo group, 3.2% in the solifenacin 5 mg group, 2.6% in the solifenacin 10 mg group, and 1.9% in the tolterodine group. The incidence of dry mouth was lowest with solifenacin 5 mg (14%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Constipation was reported in 7.2 and 7.8% of patients treated with solifenacin 5 and 10 mg, respectively, in 2.6% of patients treated with tolterodine and in 1.9% of placebo patients. Blurred vision was reported in 3.6% of patients receiving solifenacin 5 mg, 5.6% receiving solifenacin 10 mg, 1.5% receiving tolterodine, and 2.6% receiving placebo. Secondary: Not reported
Yamaguchi et al.[84] (2011) Solifenacin 2.5 mg plus tamsulosin 0.2 mg once daily (TAM+SOL 2.5) vs solifenacin 5 mg plus tamsulosin 0.2 mg once daily (TAM+SOL 5) vs tamsulosin 0.2 mg once daily plus placebo (TAM+PBO)	DB, MC, PC, RCT Men ≥50 years of age with LUTS and residual OAB symptoms despite treatment with tamsulosin for ≥6 weeks, ≥2 urgency episodes per 24 hours in a 3-day bladder diary, Qmax ≥5 mL/s, and PVR volume <50 mL	N=638 12 weeks	Primary: Mean change in urgency episodes per 24 hours Secondary: Mean changes in micturitions, nocturia episodes, urgency incontinence episodes, IPSS, IPSS-QOL, and OABSS	Primary: The mean number of urgency episodes per 24 hours decreased by 2.2 and 2.4 episodes in the TAM+SOL 2.5 and TAM+SOL 5 groups, respectively. TAM+SOL 5 showed a significant improvement in urgency episodes compared to TAM+PBO (P=0.049). Secondary: The number of micturitions per 24 hours was reduced by 1.27 episodes in the TAM+SOL 2.5 group and by 1.06 episodes in TAM+SOL 5 groups, and both of these were significantly better than TAM+PBO (0.22 episodes; P<0.01). Compared to TAM+PBO, TAM+SOL 2.5 and TAM+SOL 5 did not significantly reduce the number of nocturia episodes and urgency incontinence. IPSS storage symptom score was significantly improved in both solifenacin groups compared to placebo. IPSS total score, voiding symptom score, post-micturition symptom score, or QOL were no significantly better compared to placebo. For OABSS, both solifenacin groups significantly improved the total score, daytime frequency score, urgency score, and urgency incontinence score compared to placebo. The most common adverse events were dry mouth (6.2% for TAM+SOL 2.5 vs 11.3% for TAM+SOL 5), constipation (3.8% for TAM+SOL 2.5 vs 10.3% for TAM+SOL 5), increase in PVR ≥50 mL (2.9% for TAM+SOL 2.5 vs 6.1% for TAM+SOL 5), abdominal discomfort (2.4% for

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				TAM+SOL 2.5 vs 1.9% for TAM+SOL 5), and creatinine phosphokinase increase (1.9% for TAM+SOL 2.5 vs 2.3% for TAM+SOL 5). A total of four patients in TAM+SOL 5 had urinary retention requiring temporary cauterization.
Kreder et al.[85] (2002) Tolterodine ER 4 mg once daily	ES, OL Patients ≥18 years of age with urinary frequency (≥8 micturitions/24 hours), urge incontinence (≥5 incontinence episodes/week) and urgency for ≥6 months	N=1,077 12 months	Primary: Safety and tolerability Secondary: Efficacy	Primary: The most common adverse events were autonomic nervous system disorders (13.2%), gastrointestinal disorders (11.4%), general body disorders (14.5%), respiratory disorders (9.8%), urinary disorders (9.1%) and musculoskeletal disorders (6.0%). The most frequently report adverse event was dry mouth, which occurred in 12.9% of patients. Approximately 10% of patients withdrew from the study due to adverse events. The most common adverse events leading to withdrawal were dry mouth (1.8%), headache (0.8%), abdominal pain (0.8%), dizziness (0.7%), UTI (0.7%), dyspepsia (0.6%), constipation (0.6%), xerophthalmia (0.5%), and micturition disorders (0.5%). Secondary: The number of urge incontinence episodes/week was significantly decreased with tolterodine compared to baseline (median change, -83%). The number of micturitions/24 hours significantly decreased with tolterodine compared to baseline (median change, -21%). The change in volume voided/micturition significantly increased with tolterodine compared to baseline (median change, 25%). Approximately 75% of patients who received tolterodine perceived improvement after 12 months of therapy.
Takei et al.[86] (2005) Tolterodine ER 4 mg once daily	ES, OL Japanese patients ≥20 years of age with OAB	N=188 12 months	Primary: Safety and tolerability Secondary:	Primary: The most common adverse event was dry mouth (33.5%). The incidence decreased during the course of the OL extension (24.5% during the first three months vs 4.3% during the six to 12-month periods).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	symptoms including urinary urgency, urinary frequency (≥8 micturitions/24 hours) and urge incontinence (≥5 episodes/week) for ≥6 months		Efficacy	Approximately 23% of patients withdrew prematurely due to adverse events (10.0%), lack of efficacy (8.0%), consent withdrawal (3.7%), lost to follow-up (0.5%) and protocol violation (0.5%). Secondary: The number of incontinence episodes/week was decreased with tolterodine (mean change, -77.2%). The number of micturitions/24 hours significantly decreased with tolterodine (mean change, -21.3%; P<0.0001). The change in volume voided/micturition significantly increased with tolterodine (mean change, 19.6%; P<0.0001).
Choo et al.[87] (2008) Tolterodine ER 4 mg once daily	OL Patients ≥18 years of age with OAB who had urinary frequency (≥8 micturitions/24 hours) and urgency (≥2 episodes/24 hours) with or without urgency incontinence	N=60 12 weeks	Primary: Rate of PGA by a visual analogue scale Secondary: Changes in symptom severity, voiding diary and PPBC, and willingness to continue treatment	Primary: The median rate of PGA was: frequency (60%; 95% CI, 46.9 to 63.6), urgency (60%; 95% CI, 46.2 to 64.9), urge incontinence (80%; 95% CI, 34.2 to 80.0), nocturia (50%; 95% CI, 39.4 to 57.6) and tenesmus (30%; 95% CI, 25.4 to 52.2). Secondary: The median percentage reduction in symptom severity was as follows: frequency (45%; 95% CI, 36.2 to 54.4), urgency (55%; 95% CI, 40.1 to 60.4), urgency incontinence (71%; 95% CI, 39.2 to 76.8), nocturia (52%; 95% CI, 40.2 to 59.7) and tenesmus (26%; 95% CI, 16.9 to 50.4). Patients reported that the most troublesome symptoms were daytime frequency (50.0%), nocturia (17.9%), urgency incontinence (16.1%), urgency (10.7%) and tenesmus (5.4%). Frequency (-2.7), urgency (-4.2), urgency incontinence (-1.0), and nocturia (-0.7) were significantly reduced with tolterodine (all, P<0.01). The mean voided volume significantly increased with tolterodine (32 mL; P=0.05). Approximately 90% of patients experienced an improvement of at least one point in their bladder condition, and 62.5% reported improvements of at least two points on the PPBC questionnaire.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				A total of 73.2% of patients wished to continue treatment after receiving three months of treatment. The most common adverse events were dry mouth (21.7%), constipation or indigestion (10.0%), headache (5.0%), UTI (3.3%) and peripheral edema (1.7%).
Van Kerrebroeck et al.[88] (2001) Tolterodine ER 4 mg once daily vs tolterodine IR 2 mg twice daily vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with urinary frequency (≥8 micturitions/24 hours) and urge incontinence (≥5 incontinence episodes/week) for ≥6 months	N=1,529 12 weeks	Primary: Incontinence episodes/week, number of micturition/24 hours, volume voided/micturition, and the number of pads used/24 hours Secondary: Not reported	Primary: The mean change in incontinence episodes/week was significantly better with tolterodine ER (-11.8; P=0.0001) and tolterodine IR (-10.6; P=0.0005) compared to placebo (-6.9). The median percentage reductions in incontinence episodes/week were: tolterodine ER, 71%; tolterodine IR, 60%; and placebo, 33%. Tolterodine ER was 18% more effective than tolterodine IR (P<0.05). The mean change in number of micturitions/24 hours was significantly better with tolterodine ER (-1.8; P=0.0047) and tolterodine IR (-1.7; P=0.0079) compared to placebo (-1.2). The mean change in volume voided/micturition was significantly greater with tolterodine ER (34 mL; P=0.0001) and tolterodine IR (29 mL; P=0.0001) compared to placebo (14 mL). The mean change in number of pads used/24 hours was significantly lower with tolterodine ER (-0.5; P=0.0145) and tolterodine IR (-0.5; P=0.0035) compared to placebo (-0.2). The most common adverse events in all treatment groups were dry mouth, constipation, and headache. With the exception of dry mouth, the incidence of adverse events was comparable between active treatment and placebo. The rate of dry mouth was 23, 30, and 8% for tolterodine ER, tolterodine IR, and placebo, respectively. Patients receiving tolterodine ER had 23% less dry mouth than those taking tolterodine IR (P=0.02). Discontinuation rates due to adverse events were similar in all the treatment groups (tolterodine ER, 5%; tolterodine IR, 5%; placebo, 6%). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Swift et al.[89] (2003) Tolterodine ER 4 mg once daily vs tolterodine IR 2 mg twice daily vs placebo	DB, MC, PC, RCT (Subgroup analysis) Women ≥18 years of age with urinary frequency (≥8 micturitions/24 hours) and urge incontinence (≥5 incontinence episodes/week) for ≥6 months	N=1,235 12 weeks	Primary: Incontinence episodes/week, number of micturition/24 hours, volume voided/micturition, and the number of pads used/24 hours Secondary: Not reported	Primary: The mean change in incontinence episodes/week was significantly better with tolterodine ER (-11.8; P=0.001) and tolterodine IR (-10.1; P=0.001) compared to placebo (-7.2). The difference between tolterodine ER and tolterodine IR was significant (P=0.036). The median percentage reductions in incontinence episodes/week were: tolterodine ER, 71%; tolterodine IR, 57%; and placebo, 33%. The mean change in number of micturitions/24 hours was significantly better with tolterodine ER (-1.9; P=0.001) and tolterodine IR (-1.7; P=0.005) compared to placebo (-1.2). There was no significant difference between tolterodine ER and tolterodine IR. The mean change in volume voided/micturition was significantly greater with tolterodine ER (37.9 ml; P=0.001) and tolterodine IR (32.5 mL; P=0.001) compared to placebo (13.3 mL). There was no significant difference between tolterodine ER and tolterodine IR. The mean change in number of pads used/24 hours was significantly lower with tolterodine ER (-0.6; P=0.001) and tolterodine IR (-0.5; P=0.001) compared to placebo (-0.2). There was no significant difference between tolterodine ER and tolterodine IR. Dry mouth, constipation, headache and UTI were the most common adverse events in all treatment groups. With the exception of dry mouth, the incidence of adverse events was comparable between active treatment and placebo. There was no significant difference in dry mouth with tolterodine ER or tolterodine IR (P=0.06). Discontinuation rates due to adverse events were similar in all the treatment groups (tolterodine ER, 5%; tolterodine IR, 5%; placebo, 6%). Secondary: Not reported
Homma et al.[90] (2003) Tolterodine ER	AC, DB, PC, RCT, Patients ≥20 years of age with OAB	N=608 12 weeks	Primary: Incontinence episodes/week	Primary: The number of incontinence episodes/24 hours was significantly decreased with tolterodine (median -78.6%; P=0.0027) and oxybutynin (median -76.5%; P=0.0168) compared to placebo (-46.4%). There was no

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
4 mg once daily vs oxybutynin IR 3 mg three times daily vs placebo	and symptoms of urinary urgency, urinary frequency (≥8 micturitions/24 hours) and urge incontinence (≥5 episodes/week) for ≥6 months		Secondary: Voids/24 hours and mean volume voided/void, median number of incontinence pads used/24 hours, patient perception of bladder condition, patient perception of urgency, and QOL using the KHQ	significant difference between tolterodine and oxybutynin (P=0.4469). Secondary: The number of voids/24 hours decreased with tolterodine (-2.0; P<0.001) and oxybutynin (-2.1; P=0.0114) compared to placebo (-1.1). There was no significant difference among the treatment groups (P=0.3132). The volume voided/void increased significantly with tolterodine (17.2 mL; P=0.0086) and oxybutynin (22.3 mL; P<0.001) compared to placebo (6.6 mL). The number of pads used/24 hours was not significantly different among the treatment groups. Approximately 72% of patients treated with tolterodine and 73% treated with oxybutynin perceived improvement after 12 weeks of treatment compared to 59% of patients treated with placebo. The difference between tolterodine and placebo was NS (P=0.515). There was no significant difference between tolterodine and oxybutynin (P=0.9394). Significantly more patients reporting at least some benefit with tolterodine (79%; P=0.0091; little benefit 36%; much benefit, 42%) and oxybutynin (81%; P<0.001; little benefit 29%; much benefit 53%) than with placebo (66%; little benefit 40%; much benefit 25%). There was no significant difference between tolterodine and oxybutynin in the assessment of treatment benefit (P=0.2240). Treatment with tolterodine and oxybutynin resulted in significantly greater mean reductions in both the incontinence impact domain and role limitation domain scores (KHQ questionnaire) compared to placebo. There was no significant difference between the improvements with tolterodine and oxybutynin for either domain. Tolterodine and oxybutynin were associated with improvements in other KHO domains, including physical limitations, social limitations, personal relationships, sleep/energy, severity measures, and the severity of urinary symptoms compared to placebo. The differences in improvements between tolterodine and oxybutynin were NS for any of these domains.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Dry mouth was the most common adverse event reported with tolterodine (33.5%), oxybutynin (53.7%) and placebo (9.8%). Dry mouth was more common in patients receiving oxybutynin than tolterodine (P<0.001). Other adverse events occurring in >5% of patients were constipation, abdominal pain/tenderness, dyspepsia, difficulty in voiding and headache. Eye disorders occurred in significantly more patients receiving oxybutynin than tolterodine (P<0.0383). The incidence of nervous system disorders was lower in the tolterodine group (8.4%) than in the oxybutynin group (12.7%) or placebo group (11.5%). More patients on oxybutynin withdrew due to adverse events compared to tolterodine (P<0.001).
Sussman et al.[91] (2002) Trial 1 Tolterodine ER 2 to 4 mg once daily Trial 2 Oxybutynin ER 5 to 10 mg once daily	OL, RCT Patients ≥18 years of age with OAB and symptoms of urinary frequency and urgency with or without urge incontinence	Trial 1 N=669 8 weeks Trial 2 N=620 8 weeks	Primary: Patient perception of bladder condition and patient assessment of treatment benefit Secondary: Physician assessment of treatment benefit	Primary: Seventy percent of patients in the tolterodine 4 mg group perceived an improvement in their bladder condition compared to 60% in the tolterodine 2 mg group, 59% in the oxybutynin 5 mg group, and 60% in the oxybutynin10 mg group (all P<0.01 vs tolterodine 4 mg). There was a greater percentage of patients who reported an improved bladder condition with tolterodine 4 mg compared to oxybutynin 10 mg (77 vs 65%; P<0.01) in those whose perception of bladder condition was moderate to severe at baseline. There was no significant difference in the perception of their bladder condition among treatment-naïve patients (P=0.11) and those who had received prior antimuscarinic therapy (P=0.11). Secondary: There was no significant difference in patient assessment or physician's assessment of treatment benefit between tolterodine and oxybutynin. Dry mouth was dose-dependent in both trials (tolterodine 2 mg vs tolterodine 4 mg; P=0.09; oxybutynin 5 mg vs oxybutynin 10 mg; P=0.05). Patients treated with tolterodine 4 mg reported a significantly lower severity of dry mouth compared to oxybutynin 10 mg (P=0.03).
Chung et al.[92]	OL	N=51	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2010) Tolterodine ER 4 mg once daily and dutasteride 0.5 mg once daily	Men ≥45 years of age on dutasteride 0.5 mg for at least 6 months who failed alpha-blocker therapy, prostate >30 g, an IPSS ≥12, IPSS QOL item ≥3, ≥8 voids per 24 hours, ≥3 urgency episodes per 24 hours with or without urgency incontinence, and self-rated bladder condition on patient perception of bladder condition of hours at least "some moderate bother"	12 weeks	Change in frequency, nocturnal OAB micturition, IPSS, Qmax, change in PVR, adverse events, and episodes of urinary retention requiring a catheter Secondary: Not reported	Tolterodine ER significantly reduced frequency and urgency. Specifically, tolterodine reduced 24 hours micturition frequency (-3.2; P<0.02), OAB episodes (19.2%; P<0.03), severe OAB episodes (71.4%; P<0.05), and nighttime voiding (-0.9; P<0.003). Patients reported a reduction in 24 hours frequency from baseline 11.9 episodes to 10.2 episodes after three months of dutasteride, which further decreased to 8.7 after 12 weeks of tolterodine ER. IPSS decreased with the initial addition of dutasteride (19.3 to 14.3) and further decreased with the addition of tolterodine ER (7.1; P<0.001). There were no significant decreases in Qmax with the addition of tolterodine ER and tolterodine ER did not significantly increase PVR. Additionally, zero patients required catheterization. Four patients (7.5%) experienced dry mouth, one patient (2%) had constipation, and sexual function decreased in two patients (3.9%). Secondary: Not reported
Chung et al.[93] (2011) Tolterodine ER 4 mg once daily plus doxazosin 4 mg and/or dutasteride 0.5 mg once daily vs doxazosin 4 mg and/or dutasteride 0.5 mg once daily	OS, PRO, RCT Male patients ≥70 years of age with an IPSS score >8 and a storage subscore of >5, QOL index score >3, total prostate volume >20 mL, Qmax <15 mL/second, and with urodynamic confirmed BPH/BOO	N=153 12 months	Primary: Improvement in IPSS subscores (voiding and storage) at 12 months Secondary: Change in PVR volume, and QOL-I	Primary: The mean IPSS-voiding (8.5 to 2.88 with tolterodine [P<0.001], 9.83 to 4.78 without tolterodine [P<0.001]), IPSS-storage (9.44 to 5.18 with tolterodine [P<0.001], 8.34 to 6.92 without tolterodine [P<0.001]), and IPSS-total (18.1 to 8.06 with tolterodine [P<0.001], 18.2 to 11.7 without tolterodine [P<0.001]) improved similarly in both groups by 12 months follow-up. The patients receiving tolterodine ER experienced a better reduction of IPSS-storage symptoms (4.26 vs 1.42; P<0.001). Secondary: The change of PVR in the patients who received tolterodine ER did not differ significantly from those who did not (15.2 vs 8.9 mL; P=0.69). QoL-I also improved in both groups, but change was not significantly

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				different from each other (1.62 vs 1.46; P=0.551). Both groups demonstrated a significant improvement in Qmax compared to baseline, but there was not a significant difference between the two groups (P=0.275). Intolerable dry mouth, constipation, and dizziness were the most commonly reported adverse events and numerically occurred more in patients who received tolterodine ER.
Abrams et al.[94] (2001) Tolterodine IR 2 mg twice daily	ES, OL Patients ≥18 years of age with urinary frequency (≥8 micturitions/24 hours), urgency, and/or urge incontinence (≥1 incontinence episode/24 hours)	N=714 12 months	Primary: Number of micturitions/24 hours, number of urge incontinence episodes/24 hours, mean urine volume voided/micturition, safety Secondary: Not reported	Primary: The number of micturitions/24 hours significantly decreased with tolterodine (-2.4; P=0.0001; mean change, -20%). The number of urge incontinence episodes/24 hours significantly decreased with tolterodine (-1.3; P=0.0001; median change, -74%). The change in volume voided/micturition significantly increased with tolterodine (33 mL; P=0.0001; mean change, 18%). Approximately 69% of patients who received tolterodine perceived improvement after 12 months of therapy. The most frequently occurring adverse events were autonomic nervous system disorders (46%), general body disorders (22%), gastrointestinal disorders (22%) and urinary disorders (18%). The most frequently report adverse event was dry mouth, which occurred in 41% of patients (27% mild, 10% moderate, 3% severe). The most common adverse events leading to withdrawal were adverse events (15%), withdrawal of consent (13%), lost to follow-up (4%) and other (6%). A total of 34 (5%) patients withdrawing from the study due to dry mouth. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Appell et al.[95] (2001) Tolterodine IR 2 mg twice daily	ES, OL Patients ≥18 years of age with OAB, increased urinary frequency (≥8 micturitions/24 hours) and urge incontinence (≥1 incontinence episode/24 hours) or urinary frequency	N=854 9 months	Primary: Safety and tolerability Secondary: Efficacy	Primary: The most frequently reported adverse events were autonomic nervous system disorders (31%), gastrointestinal disorders (24%) and general body disorders (26%). The most frequently report adverse event was dry mouth, which occurred in 28% of patients (19% mild, 7% moderate, 2% severe). Of those patients enrolled in the OL trial, 30% did not complete nine months of therapy. The most common reasons for withdrawal were adverse events (9%), lack of efficacy (6%), lot to follow-up (6%) and withdrawal of consent (4%). Secondary: The number of micturitions/24 hours significantly decreased with tolterodine (-2.5; P=0.0001; median change, -22%). The number of urge incontinence episodes/24 hours significantly decreased with tolterodine (-2.0; P=0.0001; median change, -76%). The change in volume voided/micturition significantly increased with tolterodine (40 mL; P=0.0001; median change, 22%). Approximately 65% of patients who received tolterodine perceived improvement after nine months of therapy. Secondary: Not reported
Kilic et al.[96] (2006) Tolterodine IR 1 mg twice daily vs oxybutynin IR	PRO, RCT Children with detrusor instability (most with symptoms of nocturnal enuresis associated with daytime	N=60 ≥6 months	Primary: Urodynamic investigations before and after treatment, episodes of UUI, and adverse events Secondary:	Primary: The tolterodine group had a significant increase in the bladder capacity from 148.5 to 239.33 mL; P<0.001, an increase in compliance from 4.6 to 12.57; P<0.001, and a decrease in the maximum detrusor pressure from 79.43 to 40.4 cm H_20; P<0.001. In the oxybutynin group, a significant increase in bladder capacity from 154.67 to 255.23 mL; P<0.001, an increase in compliance from 5.13 to 13.07; P<0.001, and a decrease in the maximum detrusor pressure from

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
0.4 mg/kg three times daily	incontinence, frequency, urgency, and/or small bladder volume)		Not reported	85.47 to 39.43 cm H_20; P<0.001, were found. Increase in the bladder capacity and compliance during cystometry and reduction in the maximal bladder pressure over the period were similar for tolterodine and oxybutynin groups. While there was not a statistically significant difference between the groups, both had a significant reduction in detrusor instability after six months (100 to 30.0% for tolterodine and 100 to 23.3% for oxybutynin). Clinical response was also similar between tolterodine and oxybutynin (73.3% for tolterodine and 80.0% for oxybutynin; P>0.05). Adverse events were significantly lower in the tolterodine group compared to the oxybutynin group (13 vs 27 events; P=0.027). Eight patients in the oxybutynin group were crossed over to tolterodine due to adverse effects. Secondary: Not reported
Appell et al.[97] (1997) Tolterodine IR 1 to 2 mg twice daily vs oxybutynin IR 5 mg three times daily vs placebo	DB, MC, PC, RCT (Pooled analysis) Patients ≥18 years of age with OAB, increased urinary frequency (≥8 micturitions/24 hours) and urge incontinence (≥1 incontinence episode/24 hours) or urinary frequency	N=1,120 (4 trials) 12 weeks	Primary: Number of micturitions/24 hours, number of incontinence episodes/24 hours, and mean urinary volume voided/micturition Secondary: Not reported	Primary: The number of micturitions/24 hours significantly decreased with tolterodine 1 mg (P<0.001), tolterodine 2 mg (P<0.001), and oxybutynin (P<0.01) compared to placebo. There was no significant difference between tolterodine 2 mg and oxybutynin. The number of incontinence episodes/24 hours significantly decreased with tolterodine (1 and 2 mg) and oxybutynin compared to placebo (P<0.05). There was no significant difference between tolterodine 2 mg and oxybutynin. The change in volume voided/micturition significantly increased with tolterodine (1 and 2 mg) and oxybutynin compared to placebo (P<0.001). Approximately 39% of patients who received placebo, 41% treated with tolterodine 1 mg, 52% treated with tolterodine 2 mg (P=0.003 vs placebo), and 50% treated with oxybutynin (P=0.017 vs placebo) perceived improvement after 12 weeks of treatment.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Dry mouth was the most common adverse event (16% of the placebo group, 24% of the tolterodine 1 mg group, 40% of the tolterodine 2 mg group, and 78% of the oxybutynin group). The percentage of patients reporting dry mouth was significantly higher in the oxybutynin group than in the tolterodine or placebo groups (all, P<0.001). The percentage of patients reporting moderate or severe dry mouth was higher in the oxybutynin group (60%) compared to the tolterodine 1 mg group (4%), tolterodine 2 mg group (17%), and placebo group (6%; all, P<0.001). Other commonly reported adverse events included headache, dyspepsia, dizziness, and UTI. Dyspepsia was reported at a higher rate with oxybutynin (11%) than with tolterodine2 mg (6%; P=0.006). The proportion of patients who withdrew because of adverse events was higher in the oxybutynin group than in either of the tolterodine groups or the placebo group (all, P<0.001). Secondary: Not reported
Lee et al.[98] (2002) Tolterodine IR 2 mg twice daily vs oxybutynin IR 5 mg twice daily	DB, MC, PG, RCT Patients ≥18 years of age with OAB and symptoms of urinary urgency and frequency (≥8 micturitions/24 hour) for ≥6 months	N=228 8 weeks	Primary: Number of micturition/24 hours and incontinence episodes/24 hours Secondary: Not reported	Primary: The number of micturitions/24 hours decreased with tolterodine (-2.6) and oxybutynin (-1.8) compared to baseline. There was no significant difference among the treatment groups (P=0.14). In patients who were incontinent at baseline, the number of incontinence episodes/24 hours decreased with tolterodine (-2.2) and oxybutynin (-1.4). There was no significant difference among the treatment groups (P=0.10). Overall, 45% of patients who received tolterodine and 46% of patients who received oxybutynin reported 'much' benefit. There was no significant difference among the groups. The most frequently reported adverse events were autonomic nervous system disorders, gastrointestinal disorders, and urinary disorders. Dry mouth was the most commonly reported adverse event and was significantly higher with oxybutynin than tolterodine (P=0.001). There was a higher frequency of moderate-to-severe dry mouth with oxybutynin

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(28%) than tolterodine (9%). Secondary: Not reported
Malone-Lee et al.[99] (2001) Tolterodine IR 2 mg twice daily vs oxybutynin IR 5 mg twice daily	DB, MC, RCT Patients ≥50 years of age with OAB, increased urinary frequency (≥8 micturitions/24 hours), and symptoms of urgency and/or urge incontinence (≥1 episode/24 hours)	N=379 10 weeks	Primary: Number of micturition/24 hours, incontinence episodes/24 hours and volume voided/micturition Secondary: Not reported	Primary: The number of micturitions/24 hours decreased with tolterodine (-1.7) and oxybutynin (-1.7). There was no significant difference among the treatment groups (P=0.97). The number of incontinence episodes/24 hours decreased with tolterodine (-1.3) and oxybutynin (-1.8). There was no significant difference among the treatment groups (P=0.065). The change in volume voided/micturition increased with tolterodine (33 mL) and oxybutynin (34 mL). There was no significant difference among the treatment groups (P=0.90). Approximately 45% of patients treated with tolterodine and 41% treated with oxybutynin perceived improvement after 12 weeks of treatment. There was no significant difference among the treatment groups. Autonomic nervous system disorders and gastrointestinal problems were the most commonly reported adverse events. A higher percentage of patients experienced dry mouth with oxybutynin (61%) than with tolterodine (37%). Severe dry mouth was more common in the oxybutynin group (15%) than in the tolterodine group (4%). The proportion of patients who withdrew because of adverse events was similar in the oxybutynin group (15%) and in the tolterodine group (15%). Secondary: Not reported
Abrams et al.[100] (1998) Tolterodine IR 2 mg twice daily	DB, MC, PC, RCT Patients ≥18 years of age with OAB, increased urinary	N=293 12 weeks	Primary: Number of micturition/24 hours, incontinence episodes/24 hours	Primary: The mean change in number of micturitions/24 hours was significantly lower with tolterodine (-2.7; P=0.0022) compared to placebo (-1.6). There was no difference between oxybutynin (-2.3) and placebo (P=0.068). There was also no significant difference between tolterodine and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs oxybutynin IR 5 mg three times daily vs placebo	frequency (≥8 micturitions/24 hours), and symptoms of urgency and/or urge incontinence (≥1 episode/24 hours) for ≥6 months		and volume voided/micturition Secondary: Not reported	oxybutynin (95% CI, -1.1 to 0.1). The number of incontinence episodes/24 hours significantly decreased with oxybutynin (-1.7; P=0.023) compared to placebo (-0.9). There was no difference between tolterodine (-1.3) and placebo (P=0.22). There was also no significant difference between tolterodine and oxybutynin (95% CI, -0.2 to 1.0). The change in volume voided/micturition significantly increased with tolterodine (38 mL) and oxybutynin (47 mL) compared to placebo (6 mL; P<0.001). Approximately 47% of patients who received placebo, 50% treated with tolterodine, and 49% treated with oxybutynin perceived improvement after 12 weeks of treatment. There was no significant difference among the groups. Dry mouth was the most common adverse event. It was reported at a significantly higher rate with both tolterodine (50%) and oxybutynin (86%) than placebo (21%; P<0.001). It was also more common with oxybutynin than tolterodine (P<0.001). The proportion of patients who withdrew because of adverse events was higher in the oxybutynin group (17%) than in the tolterodine (8%) or placebo (12%) groups. Secondary: Not reported
Drutz et al.[101] (1999) Tolterodine IR 2 mg twice daily vs oxybutynin IR	DB, MC, PC, RCT Patients ≥18 years of age with OAB, increased urinary frequency (≥8 micturitions/24 hours), and symptoms of	N=277 12 weeks	Primary: Number of micturition/24 hours, incontinence episodes/24 hours and volume voided/micturition Secondary:	Primary: The number of micturitions/24 hours significantly decreased with tolterodine (-2.0; P=0.036) compared to placebo (-1.1). There was no difference between oxybutynin (-2.0) and placebo (P=0.066). There was also no significant difference between tolterodine and oxybutynin (95% CI, -0.8 to 0.8). The number of incontinence episodes/24 hours was not significantly different with tolterodine (-1.7; P=0.063) or oxybutynin (-1.7; P=0.10)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
5 mg three times daily vs placebo	urgency and/or urge incontinence (≥1 episode/24 hours)		Not reported	compared to placebo (-1.0). There was no significant difference between tolterodine and oxybutynin (95% CI, -0.7 to 0.7). The change in volume voided/micturition significantly increased with tolterodine (34 mL; P=0.0075) and oxybutynin (50 mL; P=0.0001) compared to placebo (12 mL). Dry mouth was the most common adverse event (15% of the placebo group, 30% of the tolterodine group, and 69% of the oxybutynin group). The percentage of patients reporting dry mouth was significantly higher in the oxybutynin group than in the tolterodine group (P<0.001). The percentage of patients reporting moderate or severe dry mouth was higher in the oxybutynin group (44%) compared to the tolterodine group (9%), and placebo group (7%). Other more commonly reported adverse events with oxybutynin were headache (10%) and dizziness (11%). Headache occurred in 15% of patients receiving tolterodine. The proportion of patients who withdrew because of adverse events was higher in the oxybutynin group (31%) than in the tolterodine (13%) or placebo (14%) groups. Secondary: Not reported
Leung et al.[102] (2002) Tolterodine IR 2 mg twice daily vs oxybutynin IR 5 mg three times daily	DB, MC, RCT Women ≥18 years of age with OAB, increased urinary frequency (≥8 micturitions/24 hours), and symptoms of urgency and/or urge incontinence (≥1 episode/24 hours)	N=106 10 weeks	Primary: Tolerability Secondary: Efficacy	Primary: The median drug compliance rate was 87.5% with oxybutynin and 75% in with tolterodine (P=0.778). Adverse events occurred in 49.1% of patients treated with oxybutynin and 60.4% of patients treated with tolterodine (P=0.329). The proportion of patients who withdrew was 15.1% with oxybutynin and 17.0% with tolterodine (P=1.0). Secondary: There was no significant difference in frequency of micturition (P=0.965), urgency episodes (P=0.672), incontinence episodes (P=0.993), or pad use (P=0.665) among the treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Giannitsas et al.[103] (2004) Tolterodine IR 2 mg twice daily for 6 weeks vs oxybutynin IR 5 mg three times daily for 6 weeks	OL, RCT, XO Patients ≥18 years of age with OAB who were categorized according to the characteristics of the first overactive detrusor contraction during filling cystometrogram: high volume–low pressure (grade-group I), high volume–high pressure (grade-group II), low volume–low pressure (grade-group III) and low volume–high pressure (grade-group IV)	N=128 12 weeks	Primary: Volume voided/micturition, number of micturition/24 hours, incontinence episodes/24 hours, and other urodynamic parameters in the total population and individual severity groups Secondary: Not reported	Primary: <u>Total Study Population</u> The mean volume voided/micturition was significantly increased with tolterodine (40.6 mL) and oxybutynin (43.8 mL) and there was no significant difference among the treatment groups. The mean change in number of micturitions/24 hours was -0.9 with tolterodine and -0.8 with oxybutynin (which reached statistical significance only with tolterodine). There was an increase in the 24 hour volume of urine with both treatments; however it was only statistically significant with oxybutynin. Overactivity index was significantly decreased with tolterodine and oxybutynin; there was no significant difference among the treatment groups. There was a significant increase in bladder volume at first desire to void with tolterodine and oxybutynin, which was significantly higher with oxybutynin. The volume at first overactive detrusor contraction and maximum cystometric capacity were significantly increased with tolterodine and oxybutynin; there was no significant difference among the treatment groups. There was no significant change in pressure of first overactive contraction with tolterodine or oxybutynin. <u>Low volume–High pressure Overactivity (Group IV)</u> The mean volume voided/micturition was significantly increased with tolterodine (39.7 mL) and oxybutynin (54.2 mL) and there was no significant difference among the treatment groups. The mean change in number of micturitions/24 hours was -0.9 with tolterodine and -1.0 with oxybutynin; there was no significant difference among the treatment groups. There was an increase in the 24 hour volume of urine with both treatments; however it was only statistically significant with oxybutynin. Overactivity index was significantly decreased with oxybutynin. Volume at first desire to void was significantly increased with oxybutynin and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				volume at first overactive contraction was significantly increased with tolterodine. There was no significant change in pressure of first overactive contraction with tolterodine or oxybutynin. <u>Low volume–Low pressure Overactivity (Group III)</u> The mean volume voided/micturition was significantly increased with tolterodine (48.8 mL) and oxybutynin (43.1 mL) and there was no significant difference among the treatment groups. There were no significant changes in the rest of voiding diary parameters in this group. Overactivity index was significantly reduced with tolterodine only. Volume at first desire to void was increased significantly with tolterodine and oxybutynin; there was no significant difference among the treatment groups. There were no significant changes for pressure of first overactive contraction and cystometric capacity with tolterodine or oxybutynin. <u>High volume–High pressure Overactivity (Group II)</u> Changes in clinical parameters did not reach statistical significance. Overactivity index was reduced by tolterodine and oxybutynin; there was no significant difference among the treatment groups. Oxybutynin achieved an increase in volume at first desire to void and volume at first overactive contraction. There were no significant changes in max cystometric capacity and pressure of first overactive contraction. <u>High volume–Low pressure Overactivity (Group I)</u> The small number of patients in this group did not allow for statistical analyses to be performed. Secondary: Not reported
Harvey et al.[104] (2001) Tolterodine IR	MA Patients ≥18 years of age with OAB,	4 trials 12 weeks	Primary: Incontinent episodes/24 hours, quantity of pad	Primary: The mean change in number of micturitions/24 hours was not significantly different between tolterodine and oxybutynin (WMD, 0.00; 95% CI, -0.38 to 0.38).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
1 to 2 mg twice daily vs oxybutynin IR 2.5 to 5 mg three times daily	increased urinary frequency (≥8 micturitions/24 hours), and symptoms of urgency and/or urge incontinence (≥1 episode/24 hours)		used/24-hour period, micturitions/24 hours, and voided volume/micturition Secondary: Adverse events	The number of incontinence episodes/24 hours significantly favored oxybutynin compared to tolterodine (WMD, 0.41; 95% CI, 0.04 to 0.77). The change in volume voided/micturition significantly favored oxybutynin (–8.24 mL; 95% CI, –14.11 to –2.38). This translates to an average increase in the volume voided/micturition of more than 8 mL among patients using oxybutynin compared to patients using tolterodine. Secondary: Dry mouth was significantly lower with tolterodine than oxybutynin (RR, 0.54; 95% CI, 0.48 to 0.61), including moderate to severe dry mouth (RR, 0.33; 95% CI, 0.24 to 0.45). There were fewer patients who withdrew from studies due to dry mouth with tolterodine compared to oxybutynin (RR, 0.63; 95% CI, 0.46 to 0.88).
Staskin et al.[105] (2004) Trospium 20 mg twice daily vs placebo	DB, MC, PC, RCT Patients with OAB	N=658 12 weeks	Primary: Central nervous system adverse effects and daytime sleepiness using the SSS Secondary: Not reported	Primary: After 12 weeks of treatment, 2.5% of patients receiving placebo and 1.5% of patients receiving trospium exhibited a clinically significant increase (3 points or greater) from baseline in their SSS scores. There was no significant difference between the treatment groups. In a subgroup analysis based on age (<65 and ≥65 years of age; <75 and ≥75 years of age), there was no significant difference in SSS scores among the treatment groups. Approximately 5.8% of patients receiving trospium and 5.2% of patients receiving placebo reported at least one central nervous system adverse event. Somnolence was reported by 0.3% of patients receiving trospium and 0.6% of patients receiving placebo. Sedation was reported by 0.3% of patients receiving placebo and no patients reported sedation with trospium. Secondary: Not reported
Halaska et al.[106] (2003) Trospium (TCl) 20	AC, DB, MC, RCT Patients ≥18 years of age with urge	N=358 52 weeks	Primary: Safety and efficacy Secondary:	Primary: Blood chemistry, nitrogenous metabolites, uric acid, and sodium and potassium were not adversely affected by either treatment.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg twice daily vs oxybutynin IR (OXY) 5 mg twice daily	syndrome, urge incontinence, urge incontinence as one component of mixed incontinence, or urge incontinence due to a neurological condition (detrusor hyperreflexia)		Not reported	Systolic and diastolic blood pressure were unaffected by the treatments. A pulse rate of >100 beats/min was noted in 27 patients treated with TCl (10.1%) as compared to six patients in the OXY group (6.7%). In the TCl group at 26 and 52 weeks of treatment, 49 and 63% of the trial physicians assessed tolerability as very good, respectively. In the OXY group, the assessment by the trial physicians at the same points showed very good tolerability in 36 and 42% of patients, respectively. Appraisal by the patients led to similar results. Adverse events were observed in 64.8% of patients in the TCl group and 76.7% of patients in the OXY group. Dry mouth was the most common adverse event and was reported by 33% of patients treated with TCl and 50% of those treated with OXY. UTI was reported by 12% of patients receiving TCl and 11% of patients receiving OXY. For the adverse events taken as a whole, the differences between TCl and OXY were significant with regards to time to event (P<0.01). There was also a significant difference between the two treatment groups in favor of TCl for the overall total of adverse events having probable or possible connections with the trial medication (P=0.02), for all gastrointestinal adverse events with this classification (P=0.02) and for dryness of the mouth (P<0.01). When the number of adverse events is viewed in relation to the total number of patients treated and the duration of treatment, the risk of occurrence of an adverse event/patient/week is 0.027 for TCl and 0.045 for OXY (RR, 0.6 in favor of TCl). Patients treated with TCl showed increases in maximum cystometric bladder capacity of 92 mL at 26 weeks and 115 mL at 52 weeks. The OXY group showed increases of 117 and 119.4 mL respectively. The changes from baseline were significant in both treatment arms (P=0.001). There was no significant difference between the treatment groups. The increase in volume at the first unstable contraction was 46.0 mL with TCl and 36.7 mL with OXY. There was no significant difference between the treatment groups. There was no significant difference between the treatment groups in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				volume at the first sensation to void, as well as of other urodynamic parameters. The frequency of micturition in the TCl group decreased by 1.2 micturitions/day at two weeks, 2.9 micturitions/day at 26 weeks and 3.5 micturitions/day at 52 weeks. In frequency of micturitions in the OXY group decreased by 1.5 micturitions/day at two weeks, 3.4 micturitions/day at 26 weeks and 4.2 micturitions/day at 52 weeks. Episodes of urgency in the TCl group decreased by 1.6 at two weeks, 3.2 at six weeks and 3.5 at 52 weeks. In the OXY group, episodes of urgency decreased by 1.7 at 2 weeks, 3.2 at 26 weeks and 3.6 at 52 weeks. After 52 weeks of treatment, 29 and 17% of the physicians considered the therapeutic outcome for the TCl and OXY groups as ‘‘cure’’, respectively. The results were similar with regards to patient assessments. Secondary: Not reported
Madersbacher et al.[107] (1995) Trospium (TCl) 20 mg twice daily vs oxybutynin IR (Oxy) 5 mg three times daily	DB, MC, RCT Patients with detrusor hyperreflexia	N=95 2 weeks	Primary: Maximum bladder capacity and maximum voiding detrusor pressure during micturition Secondary: Bladder compliance, residual urine, adverse events	Primary: Maximum bladder capacity in the TCl group increased significantly by 96.6 mL (P<0.001). In the Oxy group, maximum bladder capacity increased by 163.0 mL (P<0.001). There was no significant difference between the treatment groups (P=0.057). Maximum detrusor pressure during micturition decreased by 35.4 cmH_20 (P<0.001) in the TCl group and 38 cmH_20 (P<0.001) in the Oxy group. There was no significant difference between the treatment groups (P=0.63). Secondary: Bladder compliance increased by 16.96 mL/cm H_20 (P<0.001) in the TCl group and by 22.56 mL/cmH_20 in the Oxy group (P<0.001). There was no significant difference between the treatment groups (P=0.43). Residual urine increased by 76.45 mL in the TC1 group and 114.08 in the Oxy group. There was no significant difference between the treatment

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				groups (P=0.19). There was no significant difference between the treatment groups with regards to the frequency of hyper-reflexive waves (P=0.16). There were no significant changes in blood pressure among the treatment groups. The rate of adverse events was similar in both groups. Dry mouth occurred in 54% of patients in the TCl group and 56% of patients in the Oxy group. The severity grading showed that dryness of the mouth deteriorated to 'severe' in 4% of patients receiving TC1 and 23% of patients receiving Oxy. Withdrawal from the trial occurred more frequently in patients taking Oxy (16%) than in those taking TCl (6%). The Oxy patients withdrew earlier (after an average of 7.1 days) than the TCl patients (after an average of 14.3 days).
Zinner et al.[108] (2011) Trospium ER 60 mg once daily	ES, OL Patients ≥18 years of age with symptoms of OAB for ≥6 months who met the following criteria: urinary frequency ≥30 toilet voids per 3 days, ≥1 severe urgency severity rating per 3 days, and ≥3 UUI episodes per 3 days	N=944 48 weeks	Primary: Changes in the mean number of toilet voids per day and UUI episodes per day Secondary: Urgency severity associated with toilet voids, voided volume per void, daily urgency frequency associated with toilet voids, OAB-PGA, KHQ, and OAB-q	Primary: There were reductions from baseline in the number of daily toilet voids and UUI episodes in both the placebo-to-trospium and trospium-to-trospium groups. The mean change in number of toilet voids per day was -3.2 (-24.5%) in the placebo-to-trospium group and -3.4 (-25.5%) in the trospium-to-trospium group at week 48. The median change in the number of UUI episodes per day was -2.3 in both groups (-85.7%). Secondary: Urgency severity associated with toilet voids, voided volume per void, and daily urgency frequency associated with toilet voids all improved in both groups. Significant improvements in OAB-PGA findings were present with both groups. Patients in the placebo-to-trospium and trospium-to-trospium groups reported improvements from baseline in individual questions addressing toilet void frequency (84.1 and 85.1%, respectively), UUI (79.9 and 82.6%, respectively), and urgency severity (79.2 and 81.6%, respectively). Overall OAB symptoms improved in approximately 84% of patients. KHQ and OAB-q demonstrated improvements with both groups at week 48.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Overall, 552 patients (58.5%) experienced ≥1 treatment emergent adverse events, of which 197 were considered at least possibly related to study medication. Dry mouth (n=60) and constipation (n=59) were the most common adverse events reported.
Bolduc et al.[109] (2009) Combination antimuscarinic therapy (oxybutynin 10 to 30 mg, tolterodine ER 4 mg, and/or solifenacin 5 to 10 mg)	OL, PRO Children with OAB, persistent incontinence and a partial urodynamic response to an optimal dose of a well-tolerated, ER antimuscarinic drug	N=33 ≥6 months	Primary: Efficacy for continence Secondary: Safety and tolerability	Primary: Continence improved in all cases. A total of 17 (52%), 14 (42%), and two patients (6%) rated 100% improvement (complete dryness), a >90% decrease in incontinence episodes and a 50 to 89% decrease, respectively. MVV in three-day diaries improved from 165 to 330 mL. Cystometric bladder capacity improved from 192 to 380 mL without any deterioration in compliance and maximum detrusor contraction pressure decreased from 77 to 18 cm H_20 (P<0.01). Secondary: Overall, 12 patients (36%) reported no adverse effects, 16 (48%) reported mild adverse effects (dry mouth, constipation, blurred vision, and headache), and 5 (15%) had a moderate adverse effect (dry mouth). No patients discontinued therapy due to adverse effects.
Chapple et al.[110] (2008) Darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, trospium	MA Patients ≥18 years of age with OAB	73 trials ≥2 weeks	Primary: Incontinence episodes/day, number of micturitions/day, urgency episodes/day, volume voided/micturition, proportion of patients returning to continence, proportion of patients undergoing global improvements in their storage	Primary: Antimuscarinic agents were significantly more effective than placebo with regards to the mean change in the number of incontinence episodes/day. Pooled differences in mean changes ranged from 0.4 to 1.1 incontinence episodes per day. Tolterodine 2 mg IR was not more effective than placebo; however, the 4 mg ER/IR formulations were more effective than placebo. There were no significant differences among the antimuscarinic agents with the exception of fesoterodine 8 mg/day. One study found that this agent was more effective than tolterodine ER 4 mg/day (P=0.03). Antimuscarinic agents were significantly more effective than placebo with regards to the mean change in the number of micturitions/day. Pooled differences in mean changes ranged from 0.5 to 1.3 episodes per day. Three trials favoring solifenacin 10 mg/day over tolterodine IR 4 mg/day (P=0.01). Four trials favored solifenacin 10 mg/day over solifenacin 5 mg/day (P=0.02). Otherwise, there were no significant differences among the antimuscarinic agents.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			LUTS Secondary: Tolerability, safety, and HRQOL	Fesoterodine, propiverine, solifenacin, and tolterodine were significantly more effective than placebo with regards to the mean change in the number of urgency episodes/day (when this outcome was reported). Pooled differences in mean changes ranged from 0.64 to 1.56 episodes per day. Some trial data favored solifenacin 10 mg/day over tolterodine IR 4 mg/day (P<0.01) and solifenacin 5 mg/day over tolterodine IR 4 mg/day (P=0.01). Otherwise, there were no significant differences among the antimuscarinic agents. Antimuscarinic agents were significantly more effective than placebo with regards to the mean change in the volume voided/micturition (when this outcome was reported). Differences in pooled mean changes were 13 to 40 ml. Solifenacin 10 mg/day was favored over tolterodine IR 4 mg/day (P<0.01); solifenacin 10 mg/day was favored over solifenacin 5 mg/day (P<0.01); fesoterodine 8 mg/day was favored over tolterodine ER 4 mg/day (P=0.03); and oxybutynin IR 15 mg/day was favored over tolterodine IR 4 mg/day (P<0.01). The proportions of patients who had improvements in their bladder condition was significantly higher for fesoterodine 4 and 8 mg/day than for placebo (P=0.01and P=0.01, respectively). Otherwise, there were no significant differences among the antimuscarinic agents. Secondary: Compared to placebo, treatment with oxybutynin IR (15 and 7.5 to 10 mg/day) was associated with significantly higher risk of withdrawal due to any cause (P=0.04 and P<0.01, respectively). Otherwise, there was no significant difference in the proportions of patients who withdrew for any causes between active treatments and placebo. Oxybutynin IR 7.5 to 10 mg/day was associated with a significantly greater risk of withdrawal due to any cause than oxybutynin ER 5 mg/day (P=0.03); oxybutynin IR 7.5 to 10 mg/day was associated with a greater risk of withdrawal than tolterodine ER 4 mg/day (P<0.01) and tolterodine IR 4 mg/day (P=0.04); oxybutynin IR 15 mg/day was associated with a greater risk of withdrawal than tolterodine IR 4 mg/day P<0.01) and oxybutynin ER 15 mg/day (P=0.04).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Tolterodine ER 4 mg/day was associated with a significantly lower risk of withdrawal due to an adverse event than placebo (P=0.02). Formulations associated with a significantly higher risk of withdrawal due to adverse events than placebo were as follows: oxybutynin IR 7.5 to 10 mg/day (P=0.01), oxybutynin IR 15 mg/day (P<0.01), and solifenacin 10 mg/day (P=0.04). Tolterodine ER 4 mg/day was associated with lower risk of withdrawal due to an adverse event compared to oxybutynin transdermal delivery system 3.9 mg/day (P=0.01) and oxybutynin IR 15 mg/day (P<0.01); tolterodine IR 4 mg/day was associated with a lower risk than oxybutynin IR 15 mg/day (P<0.01); and oxybutynin ER 5 mg/day was associated with a lower risk than oxybutynin ER 15 mg/day (P=0.04). Otherwise, there were no significant differences among the antimuscarinic agents. Every antimuscarinic agent was associated with a significantly greater risk of adverse events than placebo, except tolterodine IR 2 mg/day (P=0.97) and oxybutynin transdermal delivery system 3.9 mg/day (P=0.07). The pooled RR for any adverse event in comparison to placebo varied between 1.13 and 2.00. The risk of adverse events was significantly lower with tolterodine IR 2 mg/day than with oxybutynin ER 5 mg/day (P<0.01) and lower with tolterodine IR 4 mg/day than with oxybutynin IR 7.5 to 10 mg/day (P<0.01) and oxybutynin IR 15 mg/day (P<0.01). There was a higher risk of adverse events with fesoterodine 8 mg/day than with fesoterodine 4 mg/day (P=0.04) and tolterodine ER 4 mg/day (P=0.04). There was a higher risk of adverse events with oxybutynin IR 7.5 to 10 mg/day than with trospium 40 mg/day (P=0.02). Dry mouth was the most frequently reported adverse event and occurred in 29.6% of patients receiving antimuscarinic therapy compared to 7.9% of patients receiving placebo. The following adverse events were reported at statistically significantly higher levels in first-named active treatments than in second-named active treatments: blurred vision (solifenacin 10 mg/day vs solifenacin 5 mg/day, solifenacin 10 mg/day vs tolterodine IR 4 mg/day); constipation (solifenacin 5 mg/day vs tolterodine ER and IR 4 mg/day, darifenacin 15 mg/day vs tolterodine IR 4 mg/day); fatigue (tolterodine ER 4 mg/day vs fesoterodine 4 or 8 mg/day); nausea

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(oxybutynin IR 15 mg/day vs oxybutynin ER 15 mg/day); and vomiting (tolterodine ER 4 mg/day vs oxybutynin ER 7.5 to 10 mg/day). Significant differences in HRQOL were reported for darifenacin, fesoterodine, oxybutynin transdermal delivery system, solifenacin, tolterodine ER and IR, and trospium compared to placebo.
Hay-Smith et al.[111] (2009) Darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, trospium	MA Patients with OAB with or without a urodynamic diagnosis of detrusor overactivity	N=11,332 (49 trials) Variable duration	Primary: QOL, patient's observations, symptoms, objective measurements, adverse events Secondary: Not reported	Primary: <u>Oxybutynin vs tolterodine (10 studies)</u> There was no significant difference between the groups in the proportion of people reporting cure/improvement (47% with tolterodine vs 44% with oxybutynin; RR, 1.06; 95% CI 0.89 to 1.26). There was no significant difference between IR tolterodine and ER oxybutynin with regards to the change in the number of leakage episodes/24 hours (WMD, -0.15; 95% CI, -0.47 to 0.16). There was no significant difference between IR tolterodine and ER oxybutynin with regards to the change in micturitions/24 hours (WMD, -0.25; 95% CI, -0.61 to 0.10). There were fewer withdrawals with tolterodine therapy (7%) compared to treatment with oxybutynin (12%; RR, 0.57; 95% CI, 0.43 to 0.75). Dry mouth was significantly lower with tolterodine than oxybutynin (RR, 0.60; 95% CI, 0.54 to 0.66). <u>Oxybutynin vs trospium (four studies)</u> Two trials reported on maximum cystometric capacity and residual volume and there was no significant difference between the groups. Dry mouth was significantly lower with trospium than oxybutynin (RR, 0.74; 95% CI, 0.59 to 0.93). <u>ER vs IR oxybutynin (four trials)</u> There was no significant difference in patient's perception of improvement (one trial). There was no significant difference between the groups in the number of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				leakage episodes/24 hours. There was a lower maximum cystometric capacity and larger volume at first contraction in the ER formulations; however, only volume at first contraction was significant. There was no significant difference in residual volume measured using ultrasound. There was no significant difference in withdrawals due to adverse events between IR and ER groups. Dry mouth was significantly lower with the ER preparations (RR, 0.77; 95% CI, 0.66 to 0.91). <u>ER vs IR tolterodine (one trial)</u> There was no significant difference between the ER and IR formulations with regards to leakage episodes or micturitions/24 hours. There was no significant difference in withdrawals due to adverse events. There were fewer reports of dry mouth for those using the ER preparation. <u>ER oxybutynin vs IR tolterodine (one trial)</u> There was no significant difference in the number of leakage episodes/24 hours. There was a significant difference in favor of oxybutynin for the number of micturitions/24 hours. There was no significant difference in the number of withdrawals due to adverse events among the treatment groups. There was no significant difference in the rate of dry mouth among the treatment groups. <u>ER tolterodine vs IR oxybutynin (one trial)</u> The risk of dry mouth was less for those taking ER tolterodine compared to oxybutynin IR. <u>Tolterodine ER vs oxybutynin ER (two trials)</u> There was no significant difference in change in leakage episodes or micturitions/24 hours (one trial).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There was no statistically significant difference between the groups in withdrawals due to adverse events. There was no significant difference in the rate of dry mouth among the treatment groups; however, there was clinical heterogeneity noted among the studies. One study found significantly fewer reports of dry mouth with oral ER tolterodine than oral ER oxybutynin. There was no difference in risk of dry mouth between oral ER tolterodine and transdermal ER oxybutynin. Secondary: Not reported
Maman et al.[112] (2014) Darifenacin, fesoterodine, mirabegron, oxybutynin, solifenacin, tolterodine, trospium	MA Patients ≥18 years of age with a diagnosis of OAB, may be referred to as detrusor overactivity or urinary urgency	N=27,309 (44 trials) Variable duration	Primary: Efficacy outcomes including micturition frequency, incontinence and urgency urinary incontinence; safety outcomes including dry mouth, constipation and blurred vision Secondary: Not reported	Primary: The results from 26 studies (22,040 patients) showed that the effect of mirabegron 50 mg did not differ significantly in terms of micturition frequency from other treatments, except solifenacin 10 mg, which was more effective (mean difference vs mirabegron 50 mg of -0.584). The estimated mean difference of tolterodine compared to mirabegron was not significant (0.157 micturition episodes per day). The results from 17 studies (13,101 patients) showed improvement with mirabegron 50 mg in the daily number of incontinence episodes per 24 hours from baseline to end of study was not significantly different from improvements with tolterodine 4 mg, oxybutynin 10 mg, darifenacin 7.5 mg and 15 mg and fesoterodine 4 mg and 8 mg. Mirabegron 50 mg was statistically superior to placebo with a mean difference estimated at 0.493 incontinence episodes per day. The results of 18 studies (16,044 patients) showed that mirabegron 50 mg was significantly less efficacious than solifenacin 10 mg in terms of urgency urinary incontinence (mean difference vs mirabegron 50 mg of -0.422 urgency incontinence episodes per day) and did not differ significantly from other antimuscarinics. All 44 trials (27,309 patients) reported a similar incidence of dry mouth with mirabegron 50 mg to placebo (OR, 1.344). All antimuscarinics were associated with a significantly higher risk of dry mouth compared with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				mirabegron 50 mg. The OR for the occurrence of dry mouth with antimuscarinics compared with mirabegron 50 mg ranged from 5.213 with solifenacin 5 mg to 40.702 with oxybutynin IR 15 mg. Data of 41 studies (25,257 patients) reported incidence of constipation associated with mirabegron 50 mg was comparable with placebo (OR, 0.732). Other antimuscarinics except darifenacin 15 mg, fesoterodine 8 mg, solifenacin 5 mg, solifenacin 10 mg and trospium 60 mg had similar incidences of constipation. The 25 studies (14,348 patients) available reported blurred vision being relatively rare and no significant difference in risk of developing blurred vision was found between treatments arms. Secondary: Not reported

Drug regimen abbreviations: ER=extended-release, IR=immediate-release, LA=long acting, SR=sustained-release, XL=extended release
Study abbreviations: AC=active control, CI=confidence interval, DD=double-dummy, DB=double-blind, ES=extension study, MA=meta-analysis, MC=multicenter, NS=not significant, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RR=relative risk, XO=crossover
Miscellaneous abbreviations: BPH=benign prostatic hyperplasia, BOO=bladder outlet obstruction, HRQOL=health-related quality of life, ICIQ-SF=International Consultation on Incontinence Questionnaire–Short Form, IIQ=incontinence impact questioner, IPSS=international prostate symptoms score, IPSS-QOL=international prostate symptoms score quality of life, KHQ=King's Health Questionnaire, LUTS=lower urinary tract symptoms, MVV=mean voided volume per void, OAB=overactive bladder, OAB-PGA=Overactive Bladder Patient Global Assessment questionnaire, OAB-q=Overactive Bladder Questionnaire, OABSS=Overactive Bladder Symptom Scores, PPBC=Patient Perception of Bladder Condition Questionnaire, PGA=patient global assessment, PRO=patient reported outcome, PVR=postvoid residual, Qmax=maximum flow rate, QOL=quality of life, QOL-I=Quality of Life Index, SMD=standard mean difference, SSS=Stanford Sleepiness Scale, TSQ=Treatment Satisfaction Questionnaire, UDI=urogenital distress inventory, UPS=Urgency Perception Scale, URI=upper respiratory infection, USS=Urinary Sensation Scale, UTI=urinary tract infection, UUI=urgency urinary incontinence, VAS=visual analog scale, VVPM=volume voided per micturition, WMD=weighted mean difference

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 9. Relative Cost of the Genitourinary Smooth Muscle Relaxants

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Darifenacin	extended-release tablet	Enablex®	$$$$	N/A
Fesoterodine	extended-release tablet	Toviaz®	$$$$	N/A
Flavoxate	tablet	N/A	N/A	$$$
Mirabegron	extended-release tablet	Myrbetriq®	$$$$	N/A
Oxybutynin	extended-release tablet, syrup, tablet, transdermal gel, transdermal patch	Ditropan XL®*, Gelnique®, Oxytrol®	$$$$$	$$$
Solifenacin	tablet	Vesicare®	$$$$	N/A
Tolterodine	extended-release capsule, tablet	Detrol®*, Detrol LA®*	$$$$$	$$$$
Trospium	extended-release capsule, tablet	N/A	N/A	$$$$

*Generic is available in at least one dosage form or strength.
N/A=Not available

X. Conclusions

Urinary incontinence and overactive bladder cause both physical and psychological morbidity, as well as adversely impact quality of life.[1] Initial treatment options include lifestyle modifications (weight loss and dietary changes) and behavioral therapy (bladder training, physical therapy, and toileting assistance). Pharmacologic

therapy is typically trialed if initial treatment is ineffective.[2,4] Antimuscarinic drugs increase bladder capacity, decrease urgency, and are useful for the treatment of urge incontinence.[4] Beta-3 adrenergic receptor agonists increase bladder capacity via relaxation of the detrusor smooth muscle. This novel mechanism may improve tolerability compared to antimuscarinic agents. [4,18] Flavoxate, oxybutynin, tolterodine, and trospium are available in a generic formulation.

Several guidelines provide recommendations on the use of the genitourinary smooth muscle relaxants for the treatment of urinary incontinence and overactive bladder. Antimuscarinic agents are the primary treatment for patients with overactive bladder symptoms (with or without urge incontinence), in addition to lifestyle modifications and behavioral therapy.[2,19-24] In general, the guidelines do not identify a single preferred agent for initial therapy. However, several recent guidelines provide general recommendations.[20-21,24] For example, two guidelines from the American Urological Association and the European Association of Urology favor the use of extended-release preparations.[20-21] In addition, guidelines from the National Institute of Health and Clinical Excellence recommend immediate-release oxybutynin, immediate-release tolterodine, or once-daily darifenacin as initial therapy.[19] Several guidelines also recommend the use of transdermal oxybutynin if anticholinergic side effects are experienced with initial therapy.[20-21,24]

In clinical trials, the genitourinary smooth muscle relaxants have been shown to modestly improve urinary symptoms, including frequency, urgency, nocturia, and incontinence episodes.[25-112] The majority of the studies were six to 12 weeks in duration; however, a few long-term (up to 36 months), open-label, non-comparative studies have also been conducted. There were relatively few active-controlled studies found in the medical literature with flavoxate, darifenacin, fesoterodine, solifenacin, or trospium. The majority of the active-controlled studies compared oxybutynin and tolterodine. Several studies have demonstrated similar efficacy with the genitourinary smooth muscle relaxants for most, but not all, of the outcomes assessed. In general, studies directly comparing immediate-release and extended-release formulations of the same drug found no differences in efficacy.[51-55,61,89] Studies directly comparing immediate-release formulations of different drugs, as well as studies directly comparing extended-release formulations of different drugs, also demonstrated similar efficacy.[26,29,37,42,58-59,77,80,96-103,106-107] Few studies have demonstrated greater efficacy with one genitourinary smooth muscle relaxant over another.[25,38,43,46,57-58,75,79,83,91] The use of the genitourinary smooth muscle relaxants for the treatment of urinary incontinence and overactive bladder has also been associated with an improvement in quality of life.[37,41,52,74,82-83,90]

Adverse events occur frequently with the genitourinary smooth muscle relaxants due to their antimuscarinic effects, which often leads to discontinuation of therapy. The most common adverse events include dry mouth, blurred vision, abdominal discomfort, drowsiness, nausea, and dizziness. These agents may also cause confusion or memory impairment in the elderly.[4] The incidence of adverse events varies among the agents and depends upon the formulation used (extended-release, immediate-release, or transdermal). Adverse events tend to be higher with the immediate-release formulations compared to extended-release formulations. In general, dry mouth occurs at a higher rate with oral oxybutynin than with the other agents.

There is insufficient evidence to support that one brand genitourinary smooth muscle relaxant is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand genitourinary smooth muscle relaxants within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand genitourinary smooth muscle relaxant is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Disease-Modifying Antirheumatic Agents
AHFS Class 923600
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I. Overview

The disease-modifying antirheumatic drugs (DMARDs) are used for a variety of inflammatory and immunologic conditions which include: rheumatoid arthritis, neonatal-onset multisystem inflammatory disease, psoriatic arthritis, plaque psoriasis, juvenile/systemic idiopathic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, and hidradenitis suppurativa. These agents achieve their therapeutic effect via several different mechanisms of action. The majority of oral and injectable agents inhibit the effect of proinflammatory cytokines, specifically interleukins or tumor necrosis factor (TNF)-α. Interleukin (IL) inhibitors include anakinra (Kineret®) and tocilizumab (Actemra®), while the TNF-α inhibitors are adalimumab (Humira®), certolizumab pegol (Cimzia®), etanercept (Enbrel®), golimumab (Simponi®, Simponi ARIA®), and infliximab (Remicade®). Abatacept (Orencia®) is a T-cell activation inhibitor, apremilast (Otezla®) is a phosohodiesterase-4 (PDE-4) inhibitor, leflunomide (Arava®) is a pyrimidine synthesis inhibitor, and tofacitinib (Xeljanz®) is a Janus kinase inhibitor.[1-14]

The interleukins (ILs) that are targeted by immunomodulator agents are IL-1 (1α and/or 1β), IL-6, IL-12, IL-17A, or IL-23. IL-1 plays an important role in the inflammatory process as a proinflammatory mediator along with TNF-α. IL-1 is also associated with cartilage breakdown as well as stimulation of bone resorption. Anakinra is a recombinant, non-glycosylated form of the naturally occurring human interleukin-1 receptor antagonist (IL-1Ra) and blocks the effect of both IL-1α and IL-1β at its receptor.[3,13-15] IL-6 is a chemical messenger that has been associated with the inflammatory process as well as other diverse processes such as T-cell activation, immunoglobulin secretion induction, hepatic acute phase protein synthesis initiation, and hematopoietic precursor cell proliferation and differentiation stimulation. Tocilizumab is a humanized monoclonal antibody that competes with IL-6 for binding to IL-6 receptor which can be found in the serum or membrane-bound.[11,13-15]

TNF-α is another proinflammatory mediator that is released by lymphocytes. Working together with IL-1 and other cytokines and growth factors, they induce certain gene expression and protein synthesis.[15] Adalimumab, golimumab, and infliximab are monoclonal antibodies that bind to both membrane-bound TNF-α and soluble TNF-α, preventing its binding to the TNF receptors. Certolizumab pegol, an antibody-binding fragment modified with polyethylene glycol (pegylated), acts in a similar fashion. Certolizumab pegol binds to membrane bound and soluble TNF-α preventing its binding to the TNF receptor. Neither of these drugs have affinity for TNF-β, which utilizes that same receptor.[2,5,7-9,13-15] Etanercept is a fusion protein that that contains the ligand binding site of the p75 TNF receptor. As etanercept mimics the TNF receptor, it has affinity for and binds both TNF-α and TNF-β. These agents have been found to be similar with respect to adverse events and interacting medications.[6,13-15]

Abatacept is the only T-cell activation inhibitor in this class of drugs. Abatacept binds to CD80 and CD86 preventing CD28 activation, which is required for the costimulatory signal necessary for full activation of the T-cell.[1,15] Apremilast is an oral small-molecule inhibitor of PDE-4 specific for cyclic adenosine monophosphate (cAMP). Cyclic AMP is an intracellular second messenger that controls a network of pro-inflammatory and anti-inflammatory mediators. PDE-4 inhibition results in increased intracellular cAMP levels, which is thought to restore a balance of pro- and anti-inflammatory signals.[4,15] Leflunomide inhibits dihydroorotate dehydrogenase, leading to antiproliferative activity which includes the inhibition of T-cell proliferation and reduction of production of autoantibodies by B cells.[10,15] Tofacitinib is an oral janus kinase inhibitor. It is a synthetic chemical compound that interferes with specific signal-transduction pathways. Through its broad effect on multiple cytokine pathways, tofacitinib may reduce tissue inflammation and joint damage in rheumatoid arthritis.[12,15]

Because many of the DMARDs are biologic agents made from living organisms and are extremely difficult to duplicate, congress has struggled to create regulations to approve generic versions of these agents. Currently, none of the injectable agents in this class are available generically; however, the recently upheld Patient Protection and Affordable Care provides a legal framework for regulatory approval of biosimilar drugs.[16]

The disease-modifying antirheumatic agents that are included in this review are listed in Table 1. Leflunomide is the only product available in a generic formulation.

Table 1. Disease-Modifying Antirheumatic Agents Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Abatacept	injection	Orencia®	none
Adalimumab	injection	Humira®	none
Anakinra	injection	Kineret®	none
Apremilast	tablet	Otezla®	none
Certolizumab pegol	injection	Cimzia®	none
Etanercept	injection	Enbrel®	none
Golimumab	injection	Simponi®, Simponi Aria®	none
Infliximab	injection	Remicade®	none
Leflunomide	tablet	Arava®*	none
Tocilizumab	injection	Actemra®	none
Tofacitinib	tablet	Xeljanz®	none

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the disease-modifying antirheumatic agents are summarized in Table 2.

Table 2. Treatment Guidelines Using the Disease-Modifying Antirheumatic Agents

Clinical Guideline	Recommendation(s)
Assessment of Spondyloarthritis International Society/European League Against Rheumatism: **2010 Update of the Assessment of Spondyloarthritis International Society/European League Against Rheumatism Recommendations for the Management of Ankylosing Spondylitis (2010)**[17]	• Treatment of ankylosing spondylitis (AS) should be tailored according to: o Current manifestations of the disease (axial, peripheral, entheseal, extra-articular symptoms and signs). o Level of current symptoms, clinical findings, and prognostic indicators (disease activity/inflammation, pain, function [disability, handicap], structural damage [hip involvement, spinal deformities]. o General clinical status (age, sex, comorbidity, concomitant drugs). o Wishes and expectations of the patient. • Disease monitoring of patients with AS should include: patient history, clinical parameters, laboratory tests, and imaging, all according to the clinical presentation, as well as the Assessment of Spondyloarthritis International Society core set. The frequency of monitoring should be decided on an individual basis depending on symptoms, severity, and drug treatment. • Optimal management of AS requires a combination of non-pharmacological and pharmacological treatments. • Non-pharmacological treatment of AS should include patient education and regular exercise. Physical therapy with supervised exercises, individually or in a group preferred. Patient associations and self help groups may be useful. • Nonsteroidal anti-inflammatory drugs (NSAIDs), including selective cyclooxygenase (COX)-2 inhibitors, are recommended as first line drug treatment for patients with AS with pain and stiffness. Continuous treatment with an NSAID is preferred for patients with persistently active, symptomatic disease. Cardiovascular, gastrointestinal and renal risks should be taken into account. • Analgesics, such as opioids and paracetamol, might be considered for pain control in patients in whom NSAIDs are insufficient, contraindicated, and/or poorly tolerated. • Corticosteroid injections directed to the local site of musculoskeletal inflammation may be considered. The use of systemic corticosteroids for axial

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	disease is not supported by evidence. • There is no evidence for the efficacy of disease modifying antirheumatic drugs (DMARDs), including methotrexate and sulfasalazine, for the treatment of axial disease. Sulfasalazine may be considered in patients with peripheral arthritis. • Anti-tumor necrosis factor α (TNF-α inhibitor) treatment should be given to patients with persistently high disease activity despite conventional treatments according to the Assessment of Spondyloarthritis International Society recommendations. There is no evidence to support the obligatory use of DMARDs before, or concomitant with, TNF-α inhibitor treatment in patients with axial disease. There is no evidence to support a different efficacy of the various TNF-α inhibitors on the axial and articular/entheseal disease manifestations; but in the presence of inflammatory bowel disease a difference in gastrointestinal efficacy needs to be taken into consideration. Switching to a second TNF-α inhibitor might be beneficial, especially in patients that have lost response. There is no evidence to support biologic agents other than TNF-α inhibitor in AS. • Total hip arthroplasty should be considered in patients with refractory pain or disability and radiographic evidence of structural damage, independent of age. Spinal corrective osteotomy may be considered in patients with severe disabling deformity. A spinal surgeon should be consulted in patients with AS and an acute vertebral fracture.

American College of Rheumatology/ Spondylitis Association of America/ Spondyloarthritis Research and Treatment Network 2015: **Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis (2015)**[18]	• In adults with active AS, treatment with nonsteroidal antiinflammatory drugs NSAIDs is recommended over no treatment with NSAIDs. Continuous treatment with NSAIDs is recommended over on-demand treatment with NSAIDs. No particular NSAID is recommended as a preferred choice.
	• In adults with active AS despite treatment with NSAIDs:
	  o Slow-acting antirheumatic drugs (SAARDs) are not recommended.
	  o TNF-α inhibitor treatment is recommended over no treatment with TNF-α inhibitors. No TNF-α inhibitor is recommended as preferred, except for patients with concomitant inflammatory bowel disease or recurrent iritis (in which case treatment with infliximab or adalimumab should be preferred over etanercept).
	• In adults with active AS despite treatment with NSAIDs and who have contraindications to TNF-α inhibitors, treatment with a SAARD is recommended over treatment with a non- TNF-α inhibitor biologic agent.
	• In adults with active AS despite treatment with the first TNF-α inhibitor used:
	  o Treatment with a different TNF-α inhibitor is recommended over adding a SAARD.
	  o Treatment with a different TNF-α inhibitor is recommended over treatment with a non- TNF-α inhibitor biologic agent.
	• In adults with active AS, treatment with systemic glucocorticoids is not recommended.
	• In adults with AS and isolated active sacroiliitis despite treatment with NSAIDs, treatment with locally administered parenteral glucocorticoids is recommended over no treatment with local glucocorticoids.
	• In adults with AS with stable axial disease and active enthesitis or peripheral arthritis despite treatment with NSAIDs, treatment with locally administered parenteral glucocorticoids is recommended over no treatment with local glucocorticoids.
	• In adults with stable AS, on-demand treatment with NASIDs is recommended over continuous treatment with NSAIDs.
	• In adults with stable AS receiving treatment with TNF-α inhibitor and NSAIDs, it is recommended to continue treatment with TNF-α inhibitor alone compared to continuing both treatments.
	• In adults with stable AS receiving treatment with TNF-α inhibitor and SAARDs,

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	it is recommended to continue treatment with TNF-α inhibitor alone compared to continuing both treatments.
Assessment of Spondyloarthritis International Society: **2010 Update of the International Assessment of Spondyloarthritis International Society Recommendations for the Use of Anti-Tumor Necrosis Factor Agents in Patients with Axial Spondyloarthritis (2010)**[19]	• All patients should have had adequate therapeutic trials of at least two NSAIDs. An adequate therapeutic trial is defined as at least two NSAIDs over a four-week period in total at a maximum recommended dose unless contraindicated. • Patients with pure axial manifestations do not have to take DMARDs before TNF-α inhibitor treatment can be started. • Patients with symptomatic peripheral arthritis should have an insufficient response to at least one local corticosteroid injection if appropriate, and should normally have had an adequate therapeutic trial of a DMARD, preferably sulfasalazine. • Patients with symptomatic enthesitis must have failed appropriate local treatment.

National Institute for Health and Clinical Excellence: **TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis (2016)**[20]	• Adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab are recommended, within their marketing authorizations, as options for treating severe active ankylosing spondylitis in adults whose disease has responded inadequately to, or who cannot tolerate, NSAIDs. Infliximab is recommended only if treatment is started with the least expensive infliximab product. People currently receiving infliximab should be able to continue treatment with the same infliximab product until they and their clinician consider it appropriate to stop.
	• Adalimumab, certolizumab pegol, and etanercept are recommended, within their marketing authorizations, as options for treating severe non-radiographic axial spondyloarthritis in adults whose disease has responded inadequately to, or who cannot tolerate, NSAIDs.
	• The choice of treatment should be made after discussion between the clinician and the patient about the advantages and disadvantages of the treatments available. This may include considering associated conditions such as extra-articular manifestations. If more than one treatment is suitable, the least expensive (taking into account administration costs and patient access schemes) should be chosen.
	• The response to adalimumab, certolizumab pegol, etanercept, golimumab, or infliximab treatment should be assessed 12 weeks after the start of treatment. Treatment should only be continued if there is clear evidence of response, defined as:
	  o a reduction in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score to 50% of the pre-treatment value or by 2 or more units and
	  o a reduction in the spinal pain visual analogue scale (VAS) by 2 cm or more.
	• Treatment with another TNF-α inhibitor is recommended for people who cannot tolerate, or whose disease has not responded to, treatment with the first TNF-α inhibitor, or whose disease has stopped responding after an initial response.
	• When using BASDAI and spinal pain VAS scores, healthcare professionals should take into account any physical, sensory, or learning disabilities, or communication difficulties that could affect the responses to the questionnaires and make any adjustments they consider appropriate.

American College of Gastroenterology: **Management of Crohn's Disease in**	<u>Mild to moderate active disease</u> • Ileal, ileocolonic, or colonic disease has commonly been treated in clinical practice with oral mesalamine 3.2 to 4.0 g daily or sulfasalazine for ileocolonic or colonic disease as 3 to 6 g daily in divided doses.

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Adults (2009)[21]	• Despite the use of oral mesalamine treatment in the past, new evidence suggests that this approach is minimally effective as compared to placebo and less effective than budesonide or conventional corticosteroids. • Alternatively, metronidazole at a dose of 10 to 20 mg/kg/day has been used in a proportion of patients not responding to sulfasalazine. • Controlled ileal release budesonide (9 mg/day) is effective when active disease is confined to the ileum and/or right colon. • Anti-tuberculous therapy has not been effective for either induction of remission or maintenance of remission in patients with Crohn's disease. <u>Moderate to severe disease</u> • Patients with moderate to severe disease are treated with prednisone 40 to 60 mg daily until resolution of symptoms and resumption of weight gain (generally seven to 28 days). • Infection or abscess requires appropriate antibiotic therapy or drainage (percutaneous or surgical). • Elemental diets are less effective than corticosteroids, but can avoid corticosteroid-induced toxicities. • Azathioprine and 6-mercaptopurine are effective for maintaining a steroid induced remission, and parenteral methotrexate at a dose of 25 mg/week is effective for steroid-dependent and steroid-refractory Crohn's disease. • The TNF-α inhibitors, adalimumab, certolizumab, and infliximab are effective in the treatment of moderate to severely active Crohn's disease in patients who have not responded despite complete and adequate therapy with a corticosteroid or an immunosuppressive agent. • Infliximab monotherapy and infliximab in combination with azathioprine are more effective than azathioprine in the treatment of patients with moderate to severe Crohn's disease who have failed to respond to first-line therapy with mesalamine and/or corticosteroids. • Adalimumab, certolizumab, and infliximab may be used as alternatives to steroid therapy in selected patients in whom corticosteroids are contraindicated or not desired. • The anti-alpha 4 integrin antibody, natalizumab, is effective in the treatment of patients with moderate to severely active Crohn's disease who have had an inadequate response or are unable to tolerate conventional Crohn's disease therapies and TNF-α inhibitor therapy. <u>Severe/fulminant disease</u> • Because of the acuteness and diversity of presentation of patients with severe Crohn's disease and the potential for development of complications, the management decisions for these patients are based more on practicality than controlled trial evidence. • Patients with persistence of Crohn's related symptoms despite introduction of conventional oral steroids or an TNF-α inhibitor (adalimumab or infliximab), or those presenting with high fever, frequent vomiting, evidence of intestinal obstruction, rebound tenderness, cachexia, or evidence of an abscess should be hospitalized. • Surgical evaluation is warranted for patients with intestinal obstruction or who have a tender abdominal mass. • An abdominal mass should be evaluated through transabdominal ultrasound, magnetic resonance imaging scan. • Once the presence of an abscess has been excluded or if the patient has been receiving oral corticosteroids, parenteral corticosteroids equivalent to 40 to 60 mg of prednisone daily or its equivalent are administered in divided doses or as a continuous infusion.

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	• There is no specific role for total parenteral nutrition in addition to steroids. Nutritional support through elemental feeding or parenteral hyperalimentation is indicated, after five to seven days, for patients who are unable to maintain adequate nutritional requirements. Perianal and fistulizing disease • Acute suppuration is an indication for surgical drainage with or without placement of non-cutting setons. • Nonsuppurative, chronic fistulization, or perianal fissuring is treated medically with antibiotics, immunosuppressives or infliximab. Maintenance therapy • Mesalamine and sulfasalazine have not had consistent maintenance benefits after medical inductive therapy. • Conventional corticosteroids should not be used as long-term agents to prevent relapse of Crohn's disease. • Budesonide at a dose of 6 mg/day reduces the time to relapse in ileal and/or right colonic disease, but does not provide significant maintenance benefits after six months. • Azathioprine/6-mercaptopurine and methotrexate have demonstrable maintenance benefits after inductive therapy with corticosteroids. • Azathioprine can maintain remissions induced by infliximab in steroid-naive patients. • Maintenance therapy with adalimumab, certolizumab, and infliximab is effective. • Infliximab monotherapy and infliximab combined with azathioprine are more effective than azathioprine for maintenance of patients with moderate to severe Crohn's disease who have failed to respond to first-line therapy with mesalamine and/or corticosteroids. • Maintenance therapy with natalizumab is effective. • Infliximab, mesalamine, metronidazole or azathioprine/mercaptopurine should be considered after ileocolonic resections to reduce the likelihood of symptomatic recurrence, whereas conventional corticosteroids and budesonide at a dose of 6 mg/day are not effective.

National Institute for Health and Clinical Excellence: **Crohn's Disease Management in Adults, Children and Young People (2012)**[22]	Monotherapy
	• Offer monotherapy with a conventional glucocorticosteroid (prednisolone, methylprednisolone or intravenous hydrocortisone) to induce remission in people with a first presentation or a single inflammatory exacerbation of Crohn's disease in a 12-month period.
	• Consider enteral nutrition as an alternative to a conventional glucocorticosteroid to induce remission for:
	  o Children in whom there is concern about growth or side effects.
	  o Young people in whom there is concern about growth.
	• In people with one or more of distal ileal, ileocaecal or right-sided colonic disease who decline, cannot tolerate or in whom a conventional glucocorticosteroid is contraindicated, consider budesonide for a first presentation or a single inflammatory exacerbation in a 12-month period.
	• In people who decline, cannot tolerate or in whom glucocorticosteroid treatment is contraindicated, consider 5-aminosalicylate (5-ASA) treatment for a first presentation or a single inflammatory exacerbation in a 12-month period.
	• Do not offer budesonide or 5-ASA treatment for severe presentations or exacerbations.
	• Do not offer azathioprine, mercaptopurine or methotrexate as monotherapy to induce remission.

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	Combination therapy
	• Consider adding azathioprine or mercaptopurine to a conventional glucocorticosteroid or budesonide to induce remission of Crohn's disease if:
	  o There are two or more inflammatory exacerbations in a 12-month period, or
	  o The glucocorticosteroid dose cannot be tapered.
	• Assess thiopurine methyltransferase (TPMT) activity before offering azathioprine or mercaptopurine. Do not offer azathioprine or mercaptopurine if TPMT activity is deficient (very low or absent). Consider azathioprine or mercaptopurine at a lower dose if TPMT activity is below normal but not deficient (according to local laboratory reference values).
	• Consider adding methotrexate to a conventional glucocorticosteroid or budesonide to induce remission in people who cannot tolerate azathioprine or mercaptopurine, or in whom TPMT activity is deficient, if:
	  o There are two or more inflammatory exacerbations in a 12-month period, or
	  o The glucocorticosteroid dose cannot be tapered.
	
	Infliximab and adalimumab
	• Infliximab and adalimumab, within their licensed indications, are recommended as treatment options for adults with severe active Crohn's disease whose disease has not responded to conventional therapy (including immunosuppressive and/or corticosteroid treatments), or who are intolerant of or have contraindications to conventional therapy.
	• Infliximab or adalimumab should be given as a planned course of treatment until treatment failure (including the need for surgery), or until 12 months after the start of treatment, whichever is shorter.
	• People should then have their disease reassessed to determine whether ongoing treatment is still clinically appropriate. People whose disease relapses after treatment is stopped should have the option to start treatment again.
	
	Remission maintenance
	• For patients that choose maintenance therapy, offer azathioprine or mercaptopurine as monotherapy to maintain remission when previously used with a conventional glucocorticosteroid or budesonide to induce remission or to maintain remission in patients not previously treated with these medications.
	• Consider methotrexate to maintain remission only in patients who:
	  o Needed methotrexate to induce remission.
	  o Did not tolerate azathioprine or mercaptopurine for maintenance.
	  o Contraindicated to azathioprine or mercaptopurine.
	• Do not offer conventional glucocorticosteroids or budesonide to maintain remission.
	
	Remission maintenance following surgery
	• After surgery ,consider azathioprine or mercaptopurine to maintain remission in people with factors such as:
	  o More than one resection.
	  o Previously complicated or debilitating disease (e.g. abscess, involvement of adjacent structures, fistulizing or penetrating disease).
	• Consider 5-ASA treatment to maintain remission after surgery.
	• Do not offer budesonide or enteral nutrition to maintain remission after surgery.

American College of Rheumatology: **Recommendations for the Treatment of**	General considerations • Recommendations for the treatment of juvenile idiopathic arthritis (JIA) are divided into five treatment groups that were developed by the core expert panel responsible for the literature review in the recommendation development. The

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Juvenile Idiopathic Arthritis: Initiation and Safety Monitoring of Therapeutic Agents for the Treatment of Arthritis and Systemic Features (2011)[23]	treatment groups are as follows: history of arthritis of four or fewer joints, history of arthritis of five or more joints, active sacroiliac arthritis, systemic arthritis with active systemic features (and without active arthritis) and systemic arthritis with active arthritis (and without active systemic features). • Glucocorticoid joint injections for active arthritis are recommended regardless of concurrent therapy (no DMARD, nonbiologic DMARD, biologic DMARD) or JIA treatment group. Due to its "superior" efficacy, triamcinolone hexacetonide should be used. • When initiating a TNF-α inhibitor (etanercept or adalimumab), continuation of methotrexate is recommended for patients that had a partial previous response. <u>History of arthritis in four or fewer joints</u> • For patients with low disease activity, no joint contractures and without features of poor prognosis, initiation of therapy with NSAID monotherapy is recommended as a treatment option. Therapy with an NSAID without additional therapy is not recommended longer than two months. • For all patients regardless of disease activity level, prognostic features or joint contractures, initiation of intra-articular joint injections (with or without additional therapy is recommended. • For patients with high disease activity and poor prognostic features, methotrexate is recommended as initial treatment (without prior therapy). For patients with high disease activity without poor prognostic features or with moderate disease activity and poor prognostic features, methotrexate is recommended after initial joint injection. For patients with low disease activity and poor prognostic features or moderate disease activity without poor prognostic features, methotrexate is recommended after repeated joint injections. • For patients with enthesitis-related arthritis category of JIA with moderate or high disease activity with and without poor prognostic features, sulfasalazine is recommended after glucocorticoid injections or an adequate trial of NSAIDs. • Initiation of a TNF-α inhibitor is recommended for patients with moderate or high disease activity with poor prognostic features after receiving glucocorticoid joint injections and three months of methotrexate at maximum tolerated dose. Initiation of a TNF-α inhibitor is also recommended in patients with high disease activity without poor prognostic features after receiving glucocorticoid joint injections and six months of methotrexate. For patients with enthesitis-related arthritis category of JIA and moderate or high disease activity, regardless of prognostic features, TNF-α inhibitors are recommended after receiving glucocorticoid joint injections and an adequate trial of sulfasalazine (without prior methotrexate). <u>History of arthritis of five or more joints</u> • Initial treatment with methotrexate is recommended in patients with high disease activity with or without poor prognostic features and in patients with moderate disease activity and poor prognostic features. For patients with low disease activity and poor prognostic features, methotrexate therapy is recommended after one month of therapy with NSAIDs. In patients with moderate disease activity without poor prognostic features, methotrexate is recommended after one to two months of therapy with NSAIDs. • Leflunomide is a treatment alternative to methotrexate as initial therapy in patients with high disease activity and poor prognostic features. In patients with high disease activity without poor prognostic features or moderate disease activity with poor prognostic features, leflunomide is a treatment alternative after a brief trial with NSAIDs. • For patients with moderate or high disease activity, regardless of prognostic features, TNF-α inhibitors are recommended after receiving methotrexate or

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	leflunomide for three months at the maximum tolerated typical doses. For patients with low disease activity with or without poor prognostic features, TNF-α inhibitors are recommended after receiving methotrexate or leflunomide for six months. • For patients with moderate or high disease activity regardless of prognostic features, switching from one TNF-α inhibitor to another is recommended as a treatment option after receiving four months of therapy with current TNF-α inhibitor. • Abatacept is recommended as a treatment option after receiving four months of therapy with a TNF-α inhibitor in patients with high disease activity regardless of prognostic features or moderate disease activity and poor prognostic features. For patients with moderate or high disease activity regardless of prognostic features or patients with low disease activity with features of poor prognosis, abatacept is recommended as a treatment option after receiving more than one TNF-α inhibitor sequentially. • Switching to a TNF-α inhibitor is recommended as a treatment option in patients that received abatacept for three months and have high disease activity with poor prognostic features and in patients that received abatacept for six months and have moderate to high disease activity with or without features of poor prognosis. <u>Active sacroiliac arthritis</u> • For patients with high disease activity and features of poor prognosis, TNF-α inhibitors are recommended after receiving an adequate trial of NSAIDs. • A TNF-α inhibitor is recommended in patients with high disease activity regardless of prognostic features or moderate disease activity with features of poor prognosis that have received three months of methotrexate, or in patients with moderate disease without poor prognosis that received six months of methotrexate. • A TNF-α inhibitor is recommended in patients with moderate or high disease activity regardless of prognostic features that have received three months of sulfasalazine, or in patients with low disease with poor prognosis that received six months of sulfasalazine. <u>Systemic arthritis with active systemic features</u> • NSAID monotherapy is appropriate during clinical evaluation for possible systemic arthritis. NSAID monotherapy is not recommended for patients with active fever and physician global assessment of overall disease activity ≥7 of 10. In patients with active fever, continuation of NSAID monotherapy longer than one month is not appropriate. • Initial therapy with systemic glucocorticoids (with or without additional concurrent therapy) is recommended for patients with active fever and physician global assessment of seven or greater. For all patients with active fever, systemic glucocorticoids are recommended following up to two weeks of NSAIDs. • Anakinra is recommended for all patients with active fever and poor prognostic features, regardless of current therapy. For patients that sustain or develop fever while receiving systemic glucocorticoid, anakinra is recommended. <u>Systemic arthritis with active arthritis</u> • NSAID monotherapy (with or without glucocorticoid joint injections) for up to one month is recommended for patients with low disease activity without features of poor prognosis. • For all patients with active arthritis, regardless of prognostic features, methotrexate is recommended after one month or less of NSAID monotherapy (with or without glucocorticoid injections).

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	• After three months of methotrexate, anakinra is recommended for patients with moderate or high disease activity with or without poor prognostic features. Anakinra is recommended for patients with high or moderate disease activity, regardless of prognostic features, and have received methotrexate and a TNF-α inhibitor or methotrexate and abatacept. Initiation of anakinra later in the disease course may be less appropriate compared to nearer to the onset of disease. • For patients with moderate or high disease activity with or without poor prognosis features, TNF-α inhibitors are recommended after receiving three months of methotrexate. Switching from anakinra to TNF-α inhibitors may be appropriate for patients with moderate to high disease activity regardless of prognostic features. • Abatacept is recommended for patients that received methotrexate and a TNF-α inhibitor and have high disease activity regardless of prognostic features or moderate disease activity and poor prognostic features.
American College of Rheumatology: **2013 Update of the 2011 American College of Rheumatology Recommendations for the Treatment of Juvenile Idiopathic Arthritis: Recommendations for the Medical Therapy of Children With Systemic Juvenile Idiopathic Arthritis and Tuberculosis Screening Among Children Receiving Biologic Medications (2013)**[24]	<u>Initial treatment of systemic JIA with active systemic features and varying degrees of synovitis</u> • Anakinra is recommended as one initial treatment option for patients with a physician global assessment (MD global) ≥5 irrespective of the active joint count (AJC), or an MD global <5 and an AJC >0. • Systemic glucocorticoid monotherapy (oral or intravenous) is recommended for a maximum period of two weeks for patients with an MD global <5 and an AJC >4 and for all patients with an MD global ≥5 irrespective of the AJC. • Initiating NSAID monotherapy in a patient without prior treatment is recommended as one approach for patients with an MD global <5 irrespective of the AJC. <u>Treatment of systemic JIA with active systemic features and varying degrees of synovitis in patients with continued disease activity</u> • Use of abatacept is recommended only in patients with an MD global ≥5 and an AJC >4 after a trial of both an IL-1 inhibitor and tocilizumab (sequentially). • Use of abatacept for patients with an AJC of zero irrespective of the MD global is inappropriate, with the exception of patients who had tried both an IL-1 inhibitor and tocilizumab (sequentially), in which case it is uncertain. • Use of abatacept for patients with an MD global <5 and an AJC >0 or an MD global ≥5 and an AJC <4 is inappropriate, with the exception of patients who had tried both an IL-1 inhibitor and tocilizumab (sequentially) or a DMARD plus either an IL-1 inhibitor or tocilizumab, in which case it is uncertain. • Use of abatacept for patients with an MD global ≥5 and an AJC >4 is inappropriate, with the exception of patients who had tried both an IL-1 inhibitor and tocilizumab (sequentially), in which case it is appropriate, or patients who had tried a DMARD plus either an IL-1 inhibitor or tocilizumab, in which case it is uncertain. • Anakinra is recommended for patients with continued disease activity after treatment with glucocorticoid monotherapy or NSAID monotherapy. • Use of a calcineurin inhibitor is recommended only for patients with an MD global ≥5 and an AJC of zero after a trial of both an IL-1 inhibitor and tocilizumab (sequentially). • Use of a calcineurin inhibitor for patients with an MD global <5 and an AJC of zero is inappropriate, with the exception of patients who received either an IL-1 inhibitor or tocilizumab, in which case it is uncertain. • Use of a calcineurin inhibitor for patients with an MD global ≥5 and an AJC of zero is inappropriate, with the exception of patients who had tried both an IL-1 inhibitor and tocilizumab (sequentially), in which case it is appropriate, or patients who had tried an IL-1 inhibitor or tocilizumab, in which case it is

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	uncertain. • Use of a calcineurin inhibitor for patients with an AJC >0 irrespective of the MD global is inappropriate, with the exception of patients who had tried both an IL-1 inhibitor and tocilizumab (sequentially) or an alternate DMARD plus either an IL-1 inhibitor or tocilizumab, in which case it is uncertain. • Canakinumab is recommended for patients with continued disease activity after treatment with glucocorticoid monotherapy, methotrexate or leflunomide, anakinra, or tocilizumab irrespective of the MD global and AJC. • Canakinumab is also recommended for patients with an MD global ≥5 irrespective of the AJC, despite prior NSAID monotherapy. • Glucocorticoid monotherapy is recommended as a treatment option after failure of NSAID monotherapy for patients with an MD global <5 and an AJC >0 and for patients with an MD global ≥5 irrespective of the AJC. Adjunct glucocorticoid therapy at any point is appropriate to consider. • Intraarticular glucocorticoid injection is recommended as adjunct therapy at any time. • Methotrexate or leflunomide is recommended for patients with an MD global <5 and an AJC >0 after treatment with glucocorticoid monotherapy, an IL-1 inhibitor, or tocilizumab. Methotrexate or leflunomide is recommended for patients with an MD global ≥5 and an AJC >0, only after a trial of an IL-1 inhibitor or tocilizumab. • Initiation of a TNF-α inhibitor is recommended for patients with an AJC >4 irrespective of the MD global after a trial of an IL-1 inhibitor or tocilizumab. Initiation of a TNF-α inhibitor is recommended for patients with an AJC >0 irrespective of the MD global after a trial of both an IL-1 inhibitor and tocilizumab (sequentially). • Use of a TNF-α inhibitor for patients with an MD global <5 and an AJC of zero is inappropriate, with the exception of patients who had tried both an IL-1 inhibitor and tocilizumab (sequentially) or a DMARD plus either an IL-1 inhibitor or tocilizumab, in which case it is uncertain. • Use of a TNF-α inhibitor for patients with an MD global ≥5 and an AJC of zero is inappropriate, with the exception of patients who had tried an IL-1 inhibitor or tocilizumab, in which case it is uncertain. • Tocilizumab is recommended as a treatment option for patients with continued disease activity following glucocorticoid monotherapy, methotrexate or leflunomide, or anakinra irrespective of the MD global and AJC. • Tocilizumab is also recommended for patients with an MD global ≥5 irrespective of the AJC despite prior NSAID monotherapy. <u>Initial treatment of systemic JIA without active systemic features and varying degrees of synovitis</u> • Intraarticular glucocorticoid injection is recommended as an initial treatment for patients with an AJC ≤4. The utility of repeating injections in the same joint(s) as the only intervention is uncertain. • Initiation of methotrexate or leflunomide is recommended for patients with an AJC >4. • Initiation of NSAID monotherapy in a patient without prior treatment for a maximum period of one month is recommended as one treatment approach for patients with an AJC >0. Continuing NSAID monotherapy for longer than two months for patients with continued disease activity is inappropriate. <u>Treatment of systemic JIA without active systemic features and varying degrees of synovitis in patients with continued disease activity</u> • Use of abatacept is recommended for patients with an AJC >0 after treatment with methotrexate or leflunomide, anakinra, or tocilizumab.

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	• Anakinra is recommended as a treatment option for patients with an AJC >4 following failed intraarticular injection or NSAID monotherapy. Use of anakinra is also recommended for patients with an AJC >0 following treatment with methotrexate or leflunomide. • Initiation of canakinumab is recommended for patients with an AJC >4 only after a trial of a DMARD plus anakinra or tocilizumab, a DMARD plus a TNF-α inhibitor, or abatacept. • Use of methotrexate or leflunomide is recommended as a treatment option for an AJC >0 following treatment with intraarticular injection, NSAID monotherapy, an IL-1 inhibitor, or tocilizumab. • Initiation of a TNF-α inhibitor is recommended for patients with an AJC >0 after treatment with methotrexate or leflunomide, anakinra, or tocilizumab. • Initiation of tocilizumab is recommended for an AJC >0 following treatment with anakinra or methotrexate or leflunomide. <u>Initial treatment of systemic JIA with features concerning for macrophage activation syndrome (MAS)</u> • Use of anakinra is recommended as one treatment option for patients with features concerning for MAS. • Use of a calcineurin inhibitor is recommended as one therapeutic option for patients with features concerning for MAS. • Use of systemic glucocorticoid monotherapy (administered by oral or intravenous route) is also recommended as a therapeutic option for patients with features concerning for MAS. • Continuing glucocorticoid monotherapy for longer than two weeks is inappropriate.
European League Against Rheumatism: **Recommendations for the Management of Psoriatic Arthritis with Pharmacological Therapies (2012)**[25]	<u>Recommendations for treatment</u> • In patients with psoriatic arthritis, NSAIDs may be used to relieve musculoskeletal signs and symptoms. • In patients with active disease (particularly those with many swollen joints, structural damage in the presence of inflammation, high erythrocyte sedimentation rate/C-reactive protein and/or clinically relevant extraarticular manifestations), treatment with DMARDs, such as methotrexate, sulfasalazine, leflunomide, should be considered at an early stage. • In patients with active psoriatic arthritis and clinically relevant psoriasis, a DMARD that also improves psoriasis, such as methotrexate, should be preferred. • Local corticosteroid injections should be considered as adjunctive therapy in psoriatic arthritis; systemic steroids at the lowest effective dose may be used with caution. • In patients with active arthritis and an inadequate response to at least one synthetic DMARD, such as methotrexate, therapy with a TNF-α inhibitor should be commenced. • In patients with active enthesitis and/or dactylitis and insufficient response to NSAIDs or steroid injections, a TNF-α inhibitor may be considered. • In patients with predominantly axial disease that is active and has insufficient response to NSAIDs, a TNF-α inhibitor should be considered. • A TNF-α inhibitor might be considered for a very active patient treatment naïve to DMARDs (particularly those with many swollen joints, structural damage in the presence of inflammation, and/ or clinically relevant extra-articular manifestations, especially extensive skin involvement). • In patients who fail to respond adequately to one TNF-α inhibitor, switching to another TNF-α inhibitor should be considered. • When adjusting therapy, factors apart from disease activity, such as comorbidities and safety issues, should be taken into account.

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European League Against Rheumatism: Recommendations For **The Management Of Psoriatic Arthritis With Pharmacological Therapies: 2015 Update (2015)**[26]	• Treatment of patients with psoriatic arthritis should aim at the best care and must be based on a shared decision between the patient and the rheumatologist, considering efficacy, safety and costs. • The primary goal of treating patients with psoriatic arthritis is to maximize health-related quality of life, through control of symptoms, prevention of structural damage, normalization of function and social participation; abrogation of inflammation is an important component to achieve these goals. • Treatment should be aimed at reaching the target of remission or, alternatively, minimal/low disease activity, by regular monitoring and appropriate adjustment of therapy. • In patients with psoriatic arthritis, NSAIDs may be used to relieve musculoskeletal signs and symptoms. • In patients with peripheral arthritis, particularly in those with many swollen joints, structural damage in the presence of inflammation, high ESR/CRP and/or clinically relevant extra-articular manifestations, conventional synthetic DMARDs should be considered at an early stage, with methotrexate preferred in those with relevant skin involvement. • Local injections of glucocorticoids should be considered as adjunctive therapy in psoriatic arthritis; systemic glucocorticoids may be used with caution at the lowest effective dose. • In patients with peripheral arthritis and an inadequate response to at least one conventional synthetic DMARD, therapy with a biological DMARD, usually a TNF-α inhibitor, should be commenced. • In patients with peripheral arthritis and an inadequate response to at least one conventional synthetic DMARD, in whom TNF-α inhibitor are not appropriate, biological DMARDs targeting IL12/23 or IL17 pathways may be considered. • In patients with peripheral arthritis and an inadequate response to at least one conventional synthetic DMARD, in whom biological DMARDs are not appropriate, a targeted synthetic DMARD such as a PDE4-inhibitor may be considered. • In patients with active enthesitis and/or dactylitis and insufficient response to NSAIDs or local glucocorticoid injections, therapy with a biological DMARD should be considered, which according to current practice is a TNF-α inhibitor. • In patients with predominantly axial disease that is active and has insufficient response to NSAIDs, therapy with a biological DMARD should be considered, which according to current practice is a TNF-α inhibitor. • In patients who fail to respond adequately to a biological DMARD, switching to another biological DMARD should be considered, including switching between TNF-α inhibitors.
National Psoriasis Foundation: **Consensus Guidelines for the Management of Plaque Psoriasis (2012)**[27]	Oral therapies • Acitretin is the only antipsoriatic retinoid available for systemic use in the United States. The use of acitretin is limited due to its slow onset of action and persistence of residual plaque psoriasis even when plaque thinning is noted. The combination of acitretin with topical calcipotriene or biological therapy or phototherapy may increase rates of clearance. Acitretin is especially useful in patients with severely sun-damaged skin, in which it may suppress actinic keratoses and even invasive malignant neoplasms. • Although it can be effective in the long term, continuous use of cyclosporine is associated with cumulative renal toxic effects, hypertension and hyperglycemia. Cyclosporine should normally be reserved for intermittent use of no longer than 12 weeks as a short-term treatment agent to control a flare of psoriasis, after which therapy is switched for long-term maintenance. When used in this intermittent fashion, a course of cyclosporine treatment can induce an average decrease of more than 75% in psoriasis severity. • Methotrexate is directly anti-inflammatory because of its effects on T-cell gene

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	expression patterns. Compared to cyclosporine, methotrexate has a more modest effect on psoriasis severity, but can be used continuously for many years with durable benefits. A major safety issue with methotrexate is the cumulative toxic effects to the liver. Biologic agents • Adalimumab may be used as first-line systemic treatment of plaque psoriasis and has a higher efficacy and lower rate of adverse effects compared to methotrexate. • Etanercept is commonly used as a first-line systemic drug for chronic plaque psoriasis. • Infliximab is administered via intravenous infusion, is a fast-acting drug that is often used as a second- or third-line biological for chronic plaque psoriasis • Ustekinumab is associated with favorable results when compared to etanercept in terms of efficacy and safety. It may be used as first-line systemic treatment for chronic plaque psoriasis. • Alefacept is generally used for intermittent use. There is little evidence to support use to achieve full clearance, and it is often used in combination regimens. It may be used as first-line systemic drug for chronic plaque psoriasis.
American Academy of Dermatology: **Guidelines of Care for the Management of Psoriasis and Psoriatic Arthritis, Sections 2, 3, and 4 (2008-2009)**[28-30]	Topical therapies • Approximately 80% of patients are affected with mild to moderate psoriasis with the majority of cases able to be successfully treated with topical agents. • Topical agents are also used adjunctively to either ultraviolet light or systemic medications for resistant lesions in patients with more severe disease. • Treatment needs vary depending on body location of disease, characteristics of the psoriasis being treated including lesion thickness, degree of erythema and amount of scaling, as well as patient preferences. • Topical corticosteroids are the cornerstone of treatment for the majority of patients with psoriasis. • Other topical agents include anthralin, coal tar, nonmedicated topical moisturizers, pimecrolimus, salicylic acid, tacrolimus, tazarotene, vitamin D analogues, and combination products. • Salicylic acid is a topical keratolytic agent that has been used for many years and has no specific FDA indication. • There are no placebo-controlled trials verifying the safety and efficacy of salicylic acid however the agent is typically used in combination with other topical therapies. Systemic therapies • Although biologics are often less toxic and not teratogenic, traditional systemic therapies (acitretin, cyclosporine, methotrexate) are still used more often due to oral route of administration and low cost. • Used more than 50 years ago, methotrexate is most commonly prescribed for severe, recalcitrant, disabling psoriasis when used in a weekly, single low-dose regimen for its effect on the immune system; concurrent folate supplementation may be warranted. • Though highly effective and known for its rapid effects, cyclosporine is associated with nephrotoxicity and hypertension; its use is restricted to one and two years in the United States and United Kingdom, respectively. • When used in conjunction with ultraviolet radiation B or psoralen and ultraviolet radiation A phototherapy or biologics, acitretin is effective for psoriasis and the treatment of choice in human immunodeficiency virus-positive patients with severe psoriasis due to its lack of significant immunosuppression; effects are dose-dependent and response is observed after three to six months. • Agents not FDA-indicated but used in psoriasis with limited supporting

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	evidence include: azathioprine, fumarates (not approved in the United States), leflunomide, mycophenolate mofetil, sulfasalazine, tacrolimus, and 6-thioguanine. Biologics • Three TNF-α inhibitors are FDA-approved for the treatment of psoriatic arthritis; adalimumab, etanercept, and infliximab (please note that the publication of these guidelines was before FDA-approval of golimumab). • Psoriatic arthritis is an inflammatory seronegative spondyloarthropathy associated with psoriasis that if left untreated can lead to persistent inflammation with progressive joint damage that can result in severe physical limitations and disability. • NSAIDs and/or intra-articular injections of corticosteroids may be appropriate treatment options in patients with milder, localized disease. • Patients with moderate to severe psoriatic arthritis that is more extensive or aggressive in nature or that significantly impacts quality of life should be treated with methotrexate, TNF-α inhibitors, or both. These treatment options are considered the standard of care. • Other DMARDs which may be used in the treatment of psoriatic arthritis include leflunomide and sulfasalazine. Antimalarials, cyclosporine, and gold are used less frequently due to the evidence for their efficacy being less convincing than for leflunomide, methotrexate, and sulfasalazine. • Although expensive, there are potential long-term cost savings and benefits associated with the use of biologics in the treatment of psoriatic arthritis, including reduced need for joint replacement surgery; reduced demands on medical, nursing, and therapy services; reduced needs for concomitant medicines; reduced demands on social services and careers; improved quality of life; improved prospect of remaining in the work force; and increased life expectancy. • Because the clinical trial efficacy data (primary endpoint of American College of Rheumatology 20% improvement) with all three FDA-approved TNF-α inhibitors are roughly equivalent, the choice of which agent to use is an individual one with the degree and severity of cutaneous involvement an important consideration. • Adalimumab and infliximab both demonstrated significant benefit for the treatment of psoriatic arthritis in clinical trials, while etanercept demonstrated significant improvements in signs and symptoms of psoriatic arthritis.
American College of Rheumatology: **2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis (2015)**[31]	Recommendations for Early RA Patients • Using a treat-to-target strategy rather than a non-targeted approach, regardless of disease activity level is strongly recommended. The ideal target should be low disease activity or remission, as determined by the clinician and the patient. In some cases, another target may be chosen because risk tolerance by patients or comorbidities may mitigate the usual choices. • For DMARD-naïve patients with early, symptomatic RA, DMARD monotherapy over double or triple DMARD therapy in patients with low disease activity is strongly recommended and DMARD monotherapy over double or triple DMARD therapy in patients with moderate or high disease activity is conditionally recommended. Methotrexate should be the preferred initial therapy for most patients with early RA with active disease. • For patients with moderate or high disease activity despite DMARD therapy (with or without glucocorticoids), treatment with a combination of DMARDs or a TNF-α inhibitor or a non-TNF biologic, with or without methotrexate (MTX) in no particular order of preference, rather than continuing DMARD monotherapy alone is strongly recommend. Biologic therapy should be used in combination with MTX over biologic monotherapy, when possible, due to

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	superior efficacy. • For patients with moderate or high disease activity despite any of the above DMARD or biologic therapies, adding low-dose glucocorticoids (defined as ≤10 mg/day of prednisone or equivalent) is conditionally recommended. Low-dose glucocorticoids may also be used in patients who need a bridge until realizing the benefits of DMARD therapy. The risk/benefit ratio of glucocorticoid therapy is favorable as long as the dose is low and the duration of therapy is short. • For patients experiencing a flare of RA, adding short-term glucocorticoids (less than three months of treatment) at the lowest possible dose for the shortest possible duration, to provide a favorable benefit-risk ratio for the patient is conditionally recommended. <u>Recommendations for Established RA Patients</u> • Using a treat-to-target strategy rather than a non-targeted approach, regardless of disease activity level is strongly recommended. • For DMARD-naïve patients with low disease activity, using DMARD monotherapy over a TNF-α inhibitor is strongly recommended. For DMARD-naïve patients with moderate or high disease activity, DMARD monotherapy over double or triple DMARD therapy and DMARD monotherapy over tofacitinib is conditionally recommend. In general, MTX should be the preferred initial therapy for most patients with established RA with active disease. • For patients with moderate or high disease activity despite DMARD monotherapy including methotrexate, using combination DMARDs <u>or</u> adding a TNF-α inhibitor <u>or</u> a non-TNF biologic <u>or</u> tofacitinib (all choices with or without methotrexate) in no particular order of preference, rather than continuing DMARD monotherapy alone is strongly recommended. Biologic therapy should be used in combination with MTX over biologic monotherapy, when possible, due to its superior efficacy. *For all scenarios for established RA below, treatment may be with or without MTX:* • For moderate or high disease activity despite TNF-α inhibitor therapy in patients currently not on a DMARD, it is strongly recommended that one or two DMARDs be added to TNF-α inhibitor therapy rather than continuing TNF-α inhibitor therapy alone. • If disease activity is moderate or high despite single TNF-α inhibitor biologic therapy, it is conditionally recommended to use a non-TNF biologic. • If disease activity is moderate or high despite non-TNF biologic therapy, using another non-TNF biologic is conditionally recommended. However, if a patient has failed multiple non-TNF biologics and they are TNF-α inhibitor -naïve with moderate or high disease activity, treatment with a TNF-α inhibitor is conditionally recommended. • For patients with moderate or high disease activity despite prior treatment with at least one TNF-α inhibitor and at least one non-TNF-biologic (sequentially, not combined), first treating with another non-TNF biologic is conditionally recommended. However, when a non-TNF biologic is not an option (e.g., patient declines non-TNF biologic therapy due to inefficacy or side effects), treatment with tofacitinib is conditionally recommended. • If disease activity is moderate or high despite the use of multiple (two or more) TNF-α inhibitor therapies (in sequence, not concurrently), non-TNF biologic therapy is conditionally recommended and then conditionally treating with tofacitinib when a non-TNF biologic is not an option. • If disease activity is moderate or high despite any of the above DMARD or biologic therapies, adding low-dose glucocorticoids is conditionally recommended. • If patients with established RA experience an RA flare while on DMARD,

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	TNF-α inhibitor, or non-TNF biologic therapy, it is conditionally recommended to add short-term glucocorticoids (less than three months of treatment) at the lowest possible dose and for shortest possible duration to provide the best benefit-risk ratio for the patient. • In patients with established RA and low disease activity but not remission, continuing DMARD therapy, TNF-α inhibitor, non-TNF biologic or tofacitinib rather than discontinuing respective medication is strongly recommended. • In patients with established RA currently in remission, tapering DMARD therapy, TNF-α inhibitor, non-TNF biologic, or tofacitinib is conditionally recommended. • It is strongly recommended not to discontinue all therapies in patients with established RA in disease remission. Recommendations for RA patients with high-risk comorbidities • In patients with established RA with moderate or high disease activity and New York Heart Association (NYHA) class III or IV congestive heart failure (CHF), using combination DMARD therapy, a non-TNF biologic, or tofacitinib rather than a TNF-α inhibitor is conditionally recommended. If patients in this population are treated with a TNF-α inhibitor and their CHF worsens while on the TNF-α inhibitor, it is conditionally recommended to switch to combination DMARD therapy, a non-TNF biologic, or tofacitinib rather than a different TNF-α inhibitor. • In patients with established RA with moderate or high disease activity and evidence of active hepatitis B infection (hepatitis surface antigen positive > 6 months), who are receiving or have received effective antiviral treatment, treating them the same as patients without this condition is strongly recommended. For patients with chronic hepatitis B who are untreated, referral for antiviral therapy is appropriate prior to immunosuppressive therapy. • In patients with established RA with moderate or high disease activity and evidence of chronic hepatitis C virus (HCV) infection, who are receiving or have received effective antiviral treatment, treating them the same as the patients without this condition is conditionally recommended. If the same patient is not requiring or receiving antiviral treatment for their hepatitis C, using DMARD therapy rather than TNF-α inhibitor is conditionally recommended. • In patients with established RA and moderate or high disease activity and a history of previously treated or untreated skin cancer (melanoma or non-melanoma), the use of DMARD therapy over biologics or tofacitinib is conditionally recommended. • In patients with established RA with moderate or high disease activity and a history of a previously treated lymphoproliferative disorder, using rituximab rather than a TNF-α inhibitor is strongly recommended and using combination DMARD therapy, abatacept, or tocilizumab rather than TNF-α inhibitor is conditionally recommended. • In patients with established RA with moderate or high disease activity and previously treated solid organ cancer, it is conditionally recommended that they be treated for RA just as one would treat an RA patient without a history of solid organ cancer. • In patients with established RA with moderate or high disease activity and previous serious infection(s), using combination DMARD therapy or abatacept rather than TNF-α inhibitor is conditionally recommended. Recommendations for the Use of Vaccines in RA patients on DMARD and/or biologic therapy

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	• In early or established RA patients aged 50 and over, giving the herpes zoster vaccine before the patient receives biologic therapy or tofacitinib for their RA is conditionally recommended. • In early or established RA patients who are currently receiving biologics, it is conditionally recommended that live attenuated vaccines such as the herpes zoster (shingles) vaccine not be given. • In patients with early or established RA who are currently receiving biologics, using appropriately indicated killed/inactivated vaccines is strongly recommended.
European League Against Rheumatism: **Management Of Rheumatoid Arthritis With Synthetic And Biological Disease-Modifying Antirheumatic Drugs: 2013 Update (2013)**[32]	• Treatment of rheumatoid arthritis must be based on a shared decision between the patient and the rheumatologist. • Rheumatoid arthritis incurs high individual, societal and medical costs, all of which should be considered in its management. • Therapy with DMARDs should be started as soon as the diagnosis of rheumatoid arthritis is made. • Treatment should be aimed at reaching a target of remission or low disease activity in every patient. • Methotrexate should be part of the first treatment strategy in patients with active rheumatoid arthritis. • If methotrexate is contraindicated or is not tolerated, treatment with sulfasalazine or leflunomide should be considered. • In DMARD-naïve patients, treatment with conventional synthetic DMARD monotherapy or combination therapy of conventional synthetic DMARDs is recommended. • Low-dose glucocorticoids should be considered as part of the initial treatment strategy (in combination with one or more conventional synthetic DMARDs) for up to six months, but should be tapered as rapidly as clinically feasible. • If the treatment target is not achieved with the first DMARD strategy, in the absence of poor prognostic factors, change to another conventional synthetic DMARD strategy should be considered; when poor prognostic factors are present, addition of a biologic DMARD should be considered. • In patients with inadequate response to methotrexate and/or other conventional synthetic DMARDs, biologic DMARDs (TNF-α inhibitors, abatacept or tocilizumab) should be commenced with methotrexate; treatment with rituximab may be considered in the patients with recent history of lymphoma, latent tuberculosis with contraindications to the use of chemoprophylaxis, living in a tuberculosis-endemic region, or a previous history of demyelinating disease. • If a first biologic DMARD has failed, patients should be treated with another biologic DMARD; if a first TNF-α inhibitor therapy has failed, patients may receive another TNF-α inhibitor or a biological agent with a different mechanism of action. • Given the paucity of clinical experience and long-term safety data, tofacitinib should primarily be used when biological treatment has failed; additional clinical experience and safety data from registries, with a particular focus on serious infections, herpes zoster and malignancies, will be needed before the place of tofacitinib in the treatment sequence can be clarified. • If a patient is in persistent remission after having tapered glucocorticoids, tapering of biologic DMARDs can be considered, especially if this treatment is combined with a conventional synthetic DMARD. • In cases of sustained long-term remission, cautious reduction of the conventional synthetic DMARD dose could be considered, as a shared decision between patient and physician.
National Institute for Health and Clinical Excellence:	• In people with newly diagnosed active rheumatoid arthritis, offer a combination of DMARDs (including methotrexate and at least one other DMARD, plus short-term glucocorticoids) as first-line treatment as soon as possible, ideally

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Rheumatoid Arthritis in Adults: Management (2009)[33]	within three months of the onset of persistent symptoms. • In people with recent-onset rheumatoid arthritis receiving combination DMARD therapy and in whom sustained and satisfactory levels of disease control have been achieved, cautiously try to reduce drug doses to levels that still maintain disease control. • In people with newly diagnosed rheumatoid arthritis for which combination DMARD therapy is not appropriate, start DMARD monotherapy; placing greater emphasis on fast escalation to a clinically effective dose rather than on the choice of DMARD. • In people with established rheumatoid arthritis whose disease is stable, cautiously reduce dosages of disease modifying or biological drugs. Return promptly to disease-controlling dosages at the first sign of a flare. • When introducing new drugs to improve disease control into the treatment regimen of a person with established rheumatoid arthritis, consider decreasing or stopping their pre-existing rheumatological drugs once the disease is controlled. • In any person with established rheumatoid arthritis in whom disease-modifying or biological drug doses are being decreased or stopped, arrangements should be in place for prompt review. • Consider offering short-term treatment with glucocorticoids (oral, intramuscular or intra-articular) to rapidly improve symptoms in people with newly diagnosed rheumatoid arthritis if they are not already receiving glucocorticoids as part of DMARD combination therapy. • Offer short-term treatment with glucocorticoids for managing flares in people with recent onset or established disease, to rapidly decrease inflammation. • In people with established rheumatoid arthritis, only continue long-term treatment with glucocorticoids when the long-term complications of glucocorticoid therapy have been fully discussed, and all other treatment options (including biological drugs) have been offered. • On the balance of its clinical benefits and cost effectiveness, anakinra is not recommended for the treatment of rheumatoid arthritis, except in the context of a controlled, long-term clinical study. • Patients currently receiving anakinra for rheumatoid arthritis may suffer loss of wellbeing if their treatment were discontinued at a time they did not anticipate. Therefore, patients should continue therapy with anakinra until they and their consultant consider it is appropriate to stop. • Do not offer the combination of TNF-α inhibitor therapy and anakinra for rheumatoid arthritis. • Oral NSAIDs or COX-2 inhibitors should be used at the lowest effective dose for the shortest possible period of time. • When offering treatment with an oral NSAID or COX-2 inhibitor, the first choice should be either a standard NSAID or a COX-2 inhibitor. In either case, these should be co-prescribed with a proton pump inhibitor, choosing the one with the lowest acquisition cost. • All oral NSAIDs or COX-2 inhibitors have analgesic effects of a similar magnitude but vary in their potential gastrointestinal, liver and cardio-renal toxicity; therefore, when choosing the agent and dose, healthcare professionals should take into account individual patient risk factors, including age. When prescribing these drugs, consideration should be given to appropriate assessment and/or ongoing monitoring of these risk factors. • If a person with rheumatoid arthritis needs to take low-dose aspirin, healthcare professionals should consider other analgesics before substituting or adding an NSAID or COX-2 inhibitor (with a proton pump inhibitor) if pain relief is ineffective or insufficient. • If NSAIDs or COX-2 inhibitors are not providing satisfactory symptom control,

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	review the disease-modifying or biological drug regimen.
	• The TNF-α inhibitors adalimumab, etanercept and infliximab are recommended as options for the treatment of adults who have both of the following characteristics:
	  o Active rheumatoid arthritis as measured by disease activity score (DAS 28) >5.1 confirmed on at least two occasions, one month apart.
	  o Have undergone trials of two DMARDs, including methotrexate (unless contraindicated). A trial of a DMARD is defined as being normally of six months, with two months at standard dose, unless significant toxicity has limited the dose or duration of treatment.
	• TNF-α inhibitors should normally be used in combination with methotrexate. Where a patient is intolerant of methotrexate or where methotrexate treatment is considered to be inappropriate, adalimumab and etanercept may be given as monotherapy.
	• Treatment with TNF-α inhibitors should be continued only if there is an adequate response at six months following initiation of therapy. An adequate response is defined as an improvement in DAS 28 of 1.2 points or more.
	• After initial response, treatment should be monitored no less frequently than six-monthly intervals with assessment of DAS 28. Treatment should be withdrawn if an adequate response is not maintained.
	• An alternative TNF-α inhibitor may be considered for patients in whom treatment is withdrawn due to an adverse event before the initial six-month assessment of efficacy provided the risks and benefits have been fully discussed with the patient and documented.
	• Escalation of dose of the TNF-α inhibitors above their licensed starting dose is not recommended.
	• Treatment should normally be initiated with the least expensive drug (taking into account administration costs, required dose and product price per dose). This may need to be varied in individual cases due to differences in the mode of administration and treatment schedules.
	• Use of the TNF-α inhibitors for the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate or other DMARDs is not recommended.
	• Initiation of TNF-α inhibitors and follow-up of treatment response and adverse events should be undertaken only by a specialist rheumatological team with experience in the use of these agents.

National Institute for Health and Clinical Excellence: **Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed (2016)**[34]	• Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept, all in combination with methotrexate, are recommended as options for treating rheumatoid arthritis, only if:
	  o disease is severe, that is, a disease activity score (DAS28) greater than 5.1 and
	  o disease has not responded to intensive therapy with a combination of conventional DMARDs and
	  o the companies provide certolizumab pegol, golimumab, abatacept, and tocilizumab as agreed in their patient access schemes.
	• Adalimumab, etanercept, certolizumab pegol, or tocilizumab can be used as monotherapy for people who cannot take methotrexate because it is contraindicated or because of intolerance, when the criteria above are met.
	• Continue treatment only if there is a moderate response measured using European League Against Rheumatism (EULAR) criteria at six months after starting therapy.
	• After initial response within six months, withdraw treatment if a moderate EULAR response is not maintained.
	• Start treatment with the least expensive drug (taking into account administration costs, dose needed and product price per dose). This may need to be varied for

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	some people because of differences in the mode of administration and treatment schedules. • People whose treatment with adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab, or abatacept is not recommended in this NICE guidance, but was started before this guidance was published, should be able to continue treatment until they and their clinician consider it appropriate to stop.
American College of Gastroenterology, Practice Parameters Committee: **Ulcerative Colitis Practice Guidelines in Adults (2010)**[35]	<u>Management of mild-moderate distal colitis</u> • Topical mesalamine agents are "superior" to topical steroids or oral aminosalicylates. • The combination of oral and topical agents is "superior" to each agent used alone. • Mesalamine enemas or suppositories may still be effective in patients refractory to oral aminosalicylates or to topical corticosteroids. One meta-analysis demonstrated topical mesalamine to be "superior" to oral aminosalicylates in achieving clinical improvement in patients with mild-moderate distal colitis. • Patients who are refractory to the above therapies may require oral prednisone 40 to 60 mg daily or infliximab with an induction regimen of 5 mg/kg at weeks zero, two and six. • Oral therapy effective for achieving and maintaining remission include aminosalicylates, balsalazide, mesalamine, olsalazine and sulfasalazine. <u>Maintenance of remission in distal disease</u> • Balsalazide, mesalamine and sulfasalazine are effective in maintaining remission; combination oral and topical mesalamine is more effective than oral mesalamine alone. • Mesalamine suppositories are effective for maintenance of remission in patients with proctitis and mesalamine enemas are effective in patients with distal colitis. • Topical corticosteroids, including budesonide, have not been proven effective at maintaining remission. • When patients fail to maintain remission with the above therapies, thiopurines (6-mercaptopurine or azathioprine) and infliximab may be effective. <u>Management of mild-moderate extensive colitis: active disease</u> • Oral sulfasalazine is considered first line. • Reserve oral steroids for patients refractory to oral aminosalicylates or patients who require rapid improvement. • 6-mercaptopurine or azathioprine can be used for patients refractory to oral prednisone and are acutely ill, requiring intravenous therapy. • Infliximab is effective in patients who are steroid refractory or steroid dependent despite the use of thiopurine at adequate doses or who are intolerant to these medications. <u>Maintenance of remission for mild-moderate extensive colitis</u> • Balsalazide, mesalamine, olsalazine and sulfasalazine are effective in reducing the number of relapses. • 6-mercaptopurine or azathioprine can be used for steroid sparing in steroid dependent patients and have been shown to effectively maintain remission in patients not adequately sustained on aminosalicylates. • Infliximab effectively maintains remission in patient who responded to the infliximab induction regimen. <u>Management of severe colitis</u> • If a patient is refractory to maximum oral treatment of aminosalicylates, oral prednisone, and topical medications may be treated with infliximab if urgent

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	hospitalization is not required. • Patients that show signs of toxicity should be hospitalized to receive intravenous steroids. • Failure to significantly improve within three to five days indicates need for intravenous cyclosporine (or colectomy - weaker evidence). • Infliximab may also be used to avoid colectomy in patients failing intravenous steroids; however, long-term efficacy in this setting is unknown.

European Academy of Dermatology and Venereology: **European S1 guideline for the treatment of hidradenitis suppurativa/acne inversa (2015)**[36]	Adjuvant Therapy
	• It is recommended that adjuvant therapy is offered to patients in the form of general measures and specific help with bandaging lesions in order to improve the patients' quality of life.
	• Cigarette smoking and obesity have to be avoided.
	• Bandages used must be customized due to the anatomical variation, and should be absorbent, nonirritant. They should keep the surface dry and absorb smell. Dedicated hidradenitis suppurativa (HS)-bandages are not currently available.
	• Psychosocial support measures in HS may be of considerable benefit to the patients.
	
	Medical Therapy (non-antibiotic topical therapies)
	• Exfoliants and Peels
	  o Topical resorcinol 15% twice daily had good effect compared to previous experience in treating recurrent lesions in patients with Hurley stage I or II HS.
	  o Systemic toxicity following topical use of resorcinol is extremely rare, but physicians must be aware of the potential risk.
	• Other Therapies
	  o The use of adapalene or azelaic acid may occasionally be beneficial, but must currently be considered experimental. No formal studies have been conducted.
	
	Medical Therapy (topical antibiotics)
	• Clindamycin is the only antibiotic that has been studied as a topical agent.
	  o Studied in localized Hurley Stage I or mild stage II disease.
	  o Clindamycin lotion three times a day for three months (or prolonged if clinically indicated).
	  o A significant improvement was observed with clindamycin than to placebo using of a disease score constructed for the study.
	
	Medical Therapy (systemic antibiotics)
	• Systemic treatment is indicated when more severe or widely spread lesions are present.
	• Tetracycline
	  o More widely spread Hurley stage I or mild stage II disease.
	  o Tetracycline 500 mg three times a day for four months (or prolonged if clinically indicated).
	  o Resulted in an approximately 30% reduction in disease severity.
	• Clindamycin-Rifampicin
	  o Any stage active inflammatory HS.
	  o Clindamycin 300 mg three times a day plus rifampicin 600 mg daily for 10 weeks.
	  o All [three] studies conclude the treatment to be beneficial.
	• Other antibiotics
	  o Rifampicin-moxifloxacin-metronidazole, either alone or proceeded by systemic ceftriaxone for 12 weeks. Patients had treatment resistant stage II and III disease. Combination therapy was effective in half

Clinical Guideline	Recommendation(s)
	(28/58) the patients. ▪ Patients who showed response after 12 weeks of initial treatment were treated for an additional 12 weeks using a combination of moxifloxacin and rifampicin. Intensive treatment led to complete response in 16/28 patients. o A range of other topical and systemic antibiotics have been suggested in case reports and in expert opinion, but none have been systematically evaluated even at the level of open prospective case-series. <u>Medical Therapy (anti-inflammatory therapy)</u> • Intralesional corticosteroids o Rapid reduction in inflammation associated with acute flares and for management of recalcitrant nodules and sinus tracts. o Utilized as both monotherapy and an adjunct to systemic therapies. o When effective, clinical response (flattening, resolution or spontaneous discharge of nodules) is seen within 48 to 72 hours. o Therapy is contraindicated if clinical suspicion of bacterial infection exists. o Triamcinolone acetonide 5 to 10 mg/mL is recommended • Systemic corticosteroids o There are limited data on the use of corticosteroids in HS. o Short and long-term therapy can result in rebound flare on withdrawal. o Short-term, rapidly tapering therapy can provide benefit in reduction in inflammation associated with acute flares. o In the event of clinical relapse on dose reduction, introduction of a second line anti-inflammatory or immunosuppressive agent is recommended. o Routine long-term use is not currently recommended. o Systemic corticosteroid dose and duration should be kept to a minimum to limit long-term complications. o A dose of 0.5 to 0.7 mg/kg oral prednisolone is recommended for short-term use for acute flares; the dose should be rapidly tapered to stop over weeks. o Limited case reports and one case series describe response to the corticosteroid agents hydrocortisone, dexamethasone and prednisolone, as short-term monotherapy and long-term combination therapy. ▪ Short-term systemic hydrocortisone monotherapy (60 to 80 mg daily; 15 to 56 days) provided sustained remission at 12 months. ▪ Use of prolonged prednisolone monotherapy (60 mg reduced to 25 mg daily; duration not specified) in severe disease resulted in 65% improvement in one case. ▪ Prolonged prednisolone combination therapy (20 mg da to stop over 27 weeks) with antimicrobials followed by isotretinoin resulted in sustained clinical response in one case. • Dapsone o Reserved for patients with mild to moderate disease (Hurley stage I or II) in which standard first or second line agents fail. o Recommended dose is 25 to 200 mg/day. Higher doses are limited by adverse events. o Reported duration and response is variable; the minimum recommended duration of therapy is three months. o When effective, rapid relapse may occur on therapy withdrawal. o There are no data on maximum duration of therapy (reported range three to 48 months).

Clinical Guideline	Recommendation(s)

	• Ciclosporin A (cyclosporin)
	  o Reserved to cases where failure of response to standard first, second and third line therapies.
	  o Daily doses of two to six mg/kg have been used for variable duration (six weeks to seven months).
	  o Beneficial response to ciclosporin A is reported in four cases.
	  o Combination ciclosporin A (three mg/kg daily for four months) with tapering corticosteroids (two months) resulted in four months of remission in one case.
	• Hormones
	  o There are indications that antiandrogens, such as cyproterone acetate, and estrogens improve HS, while progestogens induce or worsen a pre-existing HS due to their androgenic properties.
	  o Indication and contraindication: Female patients with menstrual abnormalities, signs of hyperandrogenism or upper normal or high serum levels of dehydroepiandrosterone, androstenedione and/or sexual hormone-binding protein.
	  o All reported patients improved but no evidence-based data exist.
	
	<u>Medical Therapy (Biologics)</u>
	• Used for the treatment of moderate to severe HS.
	  o Improved quality of patient life.
	  o Studied in adalimumab and infliximab, however, adalimumab is considered more tolerable.
	• Adalimumab
	  o Recommended doses:
	  ▪ To condition for a curative surgical procedure: 160 mg on day zero and possibly 80 mg one week later.
	  ▪ Long-term therapy: 40 mg once weekly.
	  o There are different rates of response to adalimumab reported in case series and in a current, prospective controlled study.
	• Infliximab
	  o Recommended doses:
	  ▪ To condition for a curative surgical procedure: 5 mg/kg.
	  ▪ Long-term therapy: 5 mg/kg on day zero, two and six then every eight weeks.
	  o Response rates are varied.
	• Etanercept and ustekinumab have also been studied in case reports.
	
	<u>Medical Therapy (retinoids)</u>
	• Isotretinoin
	  o Not recommended in the treatment of HS.
	  o If given early enough in the treatment of HS, isotretinoin may potentially prevent an affected pilosebaceous unit from being occluded by ductal hyper cornification. However, its usage in HS is often disappointing and the literature data are inconsistent.
	• Acitretin/Etretinate
	  o Acitretin usage in early HS stages (Hurley I or mild II) is reasonable and could also be advocated in the chronic stages of HS with recurrent abscesses with sinus tracts (even interconnected) and/or scarring.
	  o The response rate was high.
	
	<u>Medical Therapy (analgesics)</u>
	• Non-steroidal anti-inflammatory drugs (NSAIDs)
	  o No clinical evidence exists on the use of NSAIDs in the amelioration of pain and inflammation in HS.

Clinical Guideline	Recommendation(s)
	o Their anecdotal use in the usual dosage schemas may be justified for the amelioration of acute pain related to HS. • Opiates o No clinical evidence exists for the use of opioids in the amelioration of pain in HS. o Their use should be restricted and limited to cases where all other painkillers have failed. o Codeine should be the first treatment option for this drug class. <u>Medical Therapy (miscellaneous and experimental therapies)</u> • Zinc gluconate o Maintenance treatment in Hurley stage I and II disease. o High dose (90 mg/day) is recommended o Response rate in one study of 22 patients resulted in complete remission in eight patients and partial remission in 14 patients. • Intramuscular gamma-globulin o Not recommended due to limited data (one report) • Colchicine o Not recommended due to poor efficacy. • Botulinum toxin o Experimental treatment in Hurley stage I or II disease. o Limited data from two case reports; both had good effect with one case resulting in six months of remission. <u>Therapeutic Conclusion</u> • It is recommended that HS is treated based on the subjective impact and objective severity of the disease. • Locally recurring lesions can be treated surgically, whereas medical treatment either as monotherapy or in combination with surgery is more appropriate for widely spread lesions. • Medical therapy may include antibiotics and immunosuppressants. • HS treatment algorithm: o Adjuvant therapy should be utilized for all disease severities: ▪ Pain management ▪ Treatment of superinfections ▪ Weight loss and tobacco abstinence o As disease severity increases, provide surgical interventions: ▪ Less severe disease: deroofing, LASERs, local excision ▪ More severe disease: wide surgical excision o As disease severity increases, medication therapy should include: ▪ Stage I or II (localized): topical clindamycin ▪ More severe: provide systemic treatment with 1) clindamycin + rifampicine/tetracycline or 2) acitretin ▪ Most severe: provide systemic treatment with anti-TNF biologics adalimumab or infliximab

III. Indications

The Food and Drug Administration (FDA)-approved indications for the disease-modifying antirheumatic agents are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Disease-Modifying Antirheumatic Agents[13]

Indications	Abatacept	Adalimumab	Anakinra	Apremilast	Certolizumab pegol	Etanercept	Golimumab	Infliximab	Leflunomide	Tocilizumab	Tofacitinib
Ankylosing Spondylitis		✔			✔	✔	✔	✔			
Crohn's Disease		✔			✔			✔			
Hidradenitis Suppurativa		✔									
JIA	✔	✔				✔				✔	
NOMID			✔								
Plaque Psoriasis		✔		✔		✔		✔			
Psoriatic Arthritis		✔		✔	✔	✔	✔	✔			
Rheumatoid Arthritis	✔	✔	✔		✔	✔	✔	✔	✔	✔	✔
Ulcerative Colitis		✔					✔	✔			

JIA=juvenile Idiopathic Arthritis, NOMID=Neonatal-Onset Multisystem Inflammatory Disease

IV. Pharmacokinetics

The pharmacokinetic parameters of the disease-modifying antirheumatic agents are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Disease-Modifying Antirheumatic Agents[14]

Generic Name(s)	Bioavailability (%)	Time to Peak Concentration	Half-Life
Abatacept	100 (intravenous); 78.6 (subcutaneous)	Not reported	13.0 to 14.3 days
Adalimumab	64	131±56 hours	10 to 20 days
Anakinra	95	3 to 7 hours	4 to 6 hours
Apremilast	73	2.5 hours	6 to 9 hours
Certolizumab	80	54 to 171 hours	14 days
Etanercept	58	69±34 hours	102±30 hours
Golimumab	100 (intravenous); 53 (subcutaneous)	48 to 144 hours (subcutaneous)	14 days
Infliximab	100	Not reported	8 to 10 days
Leflunomide	80	6 to 12 hours	4 to 28 days
Tocilizumab	100 (intravenous); 80 (subcutaneous)	Not reported	11 to 23 days
Tofacitinib	74	0.5 to 1.0 hour	3 hours

V. Drug Interactions

Major drug interactions with the disease-modifying antirheumatic agents are listed in Table 5.

Table 5. Major Drug Interactions with the Disease-Modifying Antirheumatic Agents[14]

Generic Name(s)	Interaction	Mechanism
Abatacept, adalimumab, anakinra,	Live vaccines	Concomitant use may result in an increased risk of secondary transmission of infection by the live vaccine.

Generic Name(s)	Interaction	Mechanism
certolizumab, etanercept, golimumab, infliximab, tocilizumab		
Abatacept, adalimumab, anakinra, etanercept, infliximab, golimumab	Other DMARDs	Concurrent use of may result in an increased risk of infections.
Interleukin-receptor blockers	Other biologic immunomodulators	Concurrent use may increase the risk of infections.
Interleukin-receptor blockers	CYP450 substrates with a narrow therapeutic index	Increased cytokine levels (interleukins) suppress the effect of CYP450 and should be normalized with interleukin-receptor blocking agents. Monitor effect of agents that may have metabolism increased.
Apremilast	CYP3A strong inducers (e.g., rifampin)	Concurrent use of apremilast and strong CYP3A4 inducers may result in decreased apremilast exposure.
Tumor Necrosis Factor Blocking Agents	Other biologic immunomodulators	Concurrent use may increase the risk of infections.
Etanercept	Cyclophosphamide	Concurrent administration may result in a higher incidence of developing noncutaneous solid malignancies.
Infliximab	Tocilizumab	Concurrent use may increase immunosuppression and the risk of infections.
Leflunomide	Methotrexate	Concurrent use of leflunomide and methotrexate may result in increased risk of hepatotoxicity and bone marrow toxicity.
Leflunomide	Warfarin	Concurrent use of leflunomide and warfarin may result in increased risk of bleeding.
Tofacitinib	Biological DMARDs	Concurrent use may increase the risk of serious infections. Coadministration should be avoided.
Tofacitinib	CYP2C19 potent and CYP3A moderate inhibitors (e.g., fluconazole)	Concurrent use may elevate tofacitinib concentrations, increasing the pharmacologic effects and risk of adverse reactions; the dose of tofacitinib should be reduced to 5 mg once daily.
Tofacitinib	CYP3A strong inhibitors (e.g., ketoconazole)	Concurrent use may elevate tofacitinib concentrations, increasing the pharmacologic effects and risk of adverse reactions; the dose of tofacitinib should be reduced to 5 mg once daily.
Tofacitinib	CYP3A strong inducers (e.g., rifampin)	Concurrent use may reduce tofacitinib concentrations, decreasing the clinical response. Coadminister with caution. Close clinical monitoring is warranted.
Adalimumab, tofacitinib	Immunosuppressants (e.g., azathioprine, cyclosporine, tacrolimus)	Concurrent use may increase the risk of added immunosuppression and serious infections. Coadministration of tofacitinib with potent immunosuppressants should be avoided.

DMARD=disease-modifying antirheumatic drug

VI. Adverse Drug Events

The most common adverse drug events reported with the disease-modifying antirheumatic agents are listed in Table 6. The boxed warnings for the disease-modifying antirheumatic agents are listed in Tables 7 to 11.

Table 6. Adverse Drug Events (%) Reported with the Disease-Modifying Antirheumatic Agents[1-13]

Adverse Event	Abatacept	Adalimumab	Anakinra*	Apremilast	Certolizumab	Etanercept	Golimumab[†]	Infliximab	Leflunomide	Tocilizumab	Tofacitinib
Gastrointestinal											
Abdominal pain	-	7	5	4	-	5 to 10	-	12	5 to 6	-	-
Diarrhea	-	-	7	8 to 17	-	8 to 16	-	12	17 to 27	-	-
Dyspepsia	6	-	-	3	-	4 to 11	-	10	5 to 6	-	-
Gastroenteritis	-	-	-	-	-	-	-	-	3	-	-
Nausea	≥10	9	8	7 to 17	-	9 to 15	-	21	9 to 13	-	-
Vomiting	-	-	14[‡]	≤4	-	3 to 5	-	-	5 to 5	-	-
Laboratory Tests											
Abnormal hepatic test	-	8	-	-	-	-	-	-	5 to 10	3 to 6	-
Alkaline phosphatase increased	-	5	-	-	-	-	-	-	2 to 4	-	-
Hematuria	-	5	-	-	-	-	-	-	-	-	-
Hypercholesterolemia	-	6	-	-	-	-	-	-	-	-	-
Hyperglycemia	-	-	-	-	-	-	-	-	1 to 3	-	-
Hyperthyroidism	-	-	-	-	-	-	-	-	1 to 3	-	-
Hyperlipidemia	-	7	-	-	-	-	-	-	1 to 3	-	-
Hypokalemia	-	-	-	-	-	-	-	-	1 to 3	-	-
Respiratory											
Bronchitis	5 to 13	-	-	1	3	-	-	10	5 to 8	-	-
Coughing	8	-	-	-	-	5 to 6	-	12	3 to 5	-	-
Flu syndrome	-	7	-	-	-	-	-	14	≤4	-	-
Nasopharyngitis	12	-	-	3	5	-	-	-	-	4 to 7	-
Non-upper respiratory infection	-	-	-	-	-	21 to 54	-	-	-	-	-
Pharyngitis	-	-	11.6[‡]	-	3	6 to 7	-	-	2 to 3	-	-
Respiratory disorder	-	-	-	-	-	5	-	-	-	-	-
Rhinitis	-	-	-	-	-	12 to 16	-	-	2 to 5	-	-
Sinusitis	5 to 13	11	7	1	-	3 to 5	-	14	1 to 2	-	-
Upper respiratory infection	≥10	17	14	4 to 9	6	38 to 65	13[§] to 16	32	15 to 27	6 to 8	-

Adverse Event	Abatacept	Adalimumab	Anakinra*	Apremilast	Certolizumab	Etanercept	Golimumab†	Infliximab	Leflunomide	Tocilizumab	Tofacitinib
Skin											
Acne	-	-	-	-	-	-	-	-	1 to 3	-	-
Eczema	-	-	-	-	-	-	-	-	2 to 3	-	-
Folliculitis	-	-	-	1	-	-	-	-	-	-	-
Pruritus	-	-	-	-	-	-	-	7	4 to 6	-	-
Rash	-	12	-	-	3	3 to 13	-	10	10 to 12	-	-
Other											
Accidental injury	-	10	-	-	-	-	-	-	5 to 7	-	-
Alopecia	-	-	-	-	-	1 to 6	-	-	9 to 17	-	-
Angina pectoris	-	-	-	-	-	-	-	-	1 to 3	-	-
Anxiety	-	-	-	-	-	-	-	-	1 to 3	-	-
Arthralgia	-	-	6, 11.6‡	-	-	-	-	-	≤4	-	-
Asthenia	-	-	-	-	-	5 to 11	-	-	-	-	-
Back pain	7	6	-	2	4	-	-	8	5 to 8	-	-
Body pain	-	-	-	-	-	-	-	8	-	-	-
Chest pain	-	-	-	-	-	-	-	-	1 to 4	-	-
Depression	-	-	-	-	-	-	-	-	1 to 3	-	-
Dizziness	9	-	-	-	-	7 to 8	-	-	-	-	-
Fatigue	-	-	-	3	3	-	-	9	-	-	-
Fever	-	-	11.6‡	-	3	2 to 3	-	7	1 to 3	-	-
Flu like symptoms	-	-	6	-	-	-	-	-	-	-	-
Headache	18	12	12, 14‡	5 to 6	5	17 to 24	-	18	7 to 13	5 to 7	-
Hypertension	7	5	-	-	5	-	-	7	9 to 10	4 to 6	-
Infections (overall)	-	-	-	-	-	-	-	-	-	20	-
Injection site pain	-	12	-	-	-	-	-	-	-	-	-
Injection site reaction	-	8	16‡, 71	-	-	37 to 43	6	-	-	7.1‖ to 10.1‖	-
Insomnia	-	-	-	2	-	-	-	-	1 to 3	-	-
Moniliasis	-	-	-	-	-	-	-	5	-	-	-
Mouth ulcer	-	-	-	-	-	2 to 6	-	-	3 to 5	-	-
Muscle Pain	-	-	-	-	-	-	-	-	-	-	-
Neuralgia	-	-	-	-	-	-	-	-	1 to 3	-	-
Oral Herpes	-	-	-	-	-	-	-	-	-	-	-
Pain	-	-	-	-	-	-	-	-	1 to 4	-	-
Palpitations	-	-	-	-	-	-	-	-	1 to 3	-	-
Paresthesia	-	-	-	-	-	-	-	-	2 to 4	-	-
Peripheral edema	-	-	-	-	-	2 to 8	-	-	-	-	-

Adverse Event	Abatacept	Adalimumab	Anakinra*	Apremilast	Certolizumab	Etanercept	Golimumab†	Infliximab	Leflunomide	Tocilizumab	Tofacitinib
Pyrexia	-	-	-	-	-	-	-	-	-	-	-
Synovitis	-	-	-	-	-	-	-	-	2 to 4	-	-
Tachycardia	-	-	-	-	-	-	-	-	1 to 3	-	-
Urinary tract infection	6	8	-	-	-	-	-	8	5	-	-
Vasculitis	-	-	-	-	-	-	-	-	1 to 3	-	-
Vertigo	-	-	-	-	-	-	-	-	1 to 3	-	-
Viral infection	-	-	-	-	-	-	5	-	-	-	-
Weight Gain	-	-	-	-	-	-	-	-	-	-	-
Weight Loss	-	-	-	10 to 12	-	-	-	-	2 to 4	-	-
Worsening of rheumatoid arthritis	-	-	19	-	-	-	-	-	-	-	-

-Event not reported or incidence <1%.
*Unless otherwise specified, adverse reaction observed in patients treated for rheumatoid arthritis.
†With or without disease modifying antirheumatic agents. Unless otherwise specified, adverse reaction observed in patients treated with subcutaneous formulation.
‡Neonatal-onset multisystem inflammatory disease during the first six months of therapy.
§Intravenous formulation (Simponi Aria®) only.
‖Subcutaneous formulation only.

Table 7. Boxed Warning for Adalimumab and Infliximab[13]

WARNING
Postmarketing cases of hepatosplenic T-cell lymphoma, a rare type of T-cell lymphoma, have been reported in patients treated with tumor necrosis factor blockers including Humira® and Remicade®. These cases have had a very aggressive disease course and have been fatal. All reported Remicade® cases have occurred in patients with Crohn's disease or ulcerative colitis and the majority was in adolescent and young adult males. All of these patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with Humira® or Remicade® at or prior to diagnosis.

Table 8. Boxed Warning for Leflunomide[13]

WARNING
Embryo-fetal toxicity: Leflunomide is contraindicated for use in pregnant women because of the potential for fetal harm. Teratogenicity and embryo-lethality occurred in animals administered leflunomide at doses lower than the human exposure level. Exclude pregnancy before the start of treatment with leflunomide in females of reproductive potential. Advise females of reproductive potential to use effective contraception during leflunomide treatment and during an accelerated drug elimination procedure after leflunomide treatment. Stop leflunomide and use an accelerated drug elimination procedure if the patient becomes pregnant. Hepatotoxicity: Severe liver injury, including fatal liver failure, has been reported in patients treated with leflunomide. Leflunomide is contraindicated in patients with severe hepatic impairment. Concomitant use of leflunomide with other potentially hepatotoxic drugs may increase the risk of liver injury. Patients with preexisting acute or chronic liver disease, or those with serum ALT greater than 2 times the upper limit of normal (ULN) before initiating treatment, are at increased risk and should not be treated with leflunomide. Monitor ALT levels at least monthly for 6 months after starting leflunomide, and thereafter every 6 to 8 weeks. If leflunomide-induced liver injury is suspected, stop leflunomide treatment, start an accelerated drug elimination procedure, and monitor liver tests weekly until normalized.

Table 9. Boxed Warning for Tocilizumab[13]

WARNING
Serious Infections Patients treated with Actemra® are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids. If a serious infection develops, interrupt Actemra® until the infection is controlled. Reported infections include: • Active tuberculosis, which may present with pulmonary or extrapulmonary disease. Patients should be tested for latent tuberculosis before Actemra® use and during therapy. Treatment for latent infection should be initiated prior to Actemra® use. • Invasive fungal infections, including candidiasis, aspergillosis, and pneumocystis. Patients with invasive fungal infections may present with disseminated, rather than localized, disease. • Bacterial, viral and other infections due to opportunistic pathogens. The risks and benefits of treatment with Actemra® should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with Actemra®, including the possible development of tuberculosis in patients who tested negative for infection prior to initiating therapy.

Table 10. Boxed Warning for adalimumab, certolizumab pegol, etanercept, golimumab, infliximab[13]

WARNING
Serious Infections Patients treated with Cimzia®, Enbrel®, Humira®, Remicade® or Simponi® are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

WARNING

Cimzia®, Enbrel®, Humira®, Remicade® and Simponi® should be discontinued if a patient develops a serious infection or sepsis.
Reported infections include:

- Active tuberculosis, including reactivation of latent tuberculosis. Patients with tuberculosis have frequently presented with disseminated or extrapulmonary disease. Patients should be tested for latent tuberculosis before Cimzia®, Enbrel®, Remicade®, or Simponi® use and during therapy. Treatment for latent infection should be initiated prior to Cimzia®, Enbrel®, Humira®, Remicade®, or Simponi® use.
- Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Empiric anti-fungal therapy should be considered in patients at risk for invasive fungal infections who develop severe systemic illness.
- Bacterial, viral and other infections due to opportunistic pathogens, including Legionella and Listeria.

The risks and benefits of treatment with Cimzia®, Enbrel®, Humira®, Remicade®, or Simponi® should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.
Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with Cimzia®, Enbrel®, Humira®, Remicade® or Simponi®, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy.

Malignancy
Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with tumor necrosis factor blockers, of which Cimzia®, Enbrel®, Humira®, Remicade® or Simponi® are members.

Table 11. Boxed Warning for Tofacitinib[13]

WARNING

Serious Infections
Patients treated with Xeljanz® are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

If a serious infection develops, interrupt Xeljanz® until the infection is controlled. Reported infections include:

- Active tuberculosis, which may present with pulmonary or extrapulmonary disease.
- Patients should be tested for latent tuberculosis before Xeljanz® use and during therapy.
- Treatment for latent infection should be initiated prior to Xeljanz® use.
- Invasive fungal infections, including cryptococcosis and pneumocystosis. Patients with invasive fungal infections may present with disseminated, rather than localized, disease.
- Bacterial, viral, and other infections due to opportunistic pathogens.

The risks and benefits of treatment with Xeljanz® should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with Xeljanz®, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy.

Malignancies
Lymphoma and other malignancies have been observed in patients treated with Xeljanz®. Epstein Barr Virus-associated post-transplant lymphoproliferative disorder has been observed at an increased rate in renal transplant patients treated with Xeljanz® and concomitant immunosuppressive medications.

VII. Dosing and Administration

The usual dosing regimens for the disease-modifying antirheumatic agents are listed in Table 12.

Table 12. Usual Dosing Regimens for the Disease-Modifying Antirheumatic Agents[1-13]

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Abatacept	Rheumatoid arthritis: Prefilled syringe and single use vial: initial (<60 kg), 500 mg IV over 30 minutes at weeks zero, two and four; (60 to 100 kg), 750 mg IV over 30 minutes at weeks zero, two and four; (>100 kg), 1,000 mg IV over 30 minutes at weeks zero, two and four; maintenance (<60 kg), 500 mg IV over 30 minutes every four weeks; (60 to 100 kg), 750 mg IV over 30 minutes every four weeks; (>100 kg), 1,000 mg IV over 30 minutes every four weeks; or initial (<60 kg), 500 mg IV over 30 minutes followed by 125 mg SC within 24 hours; (60 to 100 kg), 750 mg IV over 30 minutes followed by 125 mg SC within 24 hours; (>100 kg), 1,000 mg IV over 30 minutes followed by 125 mg SC within 24 hours; maintenance, 125 mg SC once weekly	Juvenile idiopathic arthritis (six to 17 years of age): Prefilled syringe and single use vial: initial, (<75 kg),10 mg/kg IV over 30 minutes at weeks zero, two and four; (≥75 kg), follow adult dosing not to exceed 1,000 mg/dose; maintenance (<75 kg), 10 mg/kg IV over 30 minutes every four weeks; (≥75 kg), follow adult dosing not to exceed 1,000 mg/dose	Prefilled syringe: 125 mg/mL Vial: 250 mg
Adalimumab	Ankylosing spondylitis, psoriatic arthritis: Prefilled pen and syringe, single use vial: initial/maintenance, 40 mg SC every other week Crohn's disease, ulcerative colitis: Prefilled pen and syringe, single use vial: initial, 160 mg SC at week zero (may administer as four injections in one day or two injections daily for two consecutive days), followed by 80 mg SC during week two (day 15); maintenance, 40 mg SC every other week starting at week four (day 29) Hidradenitis Suppurativa: Prefilled pen and syringe, single use vial: 160 mg (four 40 mg injections) on day one, then 80 mg (two 40 mg injections) on day 15, then 40 mg weekly starting on day 29 Plaque psoriasis: Prefilled pen and syringe, single use vial: initial, 80 mg SC; maintenance, 40 mg SC every other week starting one week after the initial dose Rheumatoid arthritis: Prefilled pen and syringe, single use vial: initial/maintenance, 40 mg SC every other week; may increase to 40 mg SC every week in patients not receiving concomitant methotrexate	Crohn's disease (six to 17 years of age): 17 to <40 kg, 80 mg (two 40 mg injections) on day one, then 40 mg on day 15, then 20 mg every other week; ≥40 kg, 160 mg (four 40 mg injections) on day one, then two 40 mg injections on day 15, then 40 mg every other week Juvenile idiopathic arthritis (two to 17 years of age): 10 to <15 kg, 10 mg every other week; 15 to <30 kg, 20 mg SC every other week; ≥30 kg, 40 mg SC every other week (Dose has not been established for patients with a weight of <10 kg)	Prefilled pen: 40 mg/0.8 mL Prefilled syringe: 10 mg/0.2 mL 20 mg/0.4 mL 40 mg/0.8 mL
Anakinra	NOMID:	NOMID:	Prefilled

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
	Prefilled syringe: initial: 1 to 2 mg/kg daily; maintenance, dose can be individually adjusted to a maximum of 8 mg/kg daily Rheumatoid arthritis: Prefilled syringe: initial, 100 mg SC daily; maintenance, 100 mg SC daily	Prefilled syringe: initial: 1 to 2 mg/kg SC daily; maintenance, 3 to 4 mg/kg SC daily	syringe: 100 mg/0.67 mL
Apremilast	Plaque psoriasis, psoriatic arthritis: Tablet: initial, 10 mg in the morning on day one; 10 mg twice daily on day two; mg in the morning and 20 mg in the evening on day three; 20 mg twice daily on day four; 20 mg in the morning and 30 mg in the evening on day five; maintenance, 30 mg twice daily starting on day six	Safety and efficacy in the pediatric population have not been established.	Dose pack: 10 mg (4)-20 mg (4)-30 mg (19) 10 mg (4)-20 mg (4)-30 mg (47) Tablet: 30 mg
Certolizumab	Ankylosing spondylitis, psoriatic arthritis, rheumatoid arthritis: Prefilled syringe and vial: initial, 400 mg SC (as two SC injections of 200 mg) once and then repeat at weeks two and four; maintenance, 200 mg SC once every other week or 400 mg (as two SC injections of 200 mg) every four weeks Crohn's disease: Prefilled syringe and vial: initial, 400 mg SC (as two SC injections of 200 mg) once, repeat at weeks two and four; maintenance, 400 mg SC (as two SC injections of 200 mg) once every four weeks	Safety and efficacy in the pediatric population have not been established.	Prefilled syringe: 200 mg/mL Vial: 200 mg
Etanercept	Ankylosing spondylitis, psoriatic arthritis, rheumatoid arthritis: Prefilled autoinjector and syringe and vial: initial/maintenance, 50 mg SC weekly Plaque psoriasis: Prefilled autoinjector and syringe and vial: initial, 50 mg SC twice weekly for three months; maintenance, 50 mg SC weekly	Juvenile idiopathic arthritis (two to 17 years of age): Prefilled autoinjector and syringe and vial: initial and maintenance (<63 kg), 0.8 mg/kg SC weekly; (≥63 kg), 50 mg SC weekly	Prefilled "SureClick" autoinjector: 50 mg/mL Prefilled syringes: 25 mg/0.5 mL 50 mg/mL Vial: 25 mg
Golimumab	Ankylosing spondylitis, psoriatic arthritis: Prefilled autoinjector and syringe: initial, 50 mg SC once monthly; maintenance, 50 mg SC once monthly Rheumatoid arthritis: Prefilled autoinjector and syringe: initial, 50 mg SC once monthly in combination with methotrexate; maintenance, 50 mg SC once monthly in combination with methotrexate Vial (Simponi Aria®): initial, 2 mg/kg IV over	Safety and efficacy in the pediatric population have not been established.	Prefilled "SmartJect" autoinjector: 50 mg/0.5 mL 100 mg/mL Prefilled syringe: 50 mg/0.5 mL 100 mg/mL Single use vial

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
	30 minutes at weeks zero and four; maintenance, 2 mg/kg IV over 30 minutes every eight weeks; all in combination with methotrexate Ulcerative colitis: Prefilled autoinjector and syringe: initial, 200 mg SC once, followed by 100 mg SC at week two; maintenance, 100 mg SC once every four weeks		(Simponi Aria®): 50 mg/4 mL
Infliximab	Ankylosing spondylitis: Vial: initial, 5 mg/kg IV over two hours at weeks zero, two, and six; maintenance, 5 mg/kg IV over two hours every six weeks Crohn's disease: Vial: initial, 5 mg/kg IV over two hours at weeks zero, two, and six; maintenance, 5 mg/kg IV over two hours every eight weeks; may be increased to 10 mg/kg in patients who respond and then lose response Plaque psoriasis, psoriatic arthritis, ulcerative colitis: Vial: initial, 5 mg/kg IV over two hours at weeks zero, two, and six; maintenance, 5 mg/kg IV over two hours every eight weeks Rheumatoid arthritis: Vial: initial, 3 mg/kg IV over two hours at weeks zero, two, and six; maintenance, 3 mg/kg IV over two hours every eight weeks; may be increased to 10 mg/kg IV over two hours every eight weeks or 3 mg/kg IV over two hours every four weeks if incomplete response; all in combination with methotrexate	Crohn's disease, ulcerative colitis (six years of age and older): Vial: initial, 5 mg/kg IV over two hours at weeks zero, two and six; maintenance, 5 mg/kg IV over two hours every eight weeks	Single use vial: 100 mg
Leflunomide	Rheumatoid arthritis: Tablet: Use a loading dose of 100 mg once daily for three days only if the patient is not high risk for leflunomide-associated hepatotoxicity (e.g., taking concomitant methotrexate) or myelosuppression (e.g., taking concomitant immunosuppressants); maintenance, 20 mg once daily	Safety and efficacy in the pediatric population have not been established.	Tablet: 10 mg 20 mg
Tocilizumab	Rheumatoid arthritis: Prefilled syringe: initial and maintenance (<100 kg), 162 mg SC every other week, followed by 162 mg SC every week; (≥100 kg), 162 mg SC every week Vial: initial, 4 mg/kg IV every four weeks as a 60 minute infusion; maintenance, dose may be increased to 8 mg/kg IV every four weeks; maximum, 800 mg/infusion	Polyarticular juvenile idiopathic arthritis (two years of age and older): Vial: initial and maintenance (<30 kg), 10 mg/kg IV every four weeks as a 60 minute infusion; (≥30 kg), 8 mg/kg IV every four weeks as a 60 minute infusion	Prefilled syringe: 162 mg/0.9 mL Single use vial: 80 mg/4 mL 200 mg/10 mL 400 mg/20 mL

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
		Systemic juvenile idiopathic arthritis (two years of age and older): Vial: initial and maintenance (<30 kg), 12 mg/kg IV every two weeks as a 60 minute infusion; (≥30 kg), 8 mg/kg IV every two weeks as a 60 minute infusion	
Tofacitinib	Rheumatoid arthritis: Tablet: 5 mg by mouth twice daily	Safety and efficacy in the pediatric population have not been established.	Tablet: 5 mg

IV=intravenously, SC=subcutaneously
JIA=juvenile Idiopathic Arthritis, NOMID=Neonatal-Onset Multisystem Inflammatory Disease

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the disease-modifying antirheumatic agents are summarized in Table 13.

Table 13. Comparative Clinical Trials with the Disease-Modifying Antirheumatic Agents

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ankylosing Spondylitis				
van der Heijde et al.[37] (2006) Adalimumab 40 mg every other week vs placebo Patients were allowed to continue MTX, NSAIDs, prednisone or prednisone equivalent and SSZ.	DB, MC, RCT Patients ≥18 years of age with a diagnosis of AS based on the modified New York criteria with active disease BASDAI score ≥4, a total back pain score ≥4 by VAS (VAS, 0 to 10 cm) or a duration of morning stiffness ≥1 hour	N=315 24 weeks	Primary: ASAS 20 response at week 12 Secondary: ASAS 20 response at week 24, measures of disease activity, spinal mobility and function, and ASAS partial remission	Primary: An ASAS 20 response was attained in 58% of participants taking adalimumab vs 21% of participants taking placebo at week 12 (P<0.001). Secondary: A significantly greater ASAS 20 response was also noted at week 24 with adalimumab vs placebo (52 vs 18%; P<0.001). Adalimumab, compared to placebo, resulted in a significant improvement in other measures of disease activity such as a 50% improvement in BASDAI at week 12 (45 vs 16%; P<0.001) which was sustained through week 24 (42 vs 15%; P<0.001). ASAS 5/6 and ASAS 40 responses were attained in 49 vs 13% and 40 vs 13% of adalimumab vs placebo patients at week 12 (P<0.001) and 45 vs 12% and 39 vs 13% at week 24 (P<0.001), respectively. Partial remission was achieved in 21 vs 4% at week 12 and 22 vs 6% at week 24 in the adalimumab and placebo groups, respectively (P<0.001).
Landewe et al.[38] (2013) RAPID-axSpA Certolizumab 400 mg at weeks 0, 2, and 4 then 200 mg every 2 weeks (CZP 200 mg) vs	DB, MC, PC, PG, RCT Patients ≥18 years of age with a diagnosis of AS based on the ASAS criteria, with active disease BASDAI score ≥4, spinal pain ≥4, CRP>7.9 mg/L and/or sacroiliitis on	N=325 24 weeks	Primary: ASAS 20 response at week 12 Secondary: ASAS 20 response at week 24, change from baseline in BASFI, BASDAI, and BASMI linear at week 12 and 24	Primary: A greater proportion of patients treated with CZP 200 mg every two weeks (57.7%) and CZP 400 mg every four weeks (63.6%) achieved ASAS 20 response at week 12 compared to placebo (38.3%; P=0.004 and P<0.001, respectively). Secondary: The difference in ASAS 20 response was sustained through week 24 in both CZP treatment groups (P<0.001). Improvements in BASFI scores from baseline were greater in patients treated with CZP 200 mg every two weeks and CZP 400 mg every four

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
certolizumab 400 mg at weeks 0, 2, and 4 then 400 mg every 2 weeks (CZP 400 mg) vs placebo Patients receiving placebo who did not achieve an ASAS 20 response at weeks 14 and 16 were randomized to active treatment at week 16. Concurrent DMARDs (SSZ and MTX) were allowed.	MRI, chronic back pain ≥3 months, inadequate response or intolerance to ≥1 NSAID or ≥2 weeks each for ≥2 NSAIDs in the last ≥30 days			weeks compared to placebo at 12 weeks (-2.0 and -2.0 vs -0.5; P<0.001) and at 24 weeks (-2.2 and -2.2 vs -0.4; P<0.001 for both comparisons), respectively. Improvements in BASDAI scores from baseline were greater in patients treated with CZP 200 mg every two weeks and CZP 400 mg every four weeks compared to placebo at 12 weeks (-2.8 and -2.8 vs -1.2; P<0.001) and at 24 weeks (-3.1 and -3.0 vs -1.1; P<0.001 for both comparisons), respectively. Improvements in BASMI linear scores from baseline were greater in patients treated with CZP 200 mg every two weeks and CZP 400 mg every four weeks compared to placebo at 12 weeks (-0.6 and -0.5 vs -0.1; P<0.001 and P<0.05, respectively) and at 24 weeks (-0.5 and -0.5 vs -0.1; P<0.001 for both comparisons), respectively.
Gorman et al.[39] (2002) Etanercept 25 mg twice a week vs placebo Patients were allowed to continue stable doses of DMARDs, NSAIDs,	DB, RCT Patients ≥18 years of age with active inflammatory AS based on the modified New York criteria, despite accepted treatments	N=40 4 months	Primary: Measures of morning stiffness, spinal pain, functioning, patient's global assessment of disease activity, and joint swelling Secondary: Physician's global assessment of disease activity,	Primary: A response to treatment was detected in 80% of individuals receiving etanercept as opposed to 30% of individuals receiving placebo (P=0.004). Primary endpoints were reported as follows for the etanercept and placebo groups, respectively: duration of morning stiffness, 25.0±78.9 vs 60.0±65.0 minutes (P<0.001); scores for nocturnal spinal pain (0=none to 100=most severe), 15.0±24.3 vs 38.0±27.8 (P<0.001); mean swollen joint scores (0=none to 3=severe), 1.6±3.8 vs 3.7±7.6 (P=0.17); patient's global assessment of disease activity (0=none to 5=very severe), 2.0±0.6 vs 3.0±0.9 (P<0.001); and the BASFI scores (0=none to 10=severe limitations), 2.2±2.1 vs 3.1±3.0 (P<0.001). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
and oral corticosteroids.			measures of spinal mobility, scores for enthesitis and peripheral-joint tenderness, ESR and CRP levels, and adverse events	Differences in a number of secondary outcomes did reach statistical significance among those taking etanercept compared to those taking placebo including, physician's global assessment of disease activity (23.0±10.6; P<0.001), chest expansion (3.5±1.9 vs 2.9±1.7 cm; P=0.006), Modified Newcastle Enthesis Index, which is a measure of 17 enthesis on a four point pain scale (0.0±3.0 vs 1.5±8.0; P=0.001), ESR level (8.5±12.8 vs 16.5±18.7 mm/hour; P<0.001) and CRP level (0.7±1.1 vs 2.0±2.8 mg/dL; P=0.003). Injection site reactions and minor infections were the most commonly reported adverse events. The incidence in overall adverse events or specific events did not differ significantly.
Calin et al.[40] (2004) Etanercept 25 mg twice a week vs placebo Patients were allowed to continue stable doses of DMARDs (HCQ, MTX, or SSZ) one NSAID, and oral corticosteroids (≤10 mg prednisone).	DB, MC, RCT Patients 18 to 70 years of age with active AS based on the modified New York criteria	N=84 12 weeks	Primary: ASAS 20 response Secondary: ASAS 50 response, ASAS 70 response, individual components of ASAS, BASDAI, acute phase reactants, spinal mobility tests, and safety	Primary: ASAS 20 response was found in 60.0% of etanercept patients compared to 23.1% of placebo patients at 12 weeks (P<0.001). Secondary: The etanercept group was associated with the higher rates of ASAS 50 and 70 responses (48.9 and 24.4%) compared to placebo (10.3 and 10.3%) at week 12. However, only the differences in ASAS 50 response reached statistical significance at this assessment point (P<0.001). ASAS 70 response was significantly different between groups up until week eight (28.9% with etanercept vs 7.7% with placebo; P<0.05). The changes in the individual ASAS components were reported as follows for etanercept and placebo: spinal inflammation, 43.3 vs 15.9% (P=0.003); nocturnal and total pain, 43.1 vs 6.2% (P=0.000); patient's global assessment, 37.0 vs 12.6% (P=0.11); functional impairment (BASFI), 35.4 vs 3.4% (P=0.000); BASDAI composite score, 43.6 vs 13.6% (P=0.001); and BASDAI fatigue score, 42.6 vs -4.9% (P=0.000). Injection site reactions occurred more frequently with etanercept compared to placebo (33 vs 15%; P<0.05).
Davis et al.[41] (2008) Etanercept 25 mg	ES, OL Patients 18 to 70 years of age with	N=257 Up to 192 weeks	Primary: Safety (adverse events, serious adverse events,	Primary: After up to 192 weeks of treatment, the most common adverse events were injection site reactions, headache and diarrhea; no deaths were reported.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
twice weekly until week 72, then 50 mg once weekly Stable doses of corticosteroids and NSAIDs were required 2 weeks prior to enrollment; stable doses of HCQ, MTX, or SSZ were required if deemed necessary.	active AS based on the modified New York criteria		infections, serious infections, and death) and efficacy (ASAS 20 response, ASAS 5/6 response, and partial remission rates) Secondary: Not reported	For etanercept treatment the exposure adjusted serious event rate/patient year was 0.08, the exposure adjusted infection rate/patient year was 1.10, and the exposure adjusted serious infection rate/patient year was 0.02. Injection site reactions were reported in 22.2% of patients, which lead to the withdrawal of 0.4% of patients. A total of 71% of patients were considered ASAS 20 responders at week 96 and 81% of patients were considered responders at week 192. ASAS 5/6 response rates were 61% at week 96 and 60% at week 144. Partial remission response rates were 41% at week 96 and 44% at week 192. Placebo patients who switched to etanercept in the OL extension showed similar rates of efficacy maintenance. Secondary: Not reported
Braun et al.[42] (2011) ASCEND Etanercept 50 mg once weekly vs SSZ titrated to 3 g daily in divided doses	DB, MC, RCT Patients ≥18 years of age with active AS (diagnosed according to modified New York criteria) who failed treatment with ≥1 NSAID taken for ≥3 months at the maximum recommended dose and were determined to be candidates for SSZ therapy by the investigators	N=566 16 weeks	Primary: Proportion of patients achieving ASAS 20 response at week 16 Secondary: Proportion of patients achieving ASAS 20 response at weeks two, four, eight and 12; proportion of patients achieving ASAS 40 response and ASAS 5/6 response at all	Primary: At week 16, significantly greater proportion of patients in the etanercept group achieved ASAS 20 response compared to the SSZ group (75.9 vs 52.9%; P<0.0001). Secondary: Significantly greater proportion of patients in the etanercept group achieved ASAS 20 response at week two compared to patients in the SSZ group; this difference was maintained throughout the time points (P<0.0001 for all). Significantly greater proportion of patients in the etanercept group achieved ASAS 40 and ASAS 5/6 responses compared to patients in the SSZ group at all time points (P<0.0001 for all). At week 16, a greater proportion of patients achieved ASAS 40 and ASAS 5/6 responses in the etanercept group compared to the SSZ group (59.8 vs 32.6%; P<0.0001 and 45.5 vs 21.2%; P<0.0001, respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			time points	The rates of adverse events and serious adverse events were similar between the two groups.
Inman et al.[43] (2008) Golimumab 50 mg once every 4 weeks vs golimumab 100 mg once every 4 weeks vs placebo Patients who were on stable doses of HCQ, MTX, NSAID, oral corticosteroid and/or SSZ were permitted in the study.	DB, MC, PC, RCT Patients ≥18 years of age with a diagnosis of AS and no evidence of active TB and/or no evidence of latent TB on screening	N=356 24 weeks	Primary: ASAS 20 response at week 14 Secondary: Not reported	Primary: Treatment with golimumab with or without a DMARD, compared to placebo with or without a DMARD, resulted in a significant improvement in signs and symptoms as demonstrated by ASAS 20 response at week 14 (59 vs 22%; P≤0.001). All individual components of the ASAS response criteria were significantly improved in the golimumab 50 mg group compared to the placebo group at week 14. Secondary: Not reported
Braun et al.[44] (2002) Infliximab 5 mg/kg at weeks 0, 2 and 6 vs placebo Concurrent use of NSAIDs not	DB, MC, PC, RCT Adult patients (mean age of 40) with AS based on the modified New York criteria with BASDAI score ≥4 and spinal pain score ≥4	N=70 12 weeks	Primary: Improvement from baseline in BASDAI by 50% at week 12 Secondary: Improvement from baseline in spinal pain, BASFI, BASMI, SF-36, CRP, and ESR	Primary: A greater proportion of patients achieved a 50% improvement in BASDAI at week 12 in the infliximab group (53%; 95% CI, 37 to 69) compared to the placebo group (9%; 95% CI, 3 to 22). The difference between the groups was significant starting at week two and continuing through until week 12 (P<0.0001). Secondary: At week 12, the infliximab group had a significant mean improvement from baseline in spinal pain (P<0.0001), BASFI (P<0.0023), BASMI (P<0.0001), CRP (P<0.0001), and ESR (P<0.0001); while there was no significant difference in the placebo group. At 12 weeks, there were

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
exceeding the baseline dose was allowed.				significant improvements from baseline in the physical component and mental component of the SF-36 in the infliximab group (P<0.0001); however, only the improvement in the physical component was significantly greater compared to the placebo group (P<0.0001). A greater proportion of patients reported infections in the infliximab group (51%) compared to the placebo group (35%; difference, 16%; 95% CI, -7 to 40; P=0.227). A greater proportion of patients in the infliximab group experienced serious adverse events and were withdrawn from the study compared to the placebo group (3 vs 0; P=0.239).
van der Heijde et al.[45] (2005) ASSERT Infliximab 5 mg/kg at weeks 0, 2, 6, 12 and 18 vs placebo Concurrent NSAIDs, acetaminophen or tramadol were allowed during the study.	MC, PC, RCT Adult patients (median age of 40) with AS based on the modified New York criteria for at least three months with a BASDAI score ≥4, spinal pain assessment score ≥4 on a VAS and a normal chest radiograph within three months, and negative TB screening	N=279 24 weeks	Primary: Proportion of patients with ASAS 20 at week 24 Secondary: ASAS 40 response, ASAS partial remission, ASAS 5/6, disease activity (BASDAI, night pain, patient's global assessment and CRP), physical function (BASFI), range of motion (BASMI), other musculoskeletal assessments (swollen joint count and degree of tenderness) and quality of life (SF-36)	Primary: After 24 weeks, significantly greater proportion of patients were ASAS 20 responders in the infliximab group (61.2%) compared to the placebo group (19.2%; P<0.001). The difference was significant at week two and continued to week 24. Secondary: Over the 24-week study period, significantly greater proportion of patients were ASAS 40 responders in the infliximab group compared to the placebo group (P<0.001). At 24 weeks 47% of patients were ASAS 40 responders in the infliximab group compared to 12% in the placebo group (P<0.001). Significantly greater proportion of patients treated with infliximab achieved ASAS 5/6 (49%) compared to placebo treated patients (8%; P<0.001). Significantly greater proportion of patients achieved a partial ASAS response in the infliximab group (22.4%) compared to the placebo group (1.3%; P<0.001). The median improvement in all measures of disease activity (BASDAI, night pain, patient's global assessment and CRP) was significantly greater in the infliximab treated patients compared to placebo treated patients (P<0.001). The patients in the infliximab group had a significantly greater median improvement in BASFI compared to patients in the placebo group (P<0.001). There was a significantly greater median improvement in BASMI in the infliximab group compared to the placebo group (P=0.019). The infliximab treated patients had a significantly greater median improvement in swollen joint count compared to the placebo treated patients (P=0.019). There was a significantly greater improvement

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				in the physical component of the SF-36 in the infliximab group compared to the placebo group (P<0.001); there was no significant difference in the mental component (P=0.547). Compared to patients in the placebo group, a greater proportion of patients in the infliximab group experienced at least on adverse event (82.2 vs 72.0%), reported at least one infection (42.6 vs 36.0%) and had severe adverse reactions (3.5 vs 2.7%). Of the adverse events that occurred in at least 5% of patients in either group, the rates of pharyngitis, rhinitis, and increased liver enzymes were greater in the infliximab group.
Machado et al.[46] (2013) Infliximab vs etanercept vs adalimumab vs golimumab vs certolizumab vs control Concurrent use of stable doses of other	MA RCTs of patients with AS based on the modified New York criteria	N=2,820 (18 trials) 6 to 104 weeks	Primary: Proportion of patients with ASAS 20 at 12- or 14 weeks and at 30 weeks of follow-up Secondary: ASAS 40 response, ASAS 5/6, ASAS partial remission, BASDAI, BASDAI 50, BASFI, and BASMI, withdraws and safety outcomes at 12 or 14 weeks and 30 weeks of follow-up	Primary: Patients treated with TNF-blockers were more likely to achieve ASAS 20 response after 12 or 14 weeks (RR, 2.21; 95% CI, 1.91 to 2.56) and 24 weeks (RR, 2.68; 95% CI, 2.06 to 3.48) compared to controls. Treatment with golimumab was associated with the highest RR for ASAS 20 response after 12 or 14 weeks (RR, 2.74; 95% CI, 1.78 to 4.22), followed by adalimumab (RR, 2.33; 95% CI, 1.45 to 3.74), etanercept (RR, 2.13; 95% CI, 1.75 to 2.58), and infliximab (RR, 1.82; 95% CI, 1.16 to 2.58) compared to controls. Treatment with infliximab was associated with the highest RR for ASAS 20 response after 24 weeks (RR, 3.18; 95% CI, 1.99 to 5.08), followed by etanercept (RR, 2.53; 95% CI, 1.80 to 3.57) and adalimumab (RR, 2.15; 95% CI, 0.96 to 4.83) compared to controls. Secondary: Patients treated with TNF-blockers were more likely to achieve ASAS 40 response after 12 or 14 weeks (RR, 2.77; 95% CI, 2.05 to 3.75) and 24 weeks (RR, 3.32; 95% CI, 2.44 to 4.51) compared to controls. Patients treated with TNF-blockers were more likely to achieve ASAS 5/6 response after 12 or 14 weeks (RR, 3.52; 95% CI, 2.17 to 5.71) and 24 weeks (RR, 4.25; 95% CI, 2.80 to 6.46) compared to controls. Patients treated with TNF-blockers were more likely to achieve partial remission after 12 or 14 weeks (RR, 4.79; 95% CI, 2.46 to 9.34) and 24

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
medications was allowed.				weeks (RR, 4.43; 95% CI, 2.62 to 7.49) compared to controls. Patients treated with TNF-blockers achieved greater improvements in the disease activity (BASDAI) after 12 weeks (mean difference, -1.64; 95% CI, -2.06 to -1.22) and after 30 weeks (mean difference, -1.79; 95% CI, -2.27 to 1.31) compared to controls. Patients treated with TNF-blockers were more likely to achieve BASDAI 50 response at 12 or 14 weeks (RR, 2.87; 95% CI, 2.23 to 3.69) and at 24 weeks (RR, 3.39; 95% CI, 2.46 to 4.67) compared to controls. Patients treated with TNF-blockers achieved greater improvements in physical function (BASFI) at 12 weeks (mean difference, -1.39; 95% CI, -1.59 to -1.19) and at 24 weeks (mean difference, -1.52; 95% CI, -1.72 to -1.31) compared to controls. Patients treated with TNF-blockers achieved greater improvements in vertebral mobility (BASMI) at 12 weeks (mean difference, -0.53; 95% CI, -0.72 to -0.35) and at 24 weeks (mean difference, -0.60; 95% CI, -0.87 to -0.33) compared to controls. Meta-analysis of safety outcomes and withdraws did not indicate statistically significant differences between treatment and control groups after 12 or 30 weeks (P value not reported).
Crohn's Disease				
Ma et al.[47] (2009) Adalimumab	SR OL and RCT cohort studies of patients with CD who had either lost response, were intolerant or refractory to infliximab	N=1,810 (15 trials) 8 weeks to 4 years	Primary: Short-term and long-term efficacy Secondary: Adverse events	Primary: Short-term clinical response or remission was evaluated in nine trials. Forty-one to 83% of patients achieved a clinical response at four weeks, while 12 to 67% of participants attained clinical remission. Long-term remission rates ranged from 31 to 82% at six months and 19 to 68% at one year. Secondary: Serious adverse events were reported in 0 to 19% of patients and included sepsis, cellulitis, and fungal pneumonia.
Lofberg et al.[48] (2012)	MC, OL	N=945	Primary: Remission rates,	Primary: The proportion of patients in remission who received adalimumab was

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
CARE Adalimumab 160 mg at week zero, followed by 80 mg at week two, followed by 40 mg every other week At week 12 or later, patients who experienced a disease flare or did not respond to treatment could increase the adalimumab dose to 40 mg weekly.	Patients 18 to 75 years of age with a radiologic or endoscopic diagnosis of CD for ≥4 months and a HBI >7 points at screening	20 weeks	proportion of patients free of EIM at week 20 Secondary: Fistula healing, remission rates based on concomitant therapies and adverse events	43% at week four (95% CI, 40 to 46) and increased to 52% (95% CI, 49 to 55) at week 20. There was a significantly higher remission rate at week 20 among adalimumab-treated patients who were also infliximab naïve compared to patients exposed to infliximab (62 vs 42; P<0.001). A shorter disease duration (less than two years and between two and five years) was associated with higher rates of clinical remission at week four compared to a disease duration longer than five years (50, 52, and 38%, respectively; P<0.001); however the remission rates at 20 weeks were not significantly different (58, 56, and 50%, respectively; P=0.136). Overall, 53% of patients had at least one EIM at baseline, compared to 30% at week 20. Of these, 79% had resolution of at least one EIM and 51% were free of EIM signs and symptoms following 20 weeks of adalimumab treatment. The EIM resolution rates were similar across adalimumab-treated patients regardless of prior infliximab use (P=0.100) and prior infliximab response and those who discontinued treatment for other reasons (P=0.625). Secondary: Complete fistula healing occurred in 26% of patients at week 20. Fistula closure rates were numerically higher in the infliximab-naïve group at week 20 (33%) compared to the infliximab-experienced group (22%); however, the difference was not significant (P=0.275). Fistula healing rates were similar in nonresponders to infliximab compared to those who discontinued infliximab for other reasons (19 vs 23%; P=0.973). Of patients taking corticosteroids at baseline, 37% were able to discontinue them by week 20; Eleven percent and 14% of patients achieved a steroid-free remission at weeks 12 and 20, respectively. Seven percent of patients taking immunosuppressants at baseline were able to discontinue them at week 20. There were similar rates of clinical remission at week 20 between patients taking and not taking steroids at baseline (52% in both groups; P=0.976). By week 20, the rates of clinical remission were 55 and 49%,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				respectively, in patients who were and were not taking immunosuppressants at baseline (P=0.052). Adverse events occurred in 80% of patients and 11% of patients who discontinued treatment due to adverse events. Serious adverse events were reported in 19% of patients. The adverse events profiles were similar among patients who were exposed to infliximab previously and those who were treatment naïve. The most common adverse event categories were "gastrointestinal disorders" and "CD'' indicating a worsening of patient's underlying disease.
Watanabe et al.[49] (2012) (Induction study) Adalimumab 160 mg at week zero, followed by 80 mg at week two (ADA 160/80 group) vs adalimumab 80 mg at week zero, followed by 40 mg at week two (ADA 80/40 group) vs placebo (Maintenance study) adalimumab 40 mg every other week	2 DB, MC, PC, RCT Patients 15 to 75 years of age, with moderate to severely active CD, CDAI score 220 to 450 for >4 months and a diagnosis of ileal, colonic or ileocolonic CD confirmed by endoscopy or radiologic evaluation	N=90 (induction) N=83 (maintenance) 56 weeks (4 weeks induction study and 52 week maintenance study)	Primary: Induction study Proportion of patients in clinical remission (CDAI <150) at week four Maintenance Clinical remission (CDAI <150) at week 52 Secondary: Induction study Proportion of patients in clinical remission at week two and with CR-100 or CR-70 (CDAI decrease ≥100 or ≥70) at week four, changes from baseline in CDAI and IOIBD at week two and	Primary: Induction A greater proportion of patients treated with ADA 160/80 and ADA 80/40 achieved a clinical remission by week four compared to placebo (33 and 18 vs 12%, respectively; P value not reported). Maintenance By week 52, a significantly greater proportion of patients treated with adalimumab 40 mg achieved a clinical remission compared to placebo (P<0.05). Secondary: Induction At week two, clinical remission rates were higher with ADA 160/80 and ADA 80/40 compared to placebo (18 and 15 vs 4%, respectively; P value not reported). At week four, significantly greater proportion of patients receiving ADA 160/80 or ADA 80/40 experienced a CR-100 (50 and 46 vs 17%, respectively; P<0.05 for both) compared to placebo. At week four, significantly greater proportion of patients receiving ADA 160/80 experienced a CR-70 (70 vs 30%; P=0.0062); however, the improvement with the ADA 80/40 was not statistically significant. The changes in CDAI from baseline to week two and four, respectively, were, -75.9 and -101.3 in the ADA 160/80 group, -74.4 and -81.3 in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo Patients achieving a Clinical Response 70 (decrease from baseline in CDAI ≥70 points at week four) entered the blinded maintenance trial.			week four and changes in SF-36 MCS and PCS, and IBDQ scores in each treatment group at week four Maintenance Proportion of patients in clinical remission, (CDAI decrease ≥100 or ≥70) every four weeks, changes from baseline of the induction to week 52 in CDAI, IOIBD, SF-36 MCS and PCS scores, and IBDQ	ADA 80/40 group, and -27.2 and -37.5 in the placebo group. The mean changes in IOIBD score from baseline to week two and week four, respectively, were -1.2 and -1.5 in the ADA 160/80 group, -0.7 and -0.8 in the ADA 80/40 group, and -0.4 and -0.5 in the placebo group. ADA 160/80 or ADA 80/40 significantly improved SF-36 MCS from baseline to week four compared to placebo. (6.2 and 5.5 vs -1.6, respectively; P<0.05 for both). There were no statistically significant differences in SF-36 PCS and IBDQ between patients receiving ADA 160/80 compared to patients receiving placebo. Maintenance Adalimumab therapy was more effective compared to placebo at each of the four-week evaluations throughout the 52-week trial compared to placebo with regard to CR-100 (P≤0.05) and CR-70 (P≤0.01). Adalimumab was more effective compared to placebo with regard to maintaining clinical remission at weeks eight, 36, 36, 40, 48 and 52 (P<0.05). The mean changes in CDAI from baseline of the induction trial to week zero and week 52, respectively, were -147.7 and -83.7 in the adalimumab-treated patients and -139.0 and -9.1 in the placebo-treated patients. The mean changes in IOIBD from baseline to week zero and week 52, respectively, were -2.0 and -0.8 in adalimumab-treated patients and -1.2 and -0.2 in placebo-treated patients, respectively. Adalimumab 40 mg was associated with statistically significant improvements in SF-36 MCS and IBDQ compared to placebo at eight weeks (12.0 vs 2.0; P=0.03 and 34.8 vs 8.3; P=0.05, respectively); however, the changes were not significantly different at 52 weeks.
Shao et al.[50] (2009) Certolizumab	MA DB, RCTs in patients with moderate to severe	N=1,040 (3 trials) 12 to 26 weeks	Primary: Clinical response (a decrease ≥100 points from baseline in CDAI	Primary: Certolizumab was associated with an increased rate of induction of clinical response (RR, 1.36; 95% CI, 1.10 to 1.68; P=0.004) and remission (RR, 1.95; 95% CI, 1.41 to 2.70; P<0.0001) compared to placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	CD		score) and clinical remission (CDAI score ≤150 points) at week four Secondary: Safety	Secondary: Only infection was reported more frequently with certolizumab compared to placebo (60.6 vs 40.7%).
Targan et al.[51] (1997) Infliximab 5 mg/kg vs infliximab 10 mg/kg vs infliximab 20 mg/kg vs placebo	DB, MC, PC, RCT Adult patients with CD for six months with CDAI scores 220 to 400 and previously receiving mesalamine (for ≥8 weeks and a stable dose for four weeks), corticosteroids (maximum of 40 mg/day for ≥8 weeks and a stable dose for two weeks), mercaptopurine or azathioprine (for ≥6 months and stable dose for eight weeks)	N=108 12 weeks	Primary: Decrease from baseline in CDAI ≥70 points at four weeks without a change in concomitant medications Secondary: Not reported	Primary: At week four, the primary endpoint was reached in 81, 50, 64 and 17% in the 5 mg/kg, 10 mg/kg, 20 mg/kg and placebo groups, respectively. The overall response of the infliximab groups was significantly higher (65%) compared to the placebo group (P<0.001). At week two, 61% of the infliximab treated patients had a response compared to 17% of the placebo treated patients (P<0.001). A greater proportion of patients was in remission (CDAI score <150) in the infliximab group at two weeks (27%) compared to the placebo group (4%; P=0.06). At week four, 33% of the infliximab treated patients were in remission compared to 4% of the placebo treated patients (P<0.005). The response rate remained significantly higher in the infliximab treated patients through the 12 weeks of the study (41%) compared to placebo treated patients (12%; P=0.008); however, the remission rate was not significantly different at 12 weeks (24 vs 8%; P=0.31). Secondary: Not reported
Present et al.[52] (1999) Infliximab 5 mg/kg at weeks 0, 2 and 6 vs infliximab 10 mg/kg	DB, MC, PC, RCT Patients 18 to 65 years of age with ≥1 confirmed draining abdominal or perianal fistulas of ≥3 months as a complication of CD	N=94 18 weeks	Primary: Reduction ≥50% from baseline in number of draining fistulas at two or more consecutive study visits	Primary: There were significantly greater response rates in the infliximab 5 (68%) and 10 mg/kg (56%) groups compared to the placebo group (26%; P=0.002 and P=0.02, respectively). The response rates were not significantly different between the two infliximab groups. Secondary: A greater proportion of patients in the infliximab 5 (55%) and 10 mg/kg (38%) groups had complete response compared to the placebo group

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
at weeks 0, 2 and 6 vs placebo			Secondary: Proportion of patients with a complete response (absence of any draining fistula at two consecutive visits), length of time to beginning of response, and duration of response	(13%; P=0.001 and P=0.04, respectively). In the infliximab group, the median time to the onset of response was two weeks compared to six weeks in the placebo group. The duration of response was approximately three months in patients that reached the primary endpoint. The most frequently reported adverse events in the infliximab group were headache, abscess, upper respiratory tract infection and fatigue.
Hyams et al.[53] (2007) REACH Infliximab 5 mg/kg at weeks 0, 2 and 6; those responding to therapy received continued therapy every 8 weeks at weeks 14, 22, 30, 38 and 36 or every 12 weeks at weeks 18, 30 and 42 vs infliximab 5 mg/kg at weeks 0, 2 and 6; those responding to therapy received continued therapy every 12 weeks at	OL, MC, RCT Patients 6 to 17 years of age with a PCDAI >30 at baseline and who initiated immunomodulator therapy (azathioprine, mercaptopurine or MTX) ≥8 weeks before screening and at stable dose for two weeks	N=112 46 weeks	Primary: Clinical response at week 10 (decrease from baseline to week 10 in PCDAI ≥15 points and total PCDAI no more than 30) Secondary: Maintenance of clinical response and remission (PCDAI ≤10)	Primary: At week 10, 88.4% of patients responded to the induction regimen (95% CI, 82.5 to 58.9). Secondary: At week 10, 58.6% of patients were in clinical remission (95% CI, 49.8 to 68.0). At week 54, 63.4 and 55.8% of patients treated with infliximab every eight weeks achieved clinical response and clinical remission, respectively, compared to 33.3 and 23.5% of patients treated with infliximab every 12 weeks (P=0.002 and P<0.001, respectively). At week 10, there was a significant decrease in PCDAI score compared to baseline that continued at weeks 30 and 54 (all P<0.001). There was a significant decrease in corticosteroid use at week 10 compared to baseline that continued at weeks 30 to 54 (all P<0.001). Adverse events were similar between the two groups. Infection was the most common adverse event in both treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
weeks 18, 30 and 42				
Van Assche et al.[54] (2012) SWITCH Adalimumab 80 mg at week zero and 40 mg every other week Patients not randomized to adalimumab continued prior infliximab at 5 mg/kg at their regularly scheduled interval. Patients with a disease flare were able to intensify treatment as follows: adalimumab 40 mg every week and in the infliximab group, a decrease of the dosing interval with two-week decrements.	OL, PRO, RCT Patients ≥18 years with luminal CD treated with infliximab maintenance therapy started for ≥6 months with a complete clinical response (PGA assessment of signs and symptoms, but the CDAI at baseline <200) with stable infliximab dosing intervals of ≥6 weeks	N=73 54 weeks	Primary: Proportion of patients in the adalimumab group preferring adalimumab over infliximab and proportion of patients who needed rescue therapy with short courses of steroids or intensified anti-TNF dosing or who had to stop the assigned anti-TNF agent Secondary: Proportion of patients with an injection- or infusion-related reaction and proportion of patients with an increase in the CDAI of >100 above baseline and IBDQ	Primary: There was a statistically significant increase in the preference of adalimumab over infliximab for patients who changed from infliximab to adalimumab therapy at all evaluation points (P<0.05), except week 56 (P=0.08). Dose intensification or early treatment termination occurred significantly more frequently over 54 weeks in patients switched to adalimumab (47%) compared to those who continued infliximab (16%; P=0.003). Significantly more patients initiating adalimumab therapy discontinued therapy due to loss of response or intolerance compared those who continued infliximab therapy (28 vs 2%; P<0.01). Of note, the patient who discontinued infliximab was successfully treated with adalimumab and eight of the 10 patients who stopped adalimumab treatment returned to infliximab therapy. The reasons for early discontinuation of treatment were loss of tolerance in six of 10 patients on adalimumab and in the one patient receiving infliximab. Four other patients in the adalimumab group stopped for loss of efficacy. Refractory eczema with fatigue or arthralgias (n=2), general malaise and diarrhea following injections (n=2) and fatigue plus inability to comply with injections (n=2) led to adalimumab intolerance and an infusion reaction to infliximab intolerance. Secondary: There was no difference in the change from baseline in CDAI at time of early termination in the adalimumab group (184 vs 78; P=0.10). Dose intensification occurred in 27.7% of patients in the adalimumab group, three of which later stopped adalimumab for loss of response, and in and 13.5% of patients in the infliximab group (P=0.20). The median time to dose intensification was not significantly different between the adalimumab and infliximab treatment arms (24 vs 32 weeks; P=0.64). An increase in CDAI ≥100 points was observed in 18.9% of patients in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				the infliximab group and in 27.7% of patients in the adalimumab group while on the initially assigned treatment. Median IBDQ values at baseline and at week 56 were comparable in both groups and the medians stayed well in the range compatible with disease remission throughout the trial.
Behm et al.[55] (2008) Adalimumab, certolizumab, or infliximab vs placebo	SR RCTs including patients ≥18 years of age with CD who had a clinical response or clinical remission with a TNF-α blocker, or patients with CD in remission but unable to wean corticosteroids, who were then randomized to maintenance of remission with a TNF-α blocker or placebo	N=3,586 (9 trials) Duration varied	Primary: Clinical remission, clinical response, and steroid-sparing effects Secondary: Not reported	Primary: Adalimumab demonstrated the ability to maintain clinical remission and clinical response (RR, 2.69; 95% CI, 1.88 to 3.86; P<0.00001), while also having a steroid-sparing effect (data specific to clinical remission and steroid-sparing effect not reported). Certolizumab was shown to maintain both clinical remission (RR, 1.68; 95% CI, 1.30 to 2.16; P=0.000072) and clinical response (RR, 1.74; 95% CI, 1.41 to 2.13; P<0.00001) compared to placebo. Infliximab was more effective than placebo at maintaining fistula healing (RR, 1.87; 95% CI, 1.15 to 3.04; P=0.012), clinical remission (RR, 2.50; 95% CI, 1.64 to 3.80; P=0.000019), clinical response (RR, 1.66; 95% CI, 1.00 to 2.76; P=0.0046, and achieved a steroid sparing effect (RR, 3.13; 95% CI, 1.25 to 7.81; P=0.014). Secondary: Not reported
Juvenile Idiopathic/Rheumatoid Arthritis				
Ruperto et al.[56] (2008) Abatacept 10 mg/kg every 28 days vs placebo	DB, MC, PC, RCT (OL lead in period) Patients 6 to 17 years of age with JIA with at least 5 active joints and active disease and who had inadequate response to or intolerance to ≥1 DMARD	N=122 (RCT); 190 (OL lead in period) 6 months (4-month OL lead in)	Primary: Time to flare Secondary: Proportion of patients with a disease flare, changes in baseline in each of six core response variables, and assessment of safety and	Primary: In the placebo group, the median time to flare was six months; however, insufficient events occurred in the abatacept group to assess median time to flare (P=0.0002). Secondary: There was a significantly greater proportion of patients that experienced a flare in the placebo group compared to the abatacept group (53 vs 12%; P=0.0003). The HR for patients in the abatacept group to experience a flare compared to the placebo group was 0.31 (95% CI, 0.16 to 0.59). After six months or at the time of first flare, 82% of the abatacept group and 69% of the placebo group improved by ≥30% as measured by ACR

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			tolerability	(P=0.1712), 77% of the abatacept group and 52% of the placebo group improved by ≥50% as measured by ACR (P=0.0071), 53% of the abatacept group and 31% of the placebo group improved by ≥70% as measured by ACR and 40% of the abatacept group and 16% of the placebo group improved by ≥90% as measured by ACR. In the abatacept group, 30% had inactive disease compared to 11% in the placebo group (P=0.0195). Adverse events were similar between the groups.
Lovell et al.[57] (2015) Abatacept 10 mg/kg every 28 days	OL (long-term extension of above study) Patients 6 to 17 years of age with JIA with at least five active joints and active disease and who had inadequate response to or intolerance to ≥1 DMARD	N=153 5 to 7 years	Primary: Safety Secondary: ACR Pedi responses, CHAQ	Primary: The overall incidence rates of adverse events and serious adverse events reported in the cumulative study period, corresponding to a mean ±SD maximum total exposure of 62.1 ± 20.9 months, were 209.11 (95% CI, 179.11 to 242.70) and 5.62 (95% CI, 3.92 to 7.82) events per 100 patient-years of exposure, respectively. Secondary: ACR Pedi 30 responses, Pedi 70 responses, and clinically inactive disease status were maintained throughout the long-term extension phase in patients who continued to receive therapy. Improvements in the Child Health Questionnaire physical and psychosocial summary scores were maintained over time.
Lovell et al.[58] (2008) Adalimumab 24 mg/m^2 (maximum of 40 mg) every other week with or without MTX vs placebo Patients were stratified according	DB, MC, OL, RCT Patients 4 to 17 years of age with active JRA who had previously received treatment with NSAIDs	N=171 48 weeks	Primary: Rate of disease flare in patients not receiving MTX Secondary: ACR Pedi 30, 50, 70, and 90 responses at week 48, and safety	Primary: Among patients not receiving MTX, flares occurred in 43% receiving adalimumab and 71% receiving placebo (P=0.03). In patients receiving MTX, flares occurred in 37 and 65% in the adalimumab and placebo groups, respectively (P=0.02). Secondary: In patients receiving MTX, ACR Pedi 30, 50, 70, and 90 responses were reported in 63 vs 38% (P=0.03), 63 vs 35% (P=0.03), 63 vs 27% (P=0.002) and 42 vs 27% (P=0.17) in the adalimumab and placebo groups, respectively. In patients not receiving MTX therapy, ACR Pedi 30, 50, 70, and 90 responses were reported in 57 vs 32% (P=0.06), 53 vs 32% (P=0.10), 47 vs 29% (P=0.16) and 30 vs 18% (P=0.28) in the adalimumab and placebo

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
to MTX use and received OL adalimumab 24 mg/m^2 (maximum of 40 mg) every other week for 16 weeks. The patients with an ACR Pedi 30 response at week 16 were then randomly assigned to receive adalimumab or placebo.				groups, respectively. The most frequently noted adverse events were mild to moderate in nature and included infections and injection site reactions. There were seven cases of serious infection reported with adalimumab use.
Lovell et al.[59] (2000) Etanercept 0.4 mg/kg twice weekly vs placebo All patients received etanercept 0.4 mg/kg twice weekly for up to 3 months in the OL part of the study; the patients whose condition improved were then randomly assigned to either etanercept or placebo.	DB, MC, OL, RCT Patients 4 to 17 years of age with active polyarticular JRA despite treatment with NSAIDs and MTX ≥10 mg/m^2/week	N=69 7 months	Primary: Rate of disease flare Secondary: Median time to flare, safety	Primary: Seventy-four percent (51/69) of patients demonstrated improvement and were included in the DB part of the trial. The rate of disease flare was significantly higher in the placebo group compared to the etanercept group (81 vs 28%; P=0.003). Secondary: The median time to flare was reported as 116 days in the active treatment arm compared to 28 days with placebo (P<0.001). During the OL segment of the study the adverse events most often reported included injection-site reaction, upper respiratory tract infections, headache, rhinitis and gastrointestinal side effects. There were no differences noted between groups during the latter part of the study.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Concurrent analgesics, NSAIDs, or oral corticosteroids (≤10 mg/day of prednisone or equivalent) were allowed.				
Lovell et al.[60] (2006) Etanercept 0.4 mg/kg (maximum of 25 mg) twice weekly Intra-articular and soft-tissue injections of corticosteroids were permitted after 12 continuous weeks of etanercept. MTX could be added to treatment after one year. Concurrent analgesics, NSAIDs, or oral corticosteroids (≤10 mg/day of prednisone or equivalent) were allowed.	Ongoing ES, MC, OL by Lovell et al[22] (updated efficacy and safety results from the study)	N=58 Median of 4 years	Primary: JRA 30% DOI Secondary: JRA 50% DOI, JRA 70% DOI, an articular severity score (0 to 926), assessment of pain (Likert scale, 0 to 10), CRP levels, safety	Primary: Thirty-two patients were available for efficacy analysis after four years with 94% meeting the JRA 30% DOI. Secondary: Approximately 94 and 78% of participants met the JRA 50% DOI and JRA 70% DOI, respectively. At four years, the median CRP level was lowered to 0.1 mg/dL from 3.4 mg/dL at baseline, the median articular severity score was decreased to 18 from 88 at baseline, and the median patient's assessment of pain score was lowered to 0.9 from 3.6 at baseline. Duration of morning stiffness was only assessed through one year and was reported as 5 minutes at month 12 (from 53 minutes at baseline). After four years, there were five reports of serious adverse events and 0.03 serious infections (requiring intravenous antibiotics or hospitalizations)/ patient year.
Horneff et al.[61] (2004)	MC, OL	N=322	Primary: Change in indices	Primary: At 12 months, the mean number of tender joints, swollen joints, and joints

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Etanercept 0.4 mg/kg twice weekly Combination treatment with MTX or oral corticosteroids was permitted.	Patients 4 to 17 years of age with active idiopathic juvenile arthritis despite treatment with MTX	Up to 48 months, median of 12 months	of disease activity, 30, 50, and 70% improvement in idiopathic juvenile arthritis Secondary: Safety	with limited range of movement were reduced to 1.7 (SD, 3.5), 2.6 (SD, 4.7), and 7.1 (SD, 8.9) from a baseline of 9.1 (SD, 9.5), 8.4 (SD, 9.0), and 11.8 (SD, 11.8), respectively. The duration of morning stiffness was decreased to 7 (SD, 23) minutes from 45 (SD, 65) minutes and CHAQ scores (on a scale of 0=best to 3=worst) were decreased to 0.4 (SD, 0.6) from 1.0 (SD, 0.8). Patient's and PGA scores (on a scale of 0=best to 100=worst) were reduced to 16 (SD, 18) and 20 (SD, 23) from 56 (SD, 27) and 67 (SD, 25), respectively. At last report (30 months) a 30, 50, and 70% improvement was noted in approximately 60, 48, and 28% of patients remaining on etanercept, respectively. Significant improvements in all indices of disease activity were detected at all points of time (months one, three, six, 12, 18, 24, and 30; P<0.0001 with the exception of swollen joint count at 30 months; P<0.0005 and duration of morning stiffness; P<0.001). Secondary: There were 20 reports of infection or infection related events. Discontinuation of treatment was reported in 53 patients, of which 11 cases were secondary to adverse events.
De Benedetti et al.[62] (2010) TENDER (abstract) Tocilizumab 8 mg/kg every 2 weeks for patients ≥30 kg or 12 mg/kg every 2 weeks for patients <30 kg vs placebo	PC, RCT Patients 2 to 17 years of age with active systemic JIA for ≥6 months with an inadequate response to NSAIDs and corticosteroids	N=112 12 weeks	Primary: Proportion of patients with JRA ACR 30 response plus absence of fever at week 12 Secondary: Not reported	Primary: At week 12, significantly greater proportion of patients treated with tocilizumab achieved JRA 30 response plus absence of fever (85%) compared to patients treated with placebo (24%; P<0.0001). Significantly greater proportion of patients in the tocilizumab group achieved JRA ACR 50, JRA ACR 70, and JRA ACR 90 responses compared to patients in the placebo group (P<0.0001). Secondary: Not reported
Brunner et al.[63] (2012) CHERISH	DB, PC, RCT (OL lead in period)	N=166 24 weeks	Primary: Proportion of patients with JIA	Primary: Tocilizumab treated patients experienced significantly fewer JIA ACR 30 flare at week 40 compared to patients treated with placebo (25.6 vs

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(abstract) Tocilizumab 8 mg/kg every 4 weeks for patients ≥30 kg vs 8 mg/kg every 4 weeks for patients <30 kg vs 10 mg/kg every 4 weeks for patients <30 kg vs placebo	Patients 2 to 17 years of age with active polyarticular JIA for ≥6 months who failed MTX		ACR 30 flare relative to week 16 Secondary: Proportion of patients with JIA ACR 30, ACR 50, and ACR 70 responses	48.1%; P<0.0024). Secondary: At week 40, significantly greater proportion of patients in the tocilizumab group achieved JRA ACR 30 (74.4 vs 54.3%; P=0.0084), JRA ACR 50 (73.2 vs 51.9%; P=0.0050), and JRA ACR 70 (64.6 vs 42.0%; P=0.0032) response compared to patients in the placebo group. The degree of improvement was lower for these endpoints in the tocilizumab 8 mg/kg (<30 kg body weight) group compared to the other two tocilizumab groups (10 mg/kg for patients weighing <30 kg and 8 mg/kg for patients weighing ≥30 kg).
Psoriasis				
Saurat et al.[64] (2008) CHAMPION Adalimumab 80 mg at week 0, then 40 mg every other week from week 1 through week 15 vs MTX 7.5 mg at week 0, then	DB, DD, MC, RCT Patients ≥18 years of age with moderate to severe psoriasis (>10% of BSA and PASI ≥10), plaque psoriasis for >1 year, stable plaque psoriasis for >2 months, that are candidates for systemic therapy of	N=271 16 weeks	Primary: Proportion of patients achieving PASI 75 at week 16 relative to baseline Secondary: Proportion of patients achieving PASI 50, PASI 90, PASI 100, and PGA	Primary: At 16 weeks, significantly more patients in the adalimumab group (79.6%) achieved PASI 75 compared to the MTX group (35.5%; RD, 43.7%; 95% CI, 30.8 to 56.7; P<0.001) and placebo group (18.9%; RD, 60.5%; 95% CI, 44.5 to 76.6; P<0.001). The difference in treatment groups was seen starting at two weeks for adalimumab vs MTX (P<0.05) and at four weeks for adalimumab vs placebo (P<0.001). Secondary: At week 16, PASI 100 was achieved in significantly more patients in the adalimumab group (16.7%) compared to the MTX group (7.3%; P<0.04) and the placebo group (1.9%; P<0.001).Significantly more patients achieved PASI 50, PASI 90 and a PGA of clear or minimal in the adalimumab group compared to the MTX and placebo groups (P<0.001

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
increased to 10 mg weekly at week 2, then increase to 15 mg weekly at week 4; at week 8, patients not achieving PASI 50 had the dose of MTX increased to 15 mg weekly; at week 12, patients not achieving PASI 50 at week 12 and 8 had the dose of MTX increased to 25 mg weekly vs placebo	phototherapy, with plaque psoriasis despite treatment with topical agents and treatment naïve to TNF-antagonists and MTX			for all). Rates of reported infectious adverse events were not significantly different between the groups (P value not reported). Total adverse events and serious adverse events were similar.
Bagel et al.[65] (2012) Etanercept 50 mg twice- weekly for 12 weeks followed by etanercept 50 mg weekly plus placebo weekly for 12 additional weeks (Group A) vs placebo twice-weekly for 12 weeks followed by	DB, MC, PC, RCT Patients ≥18 years of age with stable moderate-to-severe plaque psoriasis covering ≥10% of BSA for ≥6 months and PASI scores ≥10 and ≥30% of SSA affected, with PSSI scores ≥15	N=124 24 weeks	Primary: Percentage change in PSSI score at week 12 Secondary: Percentage change in the PSSI score at week 24 for Group B patients, the proportion of patients achieving PSSI 75 improvement at week 12, patient satisfaction	Primary: At week 12, Group A experienced a significantly greater mean improvement in PSSI score compared to Group B (86.8 vs 20.4%; P<0.001) with significant improvements as early as week four of treatment. Secondary: At week 24, both Group A and Group B experienced improvements in PSSI scores from baseline (90.6 vs 79.1%, respectively; P value not reported). A significantly greater proportion of patients in Group A compared to Group B experienced a PSSI 75 at week 12 (86 vs 11%; P<0.0001). Significantly more etanercept-treated patients were either satisfied or very satisfied at week 12 compared to placebo (P<0.0001). At week 24, after etanercept treatment, Group B patients' satisfaction increased

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
etanercept 50 mg twice- weekly for 12 additional weeks (Group B) Patients discontinued the use of background therapies.			with treatment at week 12, and safety	significantly over their first 12 weeks on placebo (P<0.0001). More than two thirds of Group A patients continued to be satisfied or very satisfied at week 24. The rates of adverse events were comparable between groups, both at week 12 (etanercept vs placebo) and week 24 (etanercept 50 mg twice-weekly vs once-weekly). No serious adverse events were reported at week 12; however, by week 24, three patients had reported serious events. The most commonly reported adverse events were upper respiratory tract infection, injection site reactions, headache, sinus congestion, cough, and ear infection.
Bachelez et al.[66] (2015) Etanercept 50 mg twice weekly vs tofacitinib 5 mg twice daily vs tofacitinib 10 mg twice daily vs placebo	DD, MC, NI, PC, RCT Adult patients with chronic stable plaque psoriasis (for ≥12 months) who were candidates for systemic or phototherapy and had a PASI score of ≥12 and a PGA of moderate or severe, and had failed to respond to, had a contraindication to, or were intolerant to at least one conventional systemic therapy	N=1101 12 weeks	Primary: Proportion of patients at week 12 with at least a 75% reduction in the PASI score from baseline and the proportion of patients achieving a PGA score of "clear" or "almost clear" Secondary: Proportion of patients with a 50% reduction and 90% reduction in PASI score, reduction in itch severity item score, decrease in DLQI	Primary: A PASI75 response at week 12 was achieved by 130 (39.5%) of 329 patients in the tofacitinib 5 mg group, 210 (63.6%) of 330 in the tofacitinib 10 mg group, 197 (58.8%) of 335 in the etanercept group, and six (5.6%) of 107 in the placebo group. The proportions of PGA responders at week 12 were 155 (47.1%) in the tofacitinib 5 mg group, 225 (68.2%) in the tofacitinib 10 mg group, 222 (66.3%) in the etanercept group, and 16 (15.0%) in the placebo group. For both coprimary endpoints, tofacitinib 10 mg twice daily was non-inferior to etanercept and was superior to placebo, whereas tofacitinib 5 mg twice daily did not meet the non-inferiority criteria versus etanercept but met the superiority criteria versus placebo. Secondary: PASI50 and PASI90 response rates over time, and the corresponding differences between treatment groups, were similar to those based on the PASI75 outcome. Decreased in itch severity score with active treatments were greater than the clinically important difference of 1.64. At week 12, a clinically meaningful improvement in DLQI score (a reduction by five points or more) was achieved by 66.3% of patients in the tofacitinib 10 mg group, 78.2% of patients in the tofacitinib 5 mg

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				group, 74.7% of patients in the etanercept group, and 31.8% of patients in the placebo group, in patients with a baseline score of five or higher (P<0.0001 for each active treatment vs placebo).
Griffiths et al.[67] (2010) Etanercept 50 mg twice weekly vs ustekinumab 45 mg at weeks 0 and 4 vs ustekinumab 90 mg at weeks 0 and 4 Patients without a response to etanercept at week 12, received ustekinumab 90 mg at weeks 16 and 20; patients without a response to ustekinumab at week 12 received one additional study dose at week 16.	MC, PG, RCT Patients ≥18 years of age, with a diagnosis of plaque psoriasis for ≥6 months, were candidates for phototherapy or systemic therapy, had a baseline PASI score ≥12, had a score ≥3 on physician's global assessment, had ≥10% BSA involvement, and had inadequate response, intolerance, or contraindication to ≥1 conventional systemic agent (i.e., MTX, cyclosporine, or psoralen plus ultraviolet A) and no previous treatment with etanercept or ustekinumab	N=903 12 weeks	Primary: PASI 75 at week 12 Secondary: Physician's global assessment score of 0 or 1, PASI 90, difference between PASI at week 12 and 12 weeks after retreatment	Primary: A greater number of patients achieved PASI 75 in the ustekinumab 45 mg group (67.5%) and ustekinumab 90 mg group (73.8%) than in the etanercept group (56.8%; P=0.01 vs ustekinumab 45 mg; P<0.001 vs ustekinumab 90 mg). Secondary: A larger proportion of ustekinumab patients met criteria for cleared or minimal on a physician's global assessment (score of 0 or 1) compared to etanercept patients (65.1% on ustekinumab 45 mg and 70.6% on ustekinumab 90 mg vs 49.0% on etanercept; P<0.001 for each comparison vs etanercept). PASI 90 was achieved by 36.4% of ustekinumab 45 mg patients, 44.7% of ustekinumab 90 mg patients and 23.1% of etanercept patients (P<0.001, for each comparison vs etanercept). Of the patients that crossed over to ustekinumab from etanercept, 48.9% achieved a PASI 75, 23.4% achieved PASI 90, 40.4% achieved cleared or minimal on the physician's global assessment. Of patients that received retreatment with ustekinumab, 84.4% had a physician's global assessment score of 0 to 2. The most commonly occurring adverse event in the etanercept group was injection site erythema (14.7%) and was reported more often than in the two ustekinumab groups combined (0.7%). At least one serious adverse effect was reported in 1.9, 1.2 and 1.2% of patients in the ustekinumab 45 mg, 90 mg and etanercept groups, respectively.
Schmitt et al.[68] (2008) Adalimumab, cyclosporine,	MA RCTs in patients with moderate to severe psoriasis	16 trials Duration varied	Primary: PASI 75 Secondary: Tolerability	Primary: Compared to placebo a greater proportion of patients receiving adalimumab (RD, 64%; 95% CI, 61 to 68; P<0.00001), cyclosporine (RD, 33%; 95% CI, 13 to 52; P<0.0009), efalizumab (RD, 24%; 95% CI, 19 to 30; P<0.00001), etanercept 50 mg twice weekly (RD, 44%; 95% CI, 40 to

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efalizumab*, etanercept, or infliximab vs placebo				48; P<0.00001) and etanercept 25 mg twice weekly (RD, 30%; 95% CI, 25 to 35; P<0.00001) achieved PASI 75 response. The infliximab group had the greatest response (RD, 77%; 95% CI, 72 to 81; P<0.00001). Secondary: Average monthly rates of serious adverse events were 0.5% with adalimumab, 2.3% with cyclosporine, 1.2% with efalizumab, 0.6% with etanercept 50 mg twice weekly and 1.1% with infliximab. This outcome was not reported in with etanercept 25 mg twice weekly. Withdrawals due to adverse events occurred on average in 0.3% of adalimumab-treated patients, 16.1% of cyclosporine-treated patients, 1.2% of efalizumab-treated patients, 0.5% of patients on the lower dose of etanercept and 0.4% of patients on the higher dose of etanercept and 1.3% of infliximab-treated individuals/month.
Langley et al.[69] (2014) ERASURE and FIXTURE ERASURE: secukinumab 300 mg vs secukinumab 150 mg vs placebo FIXTURE: secukinumab 300 mg	DB, DD, MC, PC, PG, RCT (FIXTURE also AC) Patients 18 years of age or older with moderate-to-severe plaque psoriasis for at least six months and poorly controlled with topical treatments, phototherapy, systemic therapy or a combination of those therapies, score ≥12 on the PASI scale, 3 or 4 on the modified investigator global assessment, and 10% or more	N=2,044 (ERASURE: 737 FIXTURE: 1,306) 52 weeks	Primary: Proportion of patients that had a PASI75 and a score of 0 or 1 in the investigator's global assessment at week 12. Secondary: PASI90 at week 12, maintenance of PASI75 and a 0 or 1 response on the investigator's global assessment from week 12 to week 52, and PASI100 at week 12, , improvement in DLQI, improvement in	Primary: ERASURE A greater proportion of patients who received secukinumab 300 mg (200/245 [81.6%]) and secukinumab 150 mg (174/243 [71.6%]) had a PASI75 response at week 12 compared to placebo (11/246 [4.5%]; P<0.001 for both comparisons). Additionally, a greater proportion of patients who received secukinumab 300 mg (160/245 [65.3%]) and secukinumab 150 mg (125/244 [51.2%]) had a response of 0 or 1 on the modified investigator's global assessment at week 12 compared to placebo (6/246 [2.4%]; P<0.001 for both comparisons). FIXTURE The proportion of patients who had a PASI75 response at week 12 was 77.1% (249/323), 67.0% (219/327), 44.0% (142/323), and 4.9% (16/324) for secukinumab 300 mg, secukinumab 150 mg, etanercept, and placebo respectively. Both secukinumab 300 mg and 150 mg had a statistically significant greater proportion of patient who achieved PASI75 at week 12 compared with etanercept and placebo (P<0.001 for each secukinumab dose when compared to either etanercept or placebo).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs secukinumab 150 mg vs etanercept vs placebo All drugs were dosed once weekly at baseline and at weeks one, two and three, then every four weeks starting from week four.	involvement in body surface area		pain/itching/ scaling	The proportion of patients who had a 0 or 1 response on the modified investigator's global assessment at week 12 was 62.5% (202/323), 51.1% (167/327), 27.2% (88/323), and 2.8% (9/324) for secukinumab 300 mg, secukinumab 150 mg, etanercept, and placebo respectively. Both secukinumab 300 mg and 150 mg had a statistically significant greater proportion of patient who had a 0 or 1 response on the modified investigator's global assessment at week 12 compared with etanercept and placebo (P<0.001 for each secukinumab dose when compared to either etanercept or placebo). Secondary: <u>ERASURE</u> A greater proportion of patients who received secukinumab 300 mg (145/245 [59.2%]) and secukinumab 150 mg (95/243 [39.1%]) had a PASI90 response at week 12 compared to placebo (3/246 [1.2%]; P<0.001 for both comparisons). PASI75 was maintained from week 12 to 52 for 80.5% (161/200) and 72.4% (126/174) of patients in the secukinumab 300 mg and 150 mg groups respectively. A 0 or 1 response on the modified investigator's global assessment was maintained from week 12 to 52 for 74.4% (119/160) and 59.2% (74/125) of patients in the secukinumab 300 mg and 150 mg groups respectively. PASI100 at week 12 was reached by 28.6%, 12.8% and 0.8% of patients in the secukinumab 300 mg, secukinumab 150 mg, and placebo groups respectively. There was a statistically significant greater proportion of patients who achieved PASI100 in both the secukinumab groups compared to placebo (P<0.001 for both comparisons). Patients in both secukinumab groups reported significant improvements in DLQI, itching, pain and scaling by week 12 compared to etanercept and placebo groups (P values not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				FIXTURE A greater proportion of patients who received secukinumab 300 mg (175/323 [54.2%]) and secukinumab 150 mg (137/327 [41.9%]) had a PASI90 response at week 12 compared to placebo (5/324 [1.5%]; P<0.001 for both comparisons). Additionally both secukinumab groups had a significantly higher proportion of patients that achieved PASI90 at week 12 compared with the etanercept group (67/323 [20.7%]; P<0.001 for both comparisons). PASI75 was maintained from week 12 to 52 for 84.3% (210/249), 82.2% (180/219), and 72.5% (103/142) of patients in the secukinumab 300 mg, secukinumab 150 mg, and etanercept groups respectively. When compared to etanercept, both secukinumab 300 mg and secukinumab 150 mg had a statistically significant greater proportion of patients that maintained PASI75 from week 12 to 52 (P<0.001 and P=0.009 for the 300 mg and 150 mg dose respectively). A 0 or 1 response on the modified investigator's global assessment was maintained from week 12 to 52 for 79.7% (161/202), 67.7% (113/167), and 56.8% (50/88) of patients in the secukinumab 300 mg, secukinumab 150 mg, and etanercept groups respectively. When compared to etanercept, both secukinumab 300 mg and secukinumab 150 mg had a statistically significant greater proportion of patients that maintained 0 or 1 response on the modified investigator's global assessment from week 12 to 52 (P<0.001 and P=0.002 for the 300 mg and 150 mg dose respectively). PASI100 at week 12 was reached by 24.1%, 14.4%, 4.3% and 0% of patients in the secukinumab 300 mg, secukinumab 150 mg, etanercept, and placebo groups respectively. There was a statistically significant greater proportion of patients who achieved PASI100 in both the secukinumab groups compared to etanercept (P<0.001 for both comparisons). There was no comparison done with placebo as no patients achieved PASI100 at week 12. Patients in both secukinumab groups reported significant improvements in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				DLQI, itching, pain and scaling by week 12 compared to placebo groups (P values not reported).
Psoriatic Arthritis				
Genovese et al.[70] (2007) Adalimumab 40 mg every other week vs placebo Patients who completed a 12 week blinded phase could elect to receive OL therapy.	DB, MC, RCT Patients with moderately to severely active PsA with an inadequate response to DMARD therapy	N=100 24 weeks	Primary: ACR 20 response at week 12 Secondary: ACR 50 response, ACR 70 response, PsARC scores, assessments of disability, psoriatic lesions, and quality of life	Primary: At week 12, an ACR 20 response was achieved by 39% of adalimumab patients vs 16% of placebo patients (P=0.012). Secondary: ACR 50 and ACR 70 responses were also achieved by significantly more patients on adalimumab (25 and 14%, respectively) compared to patients on placebo at week 12 (2 and 0%, respectively; P=0.001 for ACR 50 and P=0.013 for ACR 70). A PsARC response was achieved by 51% of adalimumab patients vs 24% of placebo patients (P=0.007). At week 12, measures of skin lesions (-3.7 units with adalimumab vs -0.3 units with placebo; P≤0.001) and disability were statistically significantly improved with adalimumab. Adalimumab use was associated with significant mean improvements from baseline in components of quality of life assessments such as physical functioning (P=0.027), bodily pain (P=0.007), general health (P=0.017) and mental health (P=0.009). OL adalimumab provided continued improvement for adalimumab patients and initiated rapid improvement for placebo patients, with ACR 20 response rates of 65 and 57%, respectively, observed at week 24. Serious adverse events occurred at a similar frequency during therapy with placebo (4.1%), blinded adalimumab (2.0%), and OL adalimumab (3.1%). Adalimumab use was not associated with serious infections.
Mease et al.[71] (2005)	DB, MC, PG, RCT Patients ≥18 years	N=315 24 weeks	Primary: ACR 20 response at 12 weeks,	Primary: At week 12, 58% of the adalimumab treated patients achieved an ACR 20 response, compared to 14% of the placebo-treated patients (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Adalimumab 40 mg every other week vs placebo Stable doses of MTX were allowed and corticosteroid or DMARD rescue therapy was permitted in patients without at least a 20% reduction in swollen and tender joints by week 12.	of age with moderately to severely active PsA with active psoriatic skin lesions or a documented history of psoriasis and a history of inadequate response to NSAIDs		change in mTSS at week 24 Secondary: ACR 20 response at 24 weeks, ACR 50 and ACR 70 response at weeks 12 and 24, measures of joint disease, disability, quality of life, and severity of skin disease in patients with psoriasis involving at least 3% of BSA	The mean change in the mTSS of radiographic structural damage was -0.2 in patients receiving adalimumab and 1.0 in those receiving placebo (P<0.001). Secondary: ACR 20 response at 24 weeks was 57% with adalimumab and 15% with placebo (P<0.001). An ACR 50 response was detected in 36% of adalimumab-treated individuals at 12 weeks and 39% of adalimumab-treated individuals at week 24 compared to 4 and 6% of those on placebo, respectively (P<0.001 for both outcomes). An ACR 70 response was found in 20% in the adalimumab arm and 1% in the placebo arm at 12 weeks and 23 and 1% at 24 weeks (P<0.001). PsARC response was achieved with adalimumab in 62% at 12 weeks and 60% at 24 weeks compared to 26 and 23% on placebo, respectively (P value not reported). Among the 69 adalimumab treated patients evaluated with the PASI, 59% achieved a PASI 75 improvement response at 24 weeks, compared to 1% of placebo-treated patients (P<0.001). Disability and quality of life measures were also significantly improved with adalimumab treatment compared to placebo treatment (P<0.001 for changes in both HAQ-DI and SF-36 PCS scores at weeks 12 and 24). Changes in SF-36 MCS scores were not statistically significant between groups at both week 12 (P=0.708) and week 24 (P=0.288). The rates of overall and serious adverse events were similar among groups.
Kavanaugh et al.[72] PALACE 1 (2014)	PC, RCT Patients ≥18 years of age with a	N=504 24 weeks	Primary: Proportion of patients achieving ACR20 at week 16	Primary: At week 16, significantly more patients receiving apremilast 20 mg BID (31.3%; P=0.0140) and 30 mg BID (39.8%; P=0.0001) achieved an ACR20 response versus placebo (19.4%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Apremilast 20 mg BID vs apremilast 30 mg BID vs placebo	diagnosis of psoriatic arthritis with a minimum of both three swollen and three tender joints, despite prior treatment with traditional DMARDs and/or biologic treatment or concurrent treatment with traditional DMARDs		Secondary: Change from baseline to week 16 in HAQ-DI, safety	Secondary: At week 16, apremilast was associated with significantly greater reductions (improvements) in HAQ-DI compared with placebo. During the 24 weeks, the adverse events occurring in ≥5% of any treatment group included diarrhea, nausea, headache, and upper respiratory tract infection. Discontinuations due to adverse events were comparable across groups (placebo: 4.8%; apremilast 20 mg BID: 6.0%; apremilast 30 mg BID: 7.1%).
Papp et al.[73] (2013) Apremilast 20 mg QD vs apremilast 20 mg BID vs placebo	DB, MC, PC, PG, RCT Patients ≥18 years of age with a six-month history or longer of moderate to severe plaque psoriasis with a PASI score ≥10 and BSA involvement ≥10%	N=260 12 weeks	Primary: PSAI75 Secondary: Change from baseline in PASI, BSA involvement, and PGA, adverse events	Primary: At week 12, a significantly greater proportion of subjects receiving apremilast 20 mg BID achieved PASI75 vs those receiving placebo [21/86 (24.4%) subjects vs. 9/87 (10.3%); P=0.023]. A similar proportion of subjects receiving apremilast 20 mg QD and placebo achieved a PASI75 score at week 12 (10.3% in each group). Secondary: A statistically significantly greater proportion of subjects receiving apremilast 20 mg BID achieved PASI50 vs placebo (P<0.001). Although a greater proportion of subjects receiving apremilast 20 mg BID achieved PASI90 vs placebo, the difference was not statistically significant (P=0.113). A significantly greater mean per cent reduction in PASI score was achieved with apremilast 20 mg QD and 20 mg BID than with placebo [17.4% with placebo; 30.3% with apremilast 20 mg QD (P=0.021); 52.1% with apremilast 20 mg BID (P<0.001)] at week 12. Mean change from baseline in overall static PGA and BSA was only significant in the apremilast 20 mg BID group. The percentage of subjects reporting one or more treatment emergence adverse events was 59.8% with placebo, 67.8% with apremilast 20 mg QD and 54.1% with apremilast 20 mg BID.
Schett et al.[74]	DB, MC, PC, RCT	N=204	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2012) Apremilast 20 mg BID vs apremilast 40 mg QD vs placebo	Patients ≥18 years of age with symptomatic PsA for ≥6 months with ≥3 swollen joints and ≥3 tender joints, and to have discontinued treatment with immunosuppressants other than methotrexate for an adequate washout period	12 weeks	ACR20 Secondary: Safety	A significantly greater proportion of patients achieved an ACR20 response at week 12 among the group receiving apremilast 20 mg twice per day (43.5%) and the group receiving apremilast 40 mg once per day (35.8%), when compared with those receiving placebo (11.8%) (P<0.001 and P=0.002, respectively). In patients achieving an ACR20 response, the median time to response was four weeks. Secondary: The percentage of patients affected by ≥1 adverse event was similar across treatment groups. No significant laboratory abnormalities were observed, and no opportunistic infections were reported.
Mease et al.[75] and van der Heijde et al.[76] (2013) RAPID-PsA Certolizumab 400 mg at weeks 0, 2, and 4 then 200 mg every 2 weeks (CZP 200 mg) vs certolizumab 400 mg at weeks 0, 2, and 4 then 400 mg every 2 weeks (CZP 400 mg) vs	DB, MC, PC, RCT Patients ≥18 years of age with adult-onset active PsA for ≥6 months despite treatment with ≥1 DMARD	N=409 24 weeks	Primary: ACR 20 response at week 12, change from baseline in mTSS at week 24 Secondary: ACR 20 at week 24, HAQ-DI at week 24, PASI 75 (in patients with least 3% body surface area psoriatic skin involvement) at week 24, and change from baseline in mTSS at week 24	Primary: A greater proportion of patients treated with CZP 200 mg every two weeks (58.0%) and CZP 400 mg every four weeks (51.9%) achieved an ACR 20 response at week 12 compared to placebo (24.3%; P<0.001 for both comparisons). Secondary: A greater proportion of patients treated with CZP 200 mg every two weeks (63.8%) and CZP 400 mg every four weeks (56.3%) achieved an ACR 20 response at week 24 compared to placebo (23.5%; P<0.001 for both comparisons). At week 24, improvements in HAQ-DI scores from baseline were greater in patients treated with CZP compared to placebo (combined CZP groups: -0.50 vs -0.19; P<0.001). In patients with least 3% body surface area psoriatic skin involvement at baseline, a greater proportion of patients treated with CZP 200 mg every two weeks (62.2%) and CZP 400 mg every four weeks (60.5%) achieved PASI 75 at week 24 compared to placebo (15.1%; P<0.001 for both comparisons).

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placebo Concurrent MTX (up to 25 mg/week), SSZ (up to 3 g/day), leflunomide (up to 20 mg/day) at stable doses or oral corticosteroids (≤10 mg/day prednisone or equivalent) were allowed.				Prespecified imputation analysis led to an estimated mean mTSS change from baseline that was not statistically different between CZP and placebo groups (combined CZP groups: 18.3 vs 28.9; P≥0.05). Post hoc analysis using the median mTSS of the entire population to impute missing values in patients with fewer than two analyzable mTSS suggested that patients treated with CZP had reduced radiographic progression compared to placebo patients (combined CZP groups: 0.06 vs 0.28; P=0.007).
Mease et al.[77] (2000) Etanercept 25 mg twice weekly vs placebo Patients on stable doses of corticosteroids (equal to ≤10 mg/day of prednisone) or MTX were permitted to continue therapy.	DB, RCT Patients 18 to 70 years of age with active PsA despite NSAID therapy	N=60 12 weeks	Primary: PsARC, PASI 75 at 12 weeks Secondary: ACR 20 response, ACR 50 response, ACR 70 response, PASI 75, and improvement in target psoriasis lesions	Primary: Eighty-seven percent of etanercept treated patients met the PsARC, compared to 23% of placebo-controlled patients (P<0.0001). PASI 75 improvement was detected in 26% of etanercept-treated patients vs none of placebo treated patients (P=0.0154). Secondary: The ACR 20 was achieved by 73% of etanercept-treated patients compared to 13% of placebo-treated patients (P<0.0001), while approximately 48 and 5% achieved an ACR 50 response and 12% and 0% achieved an ACR 70 response, respectively (P=0.0001 for ACR 50; P value not reported for ACR 70). Of the 19 patients in each treatment group who could be assessed for psoriasis, 26% of etanercept-treated patients achieved a 75% improvement in PASI, compared to none of the placebo-treated patients (P=0.0154). Median target lesion improvements were 50 and 0%, for etanercept and placebo, respectively (P=0.0004). There were no significant differences detected in the rate of adverse events between groups.
Mease et al.[78]	DB, MC, RCT	N=205	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2004) Etanercept 25 mg twice weekly vs placebo Patients who completed a 24 week blinded phase could elect to receive OL therapy in a 48 week extension. Patients on stable doses of corticosteroids (equal to ≤10 mg/day of prednisone) or MTX were permitted to continue therapy.	Patients 18 to 70 years of age with active PsA despite NSAID therapy	72 weeks	ACR 20 response Secondary: ACR 50 response, ACR 70 response, change in mTSS, PsARC, PASI 75, SF-36 Health Survey, HAQ, and safety	At 12 weeks, 59% of etanercept patients met the ACR 20 improvement criteria for joint response, compared to 15% of placebo patients (P<0.0001), and results were sustained at 24 and 48 weeks. Secondary: At 24 weeks, ACR 50 and ACR 70 responses were achieved in approximately 40 and 15% of etanercept patients and 5 and 1% of placebo patients, respectively (P values not reported). The mean annualized rate of change in the mTSS with etanercept was -0.03 unit, compared to 1.00 unit with placebo (P<0.0001). A PsARC response was achieved by 72 and 70% of etanercept patients at weeks 12 and 24, respectively vs 31 and 23% of placebo patients (P values not reported). At 24 weeks, 23% of etanercept patients eligible for psoriasis evaluation achieved at least 75% improvement in the PASI, compared to 3% of placebo patients (P=0.001). SF-36 PCS scores improved more often with etanercept compared to placebo, but SF-36 MCS scores did not differ significantly between groups. HAQ scores at 24 weeks were significantly improved with etanercept (54%) over placebo (6%; P<0.0001). Injection site reactions occurred at a greater rate with etanercept than placebo (36 vs 9%; P<0.001).
Kavanaugh et al.[79] (2009) Golimumab 50 mg once every 4 weeks vs	MC, PC, RCT Patients ≥18 years of age with a diagnosis of PsA and active PsA despite current or previous DMARD	N=405 24 weeks	Primary: ACR 20 response at week 14 Secondary: Not reported	Primary: Golimumab 50 mg with or without MTX compared to placebo with or without MTX, resulted in a significant improvement in signs and symptoms as demonstrated by ACR 20 response at week 14 (51 vs 9%; P<0.001). Similar ACR 20 responses at week 14 were observed in patients with different PsA subtypes.

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golimumab 100 mg once every 4 weeks vs placebo Patients who had used or were currently using MTX, an NSAID, an oral corticosteroid, or a systemic or topical psoriasis treatment were enrolled.	or NSAID therapy and no evidence of active TB and/or no evidence of latent TB on screening			ACR responses observed in the golimumab treated groups were similar in patients receiving and not receiving concomitant MTX. Secondary: Not reported
Antoni et al.[80] (2005) Infliximab 5 mg/kg at weeks 0, 2, 6, 14 and 22 vs placebo	DB, MC, PC, PG, RCT Patients ≥18 year of age with active PsA for ≥6 months, inadequate response to current or previous DMARDs or NSAIDs, ≥1 qualifying lesion and negative serum RF	N=200 24 weeks	Primary: ACR 20 response at week 14 Secondary: PsARC, PASI 75, duration of morning stiffness, dactylitis in hands and feet, and presence or absence of enthesopathy in the feet and SF-36	Primary: At week 14, there was significantly more patients in the infliximab group that achieved an ACR 20 response (58%) compared to the placebo group (11%; P<0.001). This difference continued through week 24 (54 vs 16%; P<0.001). Secondary: A significantly greater percentage of patients in the infliximab treated group had improvement in PsARC (77%) compared to the placebo group (27%; P<0.001) at week 14 and continued through week 24 (70 vs 32%; P<0.001). At weeks 14 and 24, fewer patients in the infliximab group had digits with dactylitis (18 and 12%) compared to the placebo group (30 and 34%; P=0.025 and P<0.001, respectively). Fewer patients in the infliximab group had enthesopathy compared to the placebo group at week 14 (22 vs 34%; P=0.016) and week 24 (20 vs 37%; P=0.002). A significantly higher proportion of patients achieved PASI 75 in the

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				infliximab group compared to the placebo group at weeks 14 and 24 (64 vs 2%; P<0.001 and 60 vs 1%; P<0.001, respectively). At week 14, the physical and mental components of the SF-36 were significantly improved in the infliximab group compared to the placebo group (both P<0.001). There was also significant improvement at week 24 in the physical and mental components of the SF-36 in the infliximab group compared to the placebo group (P<0.001 and P=0.047, respectively). Adverse events were similar between the groups. There were a higher proportion of patients who discontinued treatment due to adverse events in the infliximab group compared to the placebo group (4 vs 1%). There were a greater number of patients in the infliximab group that had increased ALT compared to the placebo group (1 vs 6%).
Baranauskaite et al.[81] (2012) RESPOND Infliximab 5 mg/kg infusions at weeks 0, 2, 6 and 14 plus MTX 15 mg/week vs MTX 15 mg/week The use of NSAIDs and oral steroids (maximum dose 10 mg/day of prednisone or equivalent) was allowed if the dose was stable within	MC, OL, PC, PRO Patients ≥18 years of age who were treatment naïve and had active psoriasis in combination with peripheral articular disease with ≥1 of the following for three or more months before screening: distal interphalangeal joint involvement; polyarticular arthritis in the absence of rheumatoid nodules; arthritis mutilans; or asymmetric	N=115 16 weeks	Primary: Proportion of patients achieving an ACR 20 response at week 16 Secondary: Proportions of patients with ACR 50 and ACR 70 responses, PASI 75 in patients whose baseline PASI was 2.5 or greater, EULAR response, DAS28 scores, number of digits with dactylitis, Maastricht AS enthesitis score,	Primary: In the ITT analysis, an ACR 20 response at week 16 was achieved by significantly more patients treated with infliximab plus MTX compared to patients treated with MTX alone (86.3 vs 66.7%; P=0.021). Secondary: The ACR 50 (72.5 vs 39.6%; P=0.0009) and ACR 70 (49.0 vs 18.8%; P=0.0015) response rates at week 16 were also significantly higher in the infliximab plus MTX group at 16 weeks compared to those receiving MTX alone. In patients with a PASI ≥2.5 or at baseline, a PASI 75 response at week 16 occurred in 97.1% of patients receiving infliximab plus MTX compared to 54.3% of patients receiving MTX alone (P<0.0001). By week 16, the mean reduction in PASI score was 93.3% for patients treated with infliximab plus MTX compared to 67.4% of patients treated with MTX alone (P=0.0029). The mean DAS28 at week 16 improved by 56.5% in the infliximab plus MTX patients compared to 29.7% of patients receiving MTX alone (P<0.0001).

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four weeks before screening and kept stable throughout the study.	peripheral arthritis		fatigue scores, and duration of morning stiffness and safety	The EULAR response at week 16 was achieved in 98% of patients receiving infliximab plus MTX compared to 72.9% of those receiving MTX alone (P<0.0001). A median reduction of two digits with dactylitis was observed at week 16 in the patients treated with infliximab plus MTX, while no reduction was observed in the MTX monotherapy group (P=0.0006). Patients treated with infliximab plus MTX experienced a median reduction of two sites with enthesitis at week 16 compared to a reduction of one site in the MTX alone group (P=0.082). A significantly greater reduction from baseline in fatigue scores occurred in the infliximab plus MTX group compared to the MTX monotherapy group at week 16 (70.8 vs 44.0%, respectively; P=0.0003). At week 16, the median change in the duration of morning stiffness was -0.92 hour with combination treatment vs -0.50 hour with MTX alone (P=0.0015). The incidence of adverse events was higher in patients receiving infliximab plus MTX compared to MTX alone. Most adverse events were mild or moderate in severity. One adverse event in each group was considered severe: increased transaminases in the infliximab plus MTX group and renal colic in the MTX-alone group. Treatment related adverse events were reported in 45.6% of the infliximab plus MTX group and 24.1% in the MTX alone group. The most frequent treatment-related adverse event involved hepatic enzyme increases.
Rheumatoid Arthritis				
Westhovens et al.[82] (2009) Abatacept intravenous ~10 mg/kg on days 1, 15	DB, MC, PC, RCT Patients ≥18 years of age with RA for ≤2 years and ≥12 tender and 10	N=509 24 months	Primary: Remission rates (DAS28 <2.6) and structural damage at year one (Genant-modified	Primary: A significantly higher proportion of patients in the abatacept group achieved DAS28-defined remission compared to the placebo group after one year of treatment (41.4 vs 23.3%, respectively; P<0.001). The mean change in structural damage at year one, measured using the

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and 29 then every four weeks plus MTX 15 mg/weekly vs placebo plus MTX 15 mg/weekly	swollen joints, CRP ≥0.45 mg/dL, RF and/or anti-CCP2 seropositivity and radiographic evidence of bone erosion of the hands/wrists/feet; patients were either MTX-naive or had previous exposure of 10 mg/week or less for three weeks or less, with none administered		Sharp scoring system maximum score of 290) Secondary: ACR 50 responses, MCR (ACR 70 maintained for >6 consecutive months); DAS28 scores, erosion score (maximum possible 145) and joint-space narrowing score (JSN; maximum possible 145), physical function (improvement of >0.3 units from baseline in the; HAQ-DI), SF-36 scores, proportion of patients achieving ACR 70 and ACR 90 responses, and the proportion of patients without radiographic progression and safety	Genant-modified Sharp scoring system total scores, was significantly lower in patients treated with abatacept compared to patients treated with placebo (0.63 vs 1.06, respectively; P=0.040). Secondary: A higher proportion of patients treated with abatacept achieved an ACR 50 (57.4 vs 42.3%; P<0.001), ACR 70 (42.6 vs 27.3%; P<0.001) and ACR 90 (16.4 vs 6.7%; P=0.001) compared to patients treated with placebo after one year of treatment. After one year of abatacept therapy, 27.3% of patients achieved an MCR (ACR 70 maintained for more than six consecutive months) compared to 11.9% of patients receiving placebo alone (P<0.001). Following one year of abatacept treatment, disease activity was significantly reduced compared to patients receiving placebo (-3.22 vs -2.49; P<0.001). Patients treated with abatacept achieved significantly greater improvements from baseline in total score and erosion score compared to patients randomized to the placebo group (P=0.040 and P=0.033, respectively). The changes from baseline in JSN scores were similar between the abatacept and placebo groups (P=0.246). The proportion of patients with no radiographic progression in the abatacept group at one year was 61.2% (95% CI, 55.0 to 67.3) compared to the group receiving placebo 52.9% (95% CI, 46.6 to 59.2), with an estimated difference of 8.3% (95% CI, 21.0 to 17.5). A significantly greater proportion of patients in the abatacept group compared to the placebo group experienced a change from baseline in HAQ-DI score ≥0.3 units following one year of therapy (71.9 vs 62.1%; P=0.024). Abatacept treatment was associated with statistically significant

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				improvements in the mental and physical components of the SF-36 questionnaire compared to the placebo group (P<0.05 for both). The most frequently reported adverse events in the abatacept group were nausea, upper respiratory tract infection and headache. Six deaths were reported; two (0.8%) in the abatacept group and four (1.6%) in the placebo Of the two deaths in the abatacept group, one patient had pneumonia and severe gastrointestinal bleeding and the other had an acute myocardial infarction. The most frequent infections in patients treated with abatacept and placebo respectively, were upper respiratory tract infection in 26 (10.2%) and 26 (10.3%) patients, nasopharyngitis in 21 (8.2%) and 26 (10.3%) patients and influenza in 19 (7.4%) and 23 (9.1%) patients. Serious infections occurred in five (2.0%) abatacept-treated patients (pneumonia, gastroenteritis, cellulitis, pseudomonal lung infection and postoperative wound infection, one patient each) and five (2.0%) patients receiving placebo (pneumonia, three patients; gastroenteritis, one patient; and breast cellulitis and staphylococcal infection, both in the same patient). No patients in the abatacept group discontinued due to an infection. In the abatacept treatment group, autoimmune disorders were reported in six patients compared to five patients in the placebo group. Sixteen patients in the abatacept treatment group experienced infusion related reaction compared to five patients receiving placebo.
Genovese et al.[83] (2011) Abatacept subcutaneous 125 mg days 1 and 8 then weekly (intravenous loading dose of ~10 mg/kg was also administered on day 1)	DB, DD, MC, RCT Patients with RA (defined by ACR 1987 criteria) and functional class I, II and III (defined by ACR 1991 revised criteria) that had an inadequate response to ≥3 months of MTX therapy (≥15	N=1,457 6 months	Primary: Proportion of patients achieving ACR 20 at six months Secondary: Proportion of patients achieving ACR 50 and ACR 70	Primary: The proportion of patients achieving ACR 20 with abatacept subcutaneous (76.0%; 95% CI, 72.9 to 79.2) and abatacept intravenous (75.8%; 95% CI, 72.6 to 79.0) was not significantly different (estimated between group difference, 0.3%; 95% CI, -4.2 to 4.8). Secondary: The proportion of patients achieving ACR 50 with abatacept subcutaneous and abatacept intravenous (51.5 vs 50.3%) was not significantly different. The proportion of patients achieving ACR 70 with abatacept subcutaneous and abatacept intravenous (26.4 vs 25.1%) was not significantly different.

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vs abatacept intravenous ~10 mg/kg on days 1, 15 and 29 then every 4 weeks	mg/week), with ≥10 swollen joints, ≥12 tender joints and CRP ≥0.8 mg/dL			Adverse events were also similar between the groups.
Keystone et al.[84] (2012) ATTUNE Abatacept 125 mg subcutaneously once weekly	OL Patients ≥18 years of age with active RA previously refractory to either MTX or anti-TNFs who had received ≥4 years of intravenous abatacept in either of two previous RCTs	N=128 12 months	Primary: Safety at three months Secondary: Immunogenicity at three months, and efficacy at 12 months	Primary: Up to month three, adverse events occurred in 39.8% of patients; no individual adverse events were reported in ≥5% of patients. One adverse event (musculoskeletal pain) led to discontinuation. Overall, 75.6% of patients experienced an adverse event during the cumulative period. After month three, 12 further adverse events were reported, of which three led to discontinuation (breast cancer, sarcoidosis and brain neoplasm). No deaths were reported in the study or during follow-up. Infections reported up to month three (more than one patient) included nasopharyngitis (n=4), urinary tract infection (n=3), bronchitis (n=2), gastroenteritis (n=2), sinusitis (n=2) and upper respiratory tract infection (n=2). No serious infections, malignancies or autoimmune events were reported during the first three months. Serious infections, malignancies or autoimmune events occurring after month three were as follows: one serious infection (pneumonia)), two malignancies (breast and uterine cancer) and two autoimmune events occurred (sarcoidosis and erythema nodosum). Secondary: Eight patients were seropositive based on ELISA through month three. Of these eight, six were already positive prior to enrolment. All seropositive patients continued treatment. Adverse events experienced by the seropositive patients were not consistent with immune-mediated toxicities, except for one patient who developed sarcoidosis and discontinued treatment. None of these patients had an abatacept-induced seropositive result based on the ECL assay.

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				At baseline, mean DAS28 and HAQ-DI scores in the overall population were 3.39 and 0.94, respectively. Improvements in disease activity and physical function achieved during intravenous treatment were maintained through month 12 of subcutaneous treatment.
Haraoui et al.[85] (2011) CanACT Adalimumab 40 mg subcutaneously every other week	MC, OL, PRO Patients ≥18 years of age with RA diagnosed according to the 1987 revised ACR criteria with active disease, (≥5 swollen joints (of 66 joints evaluated) and one of the following: positive RF, ≥1 joint erosions present on x-ray, or a HAQ-DI score ≥1 and an unsatisfactory responses or intolerance to prior antirheumatic therapies	N=879 12 weeks	Primary: Mean change in DAS28 Secondary: Proportion of patients achieving clinical remission (DAS28 <2.6) and low-disease activity (DAS28 <3.2) at week 12, proportion achieving EULAR-moderate and good response, ACR 20, ACR 50, and ACR 70) responses at weeks four, eight, and 12, mean changes in ACR core components [tender joint count, swollen joint count, ESR, physician and patient assessments, and HAQ-DI	Primary: Patients treated with adalimumab achieved significantly lower DAS28 scores at week 12 compared to baseline (4.2 vs 6.1; P<0.001). Secondary: Following 12 weeks of treatment with adalimumab, 15.3 and 28.9% of patients achieved clinical remission (DAS28 <2.6) and low-disease activity (DAS28 <3.2), respectively (P values not reported). At week 12, 25.9% of patients treated with adalimumab were considered EULAR responders to treatment. The proportion of patients who experienced an ACR 20, ACR 50 and ACR 70 response at 12 weeks was 58.4, 30.6 and 12.7%, respectively (P values not reported). At week eight, the proportion of patients who experienced an ACR 20, ACR 50 and ACR 70 response was 52.2, 21.7 and 7.2%, respectively (P values not reported). At week four, the proportion of patients who experienced an ACR 20, ACR 50 and ACR 70 response, was 37.6, 10.6 and 2.4%, respectively (P values not reported). Patients treated with adalimumab experienced a decrease in the number of tender joints at week 12 compared to baseline (6.8 vs 19.9; P value not reported) and the number of swollen joints was reduced from 13.2 at baseline to 6.4 after 12 weeks (P value not reported). As measured on a VAS, patient's assessment of pain decreased from a 66.2 at baseline to 37.3 following adalimumab therapy. Patients' assessment of disease activity decreased from 65.1 at baseline to 37.4 at follow up. Similarly physician assessment of disease activity decreased

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				from 63.6 at baseline to 29.0 (P values not reported). The mean HAQ-DI score improved by an average of 0.5 units from 1.5 at baseline to 1.0 after 12 weeks of adalimumab treatment. In addition, the ESR decreased from a mean of 30.3 mm/h at baseline to 20.0 mm/h at 12 weeks (P<0.001). Adverse events were reported in 43.4% of patients treated with adalimumab. Most adverse events were mild to moderate in intensity. The most commonly reported adverse events were injection site reactions (9.9%), headache (5.2%), injection site erythema (3.5%), nausea (3%) and rash (2.8%). Of the treatment-emergent adverse events considered by the investigator to be related to study drug, injection site reaction and headache were the most frequently reported (≥5% of patients).
Keystone et al.[86] (2013) Adalimumab 40 mg subcutaneous injection every other week vs placebo All patients received concurrent MTX therapy.	ES, OL Patients ≥18 years of age with RA (defined by ACR 1987 criteria) despite ≥3 months of MTX (12.5 to 25 mg/week), tender joint count ≥9 out of 68, swollen joint count ≥6 out of 66, CRP ≥1 mg/L, and positive for RF or at least one bony erosion	N=202 10 years	Primary: ACR 20, ACR 50, ACR 70, DAS28-CRP <3.2, clinical remission (DAS 28-CRP <2.6 or SDAI ≤3.3), SDAI, HAQ-DI score, and mTSS at 10 years Secondary: Not reported	Primary: At year 10, 64.2, 49.0, and 17.6% of patients achieved ACR 50, ACR 70, and ACR 90 responses, respectively. Mean DAS28-CRP was 2.6, with 74.1% achieving DAS28-CRP <3.2 at year 10. The proportions of patients achieving DAS28-CRP and SDAI clinical remission states were 59.0 and 33.2%, respectively. From baseline to year 10, mean HAQ-DI was reduced by 50%, with 42.2% of patients achieving HAQ-DI <0.5 or normal functionality. Mean change from baseline to year 10 in mTSS was 2.8 units (annual progression rate of approximately 0.3 units/year), suggesting minimal radiographic progression over 10 years. Secondary: Not reported
Keystone et al.[87] (2008) RAPID 1	DB, MC, PG, RCT Patients ≥18 years of age with a	N=982 52 weeks	Primary: ACR 20 at 24 weeks, mean change from	Primary: A significantly greater number of ACR 20 responders at 24 weeks were found in the CZP 200 mg group (58.8%) and CZP 400 mg group (60.8%) compared to the placebo group (13.6%; P<0.001). There was no

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Certolizumab 400 mg at weeks 0, 2, and 4 then 200 mg every 2 weeks plus MTX (CZP 200 mg) vs certolizumab 400 mg at weeks 0, 2, and 4 then 400 mg every 2 weeks plus MTX (CZP 400 mg) vs placebo plus MTX Patients were randomized 2:2:1. Concurrent analgesics, NSAIDs or COX2 inhibitors, or oral corticosteroids (≤10 mg/day of prednisone or equivalent) were allowed.	diagnosis of RA (defined by ACR 1987 criteria), for ≥6 months and up to 15 years with active disease despite treatment with MTX		baseline in mTSS at 52 weeks Secondary: Mean change from baseline in mTSS at 24 weeks, HAQ-DI, ACR 20 at 52 weeks, ACR 50, and ACR 70 at 24 weeks	significant difference detected between the two CZP regimens. mTSS were significantly lower with CZP 200 mg (0.4 Sharp units) and 400 mg (0.2 Sharp units) vs placebo (2.8 Sharp units; P<0.001). Secondary: Active treatment was associated with reduced mTSS at 24 weeks compared to placebo (0.2 Sharp units for 200 and 400 mg vs 1.3 Sharp units for placebo; P<0.001). The HAQ-DI score at 52 weeks was -0.60 with CZP 200 mg, -0.63 with CZP 400 mg and -0.18 with placebo (P<0.001). ACR 20 response remained significantly higher with CZP 200 mg over 52 weeks (P<0.001 vs placebo). A significantly greater proportion of individuals achieved ACR 50 and ACR 70 with CZP 200 mg (37.1 and 21.4%) and CZP 400 mg (39.9 and 20.6%) compared to placebo (7.6 and 3.0%; P<0.001) at week 24. Infections and infestations occurred in 56.4% of CZP 200 mg patients, 58.4% of CZP 400 mg patients and 56.9% of placebo patients with serious infections occurring in 5.3, 7.3 and 2.2% of CZP 200 mg, 400 mg and placebo patients, respectively. The most frequent adverse events reported included headache, hypertension and back pain.
Smolen et al.[88] (2009) RAPID 2 Certolizumab 400 mg at weeks 0, 2, and 4 then 200 mg	DB, MC, RCT Patients ≥18 years of age with a diagnosis of RA (defined by ACR 1987 criteria) for ≥6	N=619 24 weeks	Primary: ACR 20 at 24 weeks Secondary: ACR 50, ACR 70, mTSS, SF-36	Primary: ACR 20 was attained by significantly more individuals receiving CZP 200 mg (57.3%) and CZP 400 mg (57.6%) compared to placebo (8.7%; P≤0.001). Secondary: ACR 50 and ACR 70 were achieved in a significantly greater number of

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every 2 weeks plus MTX (CZP 200 mg) vs certolizumab 400 mg at weeks 0, 2, and 4 then 400 mg every 2 weeks plus MTX (CZP 400 mg) vs placebo plus MTX Patients were randomized 2:2:1. Concurrent analgesics, NSAIDs or COX2 inhibitors, or oral corticosteroids (≤10 mg/day of prednisone or equivalent) were allowed.	months and up to 15 years with active disease despite treatment with MTX		Health Survey and individual ACR core set variables, and safety	patients in the CZP 200 mg group (32.5 and 15.9%, respectively) and CZP 400 mg group (33.1 and 10.6%, respectively) vs placebo (3.1 and 0.8%, respectively; P≤0.01). CZP 200 mg (0.2; 95% CI, -1.0 to 0.6) and CZP 400 mg (-0.4 mg; 95% CI, -0.7 to -0.1) were associated with a significantly lower change in mTSS than placebo (1.2; 95% CI, 0.5 to 2.0; P≤0.01 compared to CZP 200 mg; P≤0.001 compared to CZP 400 mg). Active treatment resulted in greater improvements in SF-36 scores vs placebo (P<0.001) and ACR core components vs placebo (P<0.001). Serious infection was reported in 3.2% of CZP 200 mg patients, 2.4% of CZP 400 mg patients and 0% of placebo patients. Tuberculosis was reported in five patients receiving certolizumab.
Fleischmann et al.[89] (2009) FAST4WARD Certolizumab 400 mg every 4 weeks vs placebo	DB, MC, RCT Patients 18 to 75 years of age with adult onset RA (defined by ACR 1987 criteria) for ≥6 months, with active disease and failed at least one prior	N=220 24 weeks	Primary: ACR 20 at 24 weeks Secondary: ACR 50, ACR 70, ACR component scores, DAS 28, patient reported outcomes, and	Primary: ACR 20 achievement at 24 weeks was significantly higher with certolizumab (45.5%) than placebo (9.3%; P<0.001). Secondary: A significantly greater proportion of ACR 50 and ACR 70 responders were found in the active treatment group vs the placebo group (22.7 vs 3.7%; P<0.001 and 5.5 vs 0%; P≤0.05, respectively). A significant improvement in all ACR components was also detected among patients on certolizumab vs placebo (P≤0.05).

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Concurrent analgesics, NSAIDs, or oral corticosteroids (≤10 mg/day of prednisone or equivalent) were allowed.	DMARD		safety	A significantly greater change in DAS 28 was also reported with active treatment (-1.5 vs -0.6 for placebo; P<0.001). Patients reported significant improvements in physical function with certolizumab as measured by HAQ-DI (P<0.001), arthritis pain (P≤0.05) and fatigue (P<0.001). Headache, nasopharyngitis, upper respiratory tract infections, diarrhea and sinusitis occurred in at least 5% of certolizumab patients. There were no reports of tuberculosis or opportunistic infections throughout the study.
Weinblatt et al.[90] (2012) REALISTIC Certolizumab 400 mg at weeks 0, 2 and 4, followed by 200 mg every 2 weeks vs placebo	DB, MC, RCT Patients ≥18 years of age with adult onset RA (defined by ACR 1987 criteria) for ≥3 months, with active disease and failed at least one prior DMARD	N=1063 12 weeks	Primary: ACR 20 at 12 weeks Secondary: ACR 50, ACR 70, DAS 28, and ACR component scores	Primary: ACR 20 achievement at 12 weeks was significantly higher with certolizumab (51.1%) than placebo (25.9%; P < 0.001). Secondary: A significantly greater proportion of ACR 50 and ACR 70 responders were found in the active treatment group vs the placebo group (26.6 vs 9.9%; P<0.001 and 13.0 vs 2.8%; P<0.001, respectively). A significant improvement in all ACR components was also detected among patients on certolizumab vs placebo (P≤0.05). At 12 weeks, 81.1% of patients on certolizumab achieved a DAS28 improvement of at least 1.2 vs 56.5% with placebo (P<0.001). The most common AEs reported were nausea, upper respiratory tract infections, flare of RA and headaches. Injection and infusion-site reactions occurred in 5.8% of certolizumab patients and 1.0% placebo patients.
Tanaka et al.[91] (2012) GO-FORTH Golimumab 50 mg once every four weeks and MTX (Group 3)	DB, MC, PC, RCT Patients 20 to 75 years of age with RA (diagnosed with ACR 1987criteria) with RA for ≥3 months and were	N=269 24 weeks	Primary: Proportion of patients achieving ACR 20 at week 14 Secondary: Proportion of	Primary: There was a significantly higher proportion of patients achieving an ACR 20 in the golimumab 50 and 100 mg groups compared to the placebo group (74.7 and 72.1 vs 27.3%; P<0.0001). Secondary: Similarly, more patients in the golimumab 50 and 100 mg groups achieved an ACR 50 compared to the placebo group (43.0 and 37.9 vs

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vs golimumab 100 mg once every four weeks and MTX (Group 2) vs placebo and MTX (Group 1)	receiving 6 to 8 mg/week oral MTX for RA for ≥3 months before study and active RA (≥4/66 swollen joints and ≥4/68 tender joints at screening/ baseline) and ≥2 of the following criteria at screening/ baseline: CRP >1.5 mg/dL, ESR by the Westergren method of >28 mm/hour, morning stiffness lasting ≥30 minute, radiographic evidence of bone erosion, or anti-cyclic citrullinated peptide antibody-positive or rheumatoid factor-positive		patients achieving an ACR 50 and ACR 70 response, ACR-N Index of Improvement, DAS28(ESR) response DAS28(ESR) remission (score <2.6), HAQ-DI, and safety	9.1%; P≤0.005). More patients receiving golimumab 50 or 100 mg achieved an ACR 70 compared to patients receiving placebo (22.1 and 13.8 vs 2.3%; P≤0.005). The ACR-N index of improvement was significantly higher in patients receiving golimumab 50 mg (30%) and golimumab 100 mg (25.85%) compared to placebo (20.00; P<0.001 for both). Significantly more patients in the golimumab 50 mg and 100 mg treatment groups achieved DAS28(ESR) scores for response to treatment compared to placebo (79.5 and 85.5 vs 37.6%; P<0.0001). A higher proportion of patients receiving golimumab 50 mg or 100 mg achieved DAS28(ESR) for remission compared to placebo at 14 weeks (31.4 and 18.4 vs 3.4%; P<0.0001). Patients randomized to golimumab 100 mg and 50 mg treatment groups experienced statistically significant improvements in HAQ-DI scores compared to placebo at 14 weeks (0.32 and 0.39 vs 0.07; P<0.0001). By week 16, 72.7, 75.6 and 78.2% of patients receiving placebo, golimumab 100 mg and 50 mg, respectively, had adverse events. Infections were the most common adverse event in the placebo (39.8%), golimumab 100 mg (38.4%) and golimumab 50 mg (33.3%) treatment groups at week 24. Serious adverse events were relatively uncommon through week 16, occurring in one patient (1.1%) in receiving placebo (intervertebral disc protrusion), one patient (1.2%) in the golimumab 100 mg group (ileus) and two patients receiving golimumab 50 mg (2.3%). By week 24, 11 (5.5%) of the 201 patients treated with golimumab 50 mg or 100 mg had discontinued golimumab due to the following adverse events: infection (n=2), skin disorders (n=2), liver function abnormality (n=2), injury (n=2), bone neoplasm (n=1), aortic dissection (n=1), gastrointestinal disorder (n=1) and elevated blood pressure (n=1 in combination with skin disorder).
Emery et al.[92]	DB, PC, RCT	N=637	Primary:	Primary:

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(2009) Golimumab 100 mg once every 4 weeks and placebo vs golimumab 50 mg once every 4 weeks and MTX vs golimumab 100 mg once every 4 weeks and MTX vs placebo and MTX	MTX naïve patients ≥18 years of age with a diagnosis of active RA for ≥3 months and not previously treated with a TNF-blocker	24 weeks	ACR 50 response at week 24 Secondary: ACR 20, 70, 90 responses at week 24	The golimumab monotherapy group was not statistically different from the MTX monotherapy group in ACR response (P=0.053). However, post-hoc modified intent-to-treat analysis (excluding three untreated patients) of the ACR 50 response showed statistically significant difference between the two groups (P=0.049). Secondary: The combined golimumab and MTX groups had greater proportion of patients achieve an ACR 20 response at week 24 compared to placebo and MTX groups (P=0.028 for both groups). ACR 70 response was not significant and ACR 90 response was significant for the golimumab 50 mg and MTX groups.
Keystone et al.[93] (2009) GO-FORWARD Golimumab 100 mg once every 4 weeks and placebo vs golimumab 50 mg once every 4 weeks and MTX vs	DB, MC, PC, RCT Patients ≥18 years of age with a diagnosis of active RA for ≥3 months despite stable dose of ≥15 mg/week of MTX and not previously treated with a TNF-blocker	N=444 24 weeks	Primary: ACR 20 response at week 14, change from baseline in HAQ at week 24 Secondary: ACR 50, 70, 90 responses and ACR-N EULAR response, remission according to DAS 28, and sustained remission (DAS 28 remission at	Primary: At week 14, an ACR 20 response was achieved by 33.1% of placebo and MTX-treated patients, 44.4% of golimumab 100 mg and placebo-treated patients (P=0.059), 55.1% of golimumab 50 mg and MTX-treated patients (P=0.001), and 56.2% of golimumab 100 mg and MTX-treated patients (P<0.001). At week 24, the median improvements from baseline in the HAQ-DI scores were -0.13 (P=0.240), -0.38 (P=0.001), and -0.50 (P<0.001), respectively. Secondary: ACR 50 and ACR-N response was significant for all the groups except placebo and MTX; ACR 70 was significant for all the groups except the placebo and MTX and golimumab and placebo groups; ACR 90 was not significant for any of the groups. Greater proportion of patients in the golimumab and MTX groups

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golimumab 100 mg once every 4 weeks and MTX vs placebo and MTX			week 14 and maintained through week 24)	achieved significant EULAR response. At week 24, clinical remission was achieved by 6.0% of placebo and MTX-treated patients, 12.0% (P=0.087) of golimumab 100 mg and placebo-treated patients, 20.2% (P=0.001) of golimumab 50 mg and MTX-treated patients, and 22.5% (P<0.001) of golimumab 100 mg and MTX-treated patients, respectively. Sustained remission was achieved by 0.8%, 6.3% (P=0.018), 10.2% (P=0.001), and 11.9% (P<0.001), respectively.
Smolen et al.[94] (2009) GO-AFTER Golimumab 50 mg once every 4 weeks vs golimumab 100 mg once every 4 weeks vs placebo Patients were allowed to continue stable doses of concomitant HCQ, MTX, or SSZ during the trial.	DB, PC, RCT Patients ≥18 years of age with a diagnosis of active RA for ≥3 months previously treated with ≥1 dose of a TNF-blocker without a serious adverse reaction	N=461 24 weeks	Primary: ACR 20 response at week 14 Secondary: ACR 50 response at week 14, DAS 28 response at week 14, ACR 20 response at week 24, and improvement from baseline in HAQ scores at week 24	Primary: Golimumab 50 and 100 mg were significantly better than placebo in improving signs and symptoms of RA according to ACR 20 (35.3 and 37.9 vs 18.1%, respectively; P<0.001). ACR 20 responders at week 14 among patients who discontinued previous TNF-blocker therapy due to lack of efficacy included 35.7 and 42.7% of patients in the golimumab 50 and 100 mg groups, respectively, compared to 17.7% of patients in the placebo group (P=0.006, golimumab 50 mg vs placebo; P<0.001, golimumab 100 mg vs placebo). Secondary: ACR 50 response at week 14 was significant for the golimumab-treated groups compared to the placebo group. DAS 28 response was significant for golimumab 50 and 100 mg groups compared to placebo (56.2 and 59.5 vs 30.3%, respectively; P<0.001). ACR 20 response at week 24 was significant for the golimumab-treated groups compared to the placebo group. At week 24, golimumab improved physical function and fatigue according to HAQ and FACIT-F scores, respectively.
Smolen et al.[95] 2012 (GO-AFTER Extension) Golimumab 50 mg	DB, MC, PC, RCT Patients ≥18 years of age with a diagnosis of active RA for ≥3 months	N=459 160 weeks	Primary: ACR 20 Secondary: ACR 50/70,DAS 28, SDAI, and	Primary: At week 160, 62.7, 66.7 and 56.8% of patients achieved ACR20 response and 59, 65 and 64% had HAQ improvement ≥0.25 unit in Groups 1, 2 and 3, respectively. Secondary:

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once every 4 weeks (Group 1) vs golimumab 50 mg once every 4 weeks. Dose could be increased to 100 mg if <20% improvement in both tender and swollen joint counts at week 16 of the original study occurred. (Group 2) vs golimumab 100 mg once every 4 weeks (Group 3)	previously treated with ≥1 dose of a TNF-blocker without a serious adverse reaction		HAQ score	At week 160, 17.3, 14.8 and 23.5% of patients achieved ACR70 response Groups 1, 2 and 3, respectively. DAS 28 response for groups 1, 2 and 3, response was 71.8, 83.8 and 71.4%, respectively. Remission as measured by DAS 28 for groups 1, 2 and 3, response was 16.9, 12.5 and 21.5%, respectively. SDAI remission for groups 1, 2 and 3, response was 11.4, 8.8 and 23.1%, respectively. SDAI scores for low disease activity (3.3 to 11) for groups 1, 2 and 3, response was 34.3, 28.8 and 25.6%, respectively. At week 160, 59, 65 and 64% had HAQ improvement ≥0.25 unit in Groups 1, 2 and 3, respectively.
Weinblatt et al.[96] (2013) GO-FURTHER golimumab 2 mg/kg, at weeks 0 and 4 and every 8 weeks plus MTX vs placebo and MTX	DB, MC, PC, RCT Adult patients with RA for ≥3 months and were receiving 15 to 25 mg/week oral MTX for RA for ≥4 weeks before study and active RA (≥6/66 swollen joints and ≥6/68 tender joints at screening/ baseline) and CRP >1.0 mg/dL,	N=592 24 weeks	Primary: Proportion of patients achieving ACR 20 at week 14 Secondary: DAS28 and HAQ-DI week 14, ACR 50 at week 24, and safety	Primary: There was a significantly higher proportion of patients achieving an ACR 20 in the golimumab group compared to the placebo group (58.5 and 24.9%: P<0.001). Secondary: Significantly more patients in the golimumab treatment groups achieved DAS28 scores for moderate-good response to treatment compared to placebo at 14 weeks (81.3 vs 40.1%; P<0.001). Patients randomized to golimumab treatment groups experienced statistically significant improvements in HAQ-DI scores compared to placebo at 14 weeks (0.5 vs 0.19; P<0.001). Significantly higher proportion of patients randomized to golimumab

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	anti- cyclic citrullinated peptide antibody-positive and/or rheumatoid factor-positive			groups achieved an ACR 50 compared to the placebo group (34.9 vs 13.2%; P≤0.001) at 24 weeks. Significantly higher proportion of patients randomized to golimumab groups achieved an ACR 50 compared to the placebo group (34.9 vs 13.2%; P≤0.001) at 24 weeks. Adverse events reported at rates ≥1.0% higher in the golimumab group vs placebo were observed for infections and infestations (24.3 vs 20.8%); nervous system disorders (6.8% vs 4.1%); gastrointestinal disorders (6.6 vs 5.6%); skin and subcutaneous tissue disorders (6.6% vs 3.6%); respiratory, thoracic and mediastinal disorders (4.8 vs 2.5%); vascular disorders (3.8 vs 2.5%); and metabolism and nutrition disorders (2.3 vs 0.0%).
Ishaq et al.[97] (2011) Leflunomide 20 mg once a day vs methotrexate 20 once a week	AC, DB, DD, RCT Patients 18 years of age or older with diagnosis of RA according to ACR criteria for at least four months and less than ten years, who had active disease and have not used a DMARD for at least 28 days prior to the study	N=240 1 year	Primary: Tender joint count, swollen joint count, physician and patient global assessment score Secondary: Morning stiffness, pain intensity, Health Assessment Questionnaire	Primary: Changes in mean scores ± one standard deviation in the tender joint count, swollen joint count, physician and patient global assessments after one year were, respectively, -8.0±7.9, -7.0±7.3, -1.0±1.0 and -1.0±1.1 in the leflunomide group and -10.0±7.9 and -9.0±7.3, -1.0±1.0, 1.0±1.0 in the methotrexate group. The difference between the baseline and the end-point measurements in all the efficacy end-points was significantly greater in patients taking methotrexate compared to patients taking leflunomide (P=0.001). Secondary: Changes in the mean scores ± one standard deviation in morning stiffness (minutes), pain intensity (mm) and the Health Assessment Questionnaire after one year were -87.3±104.1, -27.3±26.6 and -0.48±0.50 in the leflunomide group and -91.5±94.4, -35.2±24.2 and -0.54±0.47 in the methotrexate group, respectively. Withdrawal from the study due to adverse events occurred in 19 and 15% of patients in the leflunomide and methotrexate groups, respectively. Withdrawal from the study due to a lack of efficacy occurred in 7 and 3% of patients in each group, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Osiri et al.[98] (2003) Leflunomide 20 to 25 mg/day vs other DMARDs vs placebo Only results pertaining to the scope of this review are included.	MA (33 studies) Patients 18 years and of age older with active RA	N=not reported At least 12 weeks	Primary: Tender and swollen joint count, pain level, patient's and physician's global assessment, functional ability, acute phase reactants, radiographic change of bone and joint damage, ACR criteria, DAS 28 Secondary: Health Related Quality of Life Questionnaire, SF-36, reported side effects, withdrawals	Primary: Comparison / Duration (months) / Risk Ratio, 95% CI ACR 20 vs methotrexate / 3 / 0.96 (0.84, 1.10) vs methotrexate / 6 / 0.96 (0.87, 1.06) vs methotrexate / 12 / 1.08 (0.75, 1.55) vs methotrexate / 24 / 1.05 (0.81, 1.37) vs sulfasalazine / 6 / 1.03 (0.83, 1.28) vs sulfasalazine / 12 / 1.03 (0.83, 1.29) vs sulfasalazine / 24 / 0.73 (0.57, 0.93) ACR 50 vs methotrexate / 12 / 0.86 (0.52, 1.44) vs methotrexate / 24 / 0.82 (0.60, 1.10) vs sulfasalazine / 6 / 0.92 (0.64, 1.31) vs sulfasalazine / 12 / 0.93 (0.63, 1.36) vs sulfasalazine / 24 / 0.48 (0.28, 0.80) ACR 70 vs methotrexate / 12 / 0.44 (0.26, 0.77) vs methotrexate / 24 / 0.72 (0.44, 1.18) vs sulfasalazine / 6 / 0.66 (0.28, 1.55) vs sulfasalazine / 12 / 1.14 (0.57, 2.25) vs sulfasalazine / 24 / 0.70 (0.34, 1.43) DAS 28<3.2 vs methotrexate / 4 / 1.24 (0.64, 2.42) DAS 28 remission vs methotrexate / 6 / 1.0 (0.22, 4.56) DAS 28 low disease activity vs methotrexate / 6 / 1.0 (0.28, 3.63) DAS 28 moderate disease activity vs methotrexate / 6 / 1.05 (0.76, 1.44) DAS 28 high disease activity vs methotrexate / 6 / 0.5 (0.05, 5.22)
Scott et al.[99] (2001) Leflunomide 20 mg/day	DB, MC, PC, PG, RCT Patients ≥18 years of age with active RA functional class	N=358 Up to 24 months	Primary: Tender and swollen joint counts, doctor and patient global assessments, pain	Primary: In the six month cohorts, both active groups showed significant improvements in change in tender and swollen joint counts, change in patient and doctor global scores, acute phase reactants, RF, duration of morning stiffness, pain intensity, and functional ability compared with placebo and these continued in the 12 and 24 month cohorts.

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vs sulfasalazine 2 grams/day vs placebo	I, II, or III with tender joint count ≥6, swollen joint count ≥6; doctor and patient global assessment as fair, poor, or very poor; CRP >20 mg/L or ESR >28 mm/1st hour		intensity assessment, duration of morning stiffness, ESR, CRP, RF, and functional disability Secondary: Safety	At 24 months, the ACR20 response rate with leflunomide was significantly greater than with sulfasalazine (82 vs 60%; P<0.01). Leflunomide showed significant improvement in functional ability (in both mean health assessment questionnaire scores and functional disability index) compared with placebo and sulfasalazine during the six month placebo controlled phase. Secondary: During the first six months, the most frequent drug related adverse effects in the leflunomide group were diarrhea (leflunomide 17%, sulfasalazine 9%), nausea (leflunomide 10%, sulfasalazine 17%), and alopecia (leflunomide 8%, sulfasalazine 5%). No unexpected adverse events or late toxicity were noted during the two year period. Diarrhea, nausea, and alopecia were less frequent with continued treatment.
Strand et al.[100] (1999) Leflunomide 20 mg per day vs methotrexate 7.5 mg per week vs placebo	DB, MC, RCT Patients ≥18 years of age with active RA for ≥6 months	N=482 12 months	Primary: Comparison of leflunomide therapy with placebo Secondary: Comparisons of leflunomide therapy with methotrexate therapy and methotrexate therapy with placebo	Primary: The ACR20 success rate was significantly higher in the leflunomide treatment group compared with the placebo group (41 vs 19%; P<0.001). Mean changes over time in each component of the ACR response index were significantly better in the leflunomide and methotrexate treatment groups than in the placebo group (P≤0.01). Analyses of function/disability and health-related quality of life demonstrated statistically significant improvement in patients treated with leflunomide compared with patients who received placebo. Secondary: The ACR success rates in the leflunomide and methotrexate treatment groups (41 and 35%, respectively) were statistically equivalent. Responses from patients receiving methotrexate treatment were significantly better than those for patients receiving placebo. The ACR20 response rates over time for patients receiving leflunomide and methotrexate therapy were 52 and 46%, respectively. Onset of effect occurred at a mean of 8.6 weeks for patients in the leflunomide treatment group compared with 9.5 weeks for those in the methotrexate treatment group.
Cohen et al.[101] ULTRA	DB, MC, RCT	N=235	Primary: ACR responses,	Primary: At 24 months, leflunomide treatment was associated with higher ACR

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2001) Leflunomide 20 mg per day vs methotrexate 7.5 to 20 mg per week vs placebo	Patients 18 to 75 years of age with active RA for ≥6 months	24 months	tender and swollen joint counts, VAS, HAQ, SF-36, safety Secondary: Not reported	≥20% response rates than was MTX treatment (79 vs 67%; P=0.049; 95% CI, 0.1 to 24.4). ACR ≥50% response rates for patients at 24 months were numerically greater following treatment with leflunomide compared with MTX (leflunomide 56 vs MTX 43%; P=0.053). This was also the case for ACR ≥70% response rates (leflunomide 26 vs MTX 20%; P=0.361). Responses were sustained from 12 months to 24 months, reflecting a consistent treatment effect. Maximal improvements evident at 6 months in the HAQ-DI and the physical component score of the SF-36 were sustained over 12 months and 24 months; improvement in the HAQ-DI with leflunomide (−0.60) was superior to that with MTX (−0.37) at 24 months (P=0.005). Over 24 months in the ITT cohort, serious treatment-related adverse events were reported in 1.6% of the leflunomide-treated patients and 3.7% of the MTX-treated patients. Frequently reported adverse events included upper respiratory tract infections, diarrhea, nausea and vomiting, rash, reversible alopecia, and transient liver enzyme elevations. Secondary: Not reported
De Stefano et al.[102] (2010) Leflunomide-anti-TNF-α combination therapy vs MTX-anti-TNFα combination therapy The anti-TNF-alpha drugs used were etanercept, infliximab, or adalimumab	PRO, RCT Patients 18 to 65 years of age with active RA for >1 year and DAS 28 >5.1 despite MTX or leflunomide treatment	N=120 24 weeks	Primary: Discontinuation rate, DAS 28, clinician's global assessment, VAS score, HAQ, ACR, laboratory parameters Secondary: Not reported	Primary: The discontinuation rates did not differ significantly between the two combination therapies (P=0.63). There were no statistically significant differences in DAS28 variations between the two groups or among the six subgroups (P=0.82). The ACR differences between the two groups and six subgroups were no statistically significant at week four (P=0.69), week 12 (P=0.77), and week 24 (P=0.46). There were no statistically significant differences between the two groups and six subgroups in HAQ score. Secondary: Not reported

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Jones et al.[103] (2010) AMBITION Tocilizumab 8 mg/kg every 4 weeks vs MTX 7.5 to 20 mg every week or placebo for 8 weeks followed by tocilizumab 8 mg/kg from week nine on	DB, DD, PG, RCT Patients ≥18 years of age, with moderate to severe RA for ≥3 months, oral glucocorticoids (up to 10 mg/day of prednisone or equivalent) and NSAIDs were permitted if the dose was stable for ≥6 weeks	N=673 24 weeks	Primary: Proportion of patients achieving ACR 20 response at week 24 Secondary: Proportion of patients with ACR 50/70 responses at week 24 and the time to onset of ACR 20/50/70 responses, changes from baseline at week 24 in 28-joint count DAS 28, the proportion of patients in clinical remission (DAS 28 <2.6), with low disease activity (DAS 28 ≤3.2) and with good/ moderate responses at week 24, improvement in physical function was assessed by change from baseline at week 24 in HAQ-DI, and adverse events	Primary: At week 24, 70.6% of tocilizumab patients as compared to 52.1% of MTX patients achieved an ACR 20 response (P<0.001). Compared to the placebo arm, a larger proportion of patients treated with tocilizumab also achieved an ACR 20 response at week eight (55.6 vs 13.1%; 95% CI, 0.34 to 0.52). Secondary: The proportion of patients achieving ACR 50 (44.0%) and ACR 70 (28.0%) at week 24 was also statistically significant for tocilizumab as compared to MTX (P<0.001). Improvements in DAS 28 at week 24 were greater in the tocilizumab group than in the MTX group. Additionally, the proportion of patients in remission at week 24 was higher with tocilizumab (P<0.001). By week 24, tocilizumab patients were five times more likely to achieve DAS 28 remission and four times more likely to achieve at least a moderate response (OR vs MTX, 4.24; 95% CI, 2.92 to 6.14). A greater improvement in physical function was seen by a higher mean change in HAQ-DI with tocilizumab when compared to that of MTX. There was no statistically significant difference with regard to the number of adverse events experienced in the tocilizumab group compared to the MTX group (79.9 vs 77.5%; P=0.484). Infection rates/patient year were also found to be similar (1.06 vs 1.09). However, skin and subcutaneous infections were reported more frequently in the tocilizumab group (4.1 vs 1.4%; P value not reported).
Smolen et al.[104] (2008) OPTION	DB, PC, PG, RCT Patients ≥18 years	N=622 24 weeks	Primary: ACR 20 response at week 24	Primary: At week 24, significantly greater proportion of patients receiving tocilizumab 4 and 8 mg/kg had an ACR 20 response than patients who

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Tocilizumab 8 mg/kg every 4 weeks plus MTX (stable, 10 to 25 mg weekly) vs tocilizumab 4 mg/kg every 4 weeks plus MTX (stable, 10 to 25 mg weekly) vs placebo every 4 weeks plus MTX (stable, 10 to 25 mg weekly)	of age, with moderate to severe RA >6 months duration, who had an inadequate response to MTX; all other DMARDs were discontinued before the start of the study, oral glucocorticoids (≤10 mg/day of prednisone or equivalent) and NSAIDs were permitted if doses were stable for six weeks or more		Secondary: ACR 50/70, DAS 28, and EULAR responses at week 24, difference in HAQ-DI, SF-36, and FACIT-F, scores from baseline, and adverse events	received placebo (59 and 48 vs 26%, respectively; P<0.0001 for both). Secondary: Significantly greater proportion of patients in tocilizumab 4 and 8 mg/kg groups achieved ACR 50 (31 and 44 vs 11%, respectively; P<0.0001) and ACR 70 at week 24 (12 and 22 vs 2%, respectively; P<0.0001) compared to patients in the placebo group. Significantly greater proportion of patients in tocilizumab 4 and 8 mg/kg groups had reduced disease activity as measured by a DAS 28 score <2.6 (13.0 and 27.0 vs 0.8%, respectively; P<0.0002 for 4 mg/kg and P<0.0001 for 8 mg/kg groups) compared to the placebo group. EULAR response was also found to be significantly decreased in both tocilizumab 4 and 8 mg/kg groups (21 and 38 vs 3%, respectively; P<0.0001 for both) compared to the placebo group. Greater improvements in physical function were seen in both tocilizumab 4 and 8 mg/kg groups as assessed by the HAQ-DI score (-0.52 and -0.55 vs -0.34, respectively; P<0.0296 for 4 mg/kg and P<0.0082 for 8 mg/kg). Significant differences were seen with regard to changes in the SF-36 physical score in both tocilizumab 4 and 8 mg/kg groups (9.7 and 9.5 vs 5.0, respectively; P<0.0001 for both) and in the SF-36 mental score (5.7 and 7.3 vs 2.7, respectively; P<0.0394 for 4 mg/kg and P<0.0012 for 8 mg/kg). The mean change in FACIT-F score from baseline showed significant improvements in both tocilizumab 4 and 8 mg/kg groups (7.3 and 8.6 vs 4.0, respectively; P<0.0063 for 4 mg/kg and P<0.0001 for 8 mg/kg). Greater proportions of patients in the tocilizumab 4 and 8 mg/kg groups reported experiencing at least one adverse event compared to the placebo group (71 and 69 vs 63%, respectively). The rate of all infections/100 patient years was 98.7 in the tocilizumab 4 mg/kg group, 101.9 in the 8 mg/kg group, and 96.1 in the placebo group.
Genovese et al.[105]	DB, MC, PC, RCT	N=1,220	Primary:	Primary:

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(2008) TOWARD Tocilizumab 8 mg/kg plus DMARD every 4 weeks vs placebo plus DMARD every 4 weeks	Patients ≥18 years of age, with moderate to severe RA, who received stable doses of permitted DMARDs (MTX, chloroquine, HCQ, parenteral gold, SSZ, azathioprine, and leflunomide) for ≥8 weeks prior to study entry and oral glucocorticoids (≤10 mg/day of prednisone or equivalent) and NSAIDs or COX2 inhibitors if the doses were stable for ≥6 weeks	24 weeks	ACR 20 responses at week 24 Secondary: ACR 50/70 responses at week 24, number of swollen and tender joints, DAS 28, EULAR response, HAQ, FACIT-F score, and SF-36, and adverse events	At week 24, the proportion of patients in the tocilizumab group that were ACR 20 responders was significantly higher than in the control group (61 vs 25%; P<0.0001). No obvious differences were seen in ACR 20 response with regard to patients who received two or more DMARDs. Secondary: At week 24, significantly more patients in the tocilizumab group achieved ACR 50 and ACR 70 responses when compared to the placebo group (ACR 50, 30 vs 9%; ACR 70, 21 vs 3%; P<0.0001 for both). Compared to baseline, a significant decrease was seen in the number of swollen and tender joints in patients receiving tocilizumab when compared to the placebo group (swollen joint count, -10.3 vs -4.9; tender joint count, -15.7 vs -8.5; P<0.0001). Mean DAS 28 improved incrementally over time with greater changes in the tocilizumab group seen by week 24 (-3.17 and -1.16, respectively; P<0.0001). Remission rates at week 24 were also higher in the tocilizumab group when compared to the placebo group (30 vs 3%; P<0.0001). By week 24, 80% of patients in the tocilizumab group and 38% of patients in the placebo group achieved a good or moderate EULAR response (P<0.0001). At week 24, 60% of patients in the tocilizumab group had a clinically meaningful improvement in physical function as compared to 34% with placebo (change from baseline in HAQ ≥0.3). Mean changes from baseline were also significantly higher in the tocilizumab group when compared to the placebo group for the disability index of the HAQ (-0.5 vs -0.2; P<0.0001) and FACIT-F scores (8.0 vs 3.6; P<0.0001). Mean improvements from baseline in SF-36 scores were higher for both physical and mental components at week 24 in the tocilizumab group (8.9 vs 4.1 and 5.3 vs 2.3, respectively; P<0.0001 for both). The occurrence of adverse events was found to be higher with

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				tocilizumab (73 vs 61%). The most frequently occurring adverse events in both groups were infections and infestations (37.4 vs 31.6%), gastrointestinal disorders (20.8 vs 14.7%), and musculoskeletal and connective tissue disorders (13.0 vs 17.9%). Infections with a higher incidence in the tocilizumab group were upper respiratory infections (9 vs 7%), other respiratory infections (12 vs 10%), and skin and subcutaneous tissue infections (5 vs 3%).
Kremer et al.[106] (2011) LITHE Tocilizumab 8 mg/kg plus MTX (stable, 10 to 25 mg weekly) for four weeks vs tocilizumab 4 mg/kg plus MTX (stable, 10 to 25 mg weekly) for four weeks vs placebo plus MTX (stable, 10 to 25 mg weekly) for four weeks Oral corticosteroids (≤10 mg/day of prednisone or equivalent) and NSAIDs were permitted if the	DB, MC, PC, PG, RCT Patients with RA, as determined by ACR criteria that was moderate to severe and lasted for ≥6 months; inadequate response to MTX therapy, defined as a swollen joint count of ≥6, a tender joint count of ≥8, and either CRP level ≥1 mg/dl or an ESR ≥28 mm/hour; and had ≥1 radiographically confirmed joint erosion despite having received MTX for ≥12 weeks before baseline	N=1,196 12 months	Primary: Change from baseline in the total Genant-modified Sharp score and change in HAQ-DI Secondary: Change from baseline in erosion and JSN scores (at week 24 and 52), total Genant-modified Sharp score at week 24, proportions of patients with no progression of total, erosion, or JSN scores, ACR 20, ACR 50, and ACR 70, change in DAS 28, and proportions of patients with low levels of disease activity (DAS28 ≤3.2) and DAS	Primary: The proportion of patients without radiographic progression (change in total Genant-modified Sharp score ≤0 from baseline to week 52) was significantly higher in patients treated with tocilizumab 8 or 4 mg/kg (84 and 81 vs 67%; P<0.0001). The AUC of the change in the HAQ-DI score from baseline to week 52 demonstrated a significantly greater decrease in the 8 and 4 mg/kg tocilizumab groups compared to the placebo group (-144.1 and -128.4 vs -58.1 units; P<0.0001 for both comparisons). Secondary: At week 52, the ACR 20, ACR 50, and ACR 70 response rates were higher in patients treated with tocilizumab compared to placebo; however the difference was only statistically significant for the 8 mg/kg group compared to the placebo group (P<0.0001 for all response rate comparisons). The DAS28 scores were reduced over 52 weeks in all treatment groups, with mean improvements of -3.8, -3.0, and -2.0 in the tocilizumab 8 mg/kg, 4 mg/kg and placebo groups, respectively; however, the difference was only significant with the 8 mg/kg dose compared to placebo (P<0.0001). At 52 weeks, more patients treated with tocilizumab 8 mg/kg achieved remission (47.2 vs 7.9%; P<0.0001) according to the DAS28 score (<2.6) or had low disease activity (DAS28 ≤3.2) compared to placebo (63.6 vs 45.3%; P<0.0001). DAS28 remission rates continued to improve between weeks 24 and 52, with the highest proportion of patients in remission in the tocilizumab 8 mg/kg treatment group.

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dosages had been stable for ≥6 weeks before study entry.			remission (DAS28 <2.6).	The progression of structural damage from baseline to week 52 was reduced by 74 and 70% with tocilizumab 8 and 4 mg/kg, respectively, compared to patients treated with placebo (P<0.0001). The total Genant-modified Sharp score at week 52 showed a decreased frequency and severity of disease progression with tocilizumab therapy.
Yazici et al.[107] (2012) ROSE Tocilizumab 8 mg/kg plus DMARD every four weeks vs placebo plus DMARD every four weeks Permitted DMARD (at stable doses ≥7 weeks before study) included MTX, chloroquine, hydroxychloroquine, parenteral gold, SSZ, azathioprine, and leflunomide. Doses were required to remain stable throughout the study; however, dose reductions were allowed as	DB, MC, PC, RCT Patients ≥18 years of age with active RA for ≥6 months and an inadequate clinical response to DMARD in addition to ≥6 swollen joints and ≥6 tender joints at screening and baseline, with either a CRP ≥95.24 nmol/l or an ESR ≥28 mm/h or greater at screening	N=619 24 weeks	Primary: ACR 50 response at week 24 Secondary: ACR 20, ACR 50, ACR 70, EULAR response, DAS28, clinically meaningful improvement (change from baseline in DAS28 of ≥1.2), patients achieving low disease activity (DAS28 ≤3.2), clinical remission (DAS28 <2.6), ESR and CRP levels, FACIT-F, and RAPID3 scores	Primary: A significantly higher proportion of patients randomized to receive tocilizumab achieved an ACR 50 response at week 24 compared to placebo (30.1 vs 11.2%; P<0.0001). Secondary: A higher proportion of patients randomized to receive tocilizumab achieved an ACR 20 response at all time points evaluated compared to placebo (P<0.0001). Similarly, an ACR 50 response was achieved in significantly more patients in the tocilizumab group compared to placebo at all treatment weeks except week 16 (P<0.05 at all time points). A significantly greater proportion of patients in the tocilizumab group compared to the placebo group achieved an ACR 70 response at all time points from week eight onward (P<0.05 for all time points). A higher proportions of patients achieved a EULAR good response in the tocilizumab group compared to placebo at all time points starting at week four (13.2 vs 2.0%; P<0.0001). The mean DAS28 score decreased from baseline to week 24 in both treatment groups starting at week four; however, the improvement was significantly greater in tocilizumab group compared to placebo (P<0.0001). Significantly more patients achieved a clinically meaningful decrease in DAS28 (≥1.2 points from baseline) in the tocilizumab group compared to the placebo group at all time points from week four onward (87.9 vs 53.4%; P<0.0001). Moreover, a greater proportion of patients randomized to receive tocilizumab achieved a low disease activity (P<0.0001) and clinical remission at week 24 (P<0.0001) compared to those in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
clinically warranted for safety reasons.				placebo group. There were significantly greater improvements from baseline in the RAPID3 scores at 24 weeks in the tocilizumab treatment group compared to placebo (-2.33 vs -1.29; P<0.0001). There was a statistically significant improvement in mean FACIT-F scores over 24 weeks of treatment with tocilizumab compared to placebo (P<0.05). Patients treated with tocilizumab achieved significantly lower mean CRP levels at all time points evaluated compared to the placebo group (P<0.0001). Similarly, the mean ESR was significantly reduced from baseline to a greater degree with tocilizumab compared to the placebo group at week 24 (-34.72 vs -5.70 mm/h; P<0.0001).
Emery et al.[108] (2008) RADIATE Tocilizumab 8 mg/kg plus MTX (stable, 10 to 25 mg weekly) for 4 weeks vs tocilizumab 4 mg/kg plus MTX (stable, 10 to 25 mg weekly) for 4 weeks vs placebo plus MTX (stable, 10 to 25 mg weekly) for 4 weeks	DB, PC, PG Patients ≥18 years of age with moderate to severe active RA with failure to respond to one or more TNF antagonists within the past year; patients must have discontinued TNF agents (Enbrel®, Humira®, Remicade®) or DMARDs (other than MTX) before enrolling	N=499 24 weeks	Primary: ACR 20 responses Secondary: DAS 28, number of patients requiring rescue therapy, and adverse events	Primary: ACR 20 was achieved at week 24 by 50.0, 30.4 and 10.1% of patients in the 8 mg/kg, 4 mg/kg and control group respectively (P<0.001). At week four, more patients achieved ACR 20 in the 8 mg/kg tocilizumab group than those in the control group (P<0.001). Patients responded, as measured by ACR 20 response, regardless of the most recently failed TNF antagonist or the number of failed treatments. Secondary: DAS 28 remission rates at week 24 were dose related, being achieved in 30.1, 7.6, and 1.6% of 8 mg/kg, 4 mg/kg and control groups (P<0.001 for 8 mg/kg; P=0.053 for 4 mg/kg vs control). Rescue therapy with 8 mg/kg of tocilizumab plus MTX was offered at week 16 in all cases of treatment failure (<20% improvement in both tender and swollen joints). More patients in the control group (41%) and in the 4 mg/kg group (19%) received rescue therapy after week 16 compared to 11% of patients in the 8 mg/kg group. Adverse events noted were mild or moderate with overall incidences of 84.0% in the tocilizumab 8 mg/kg group, 87.1% in the tocilizumab 4

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				mg/kg group, and 80.6% in the placebo plus MTX group. The most common adverse events were infections, gastrointestinal symptoms, rash and headache. The incidence of serious adverse events was higher in the control group (11.3%) than in the tocilizumab 8 mg/kg (6.3%) and 4 mg/kg (7.4%) groups.
Dougados et al.[109] (2013) ACT-RAY Tocilizumab 8 mg/kg plus MTX (stable >15 mg weekly) every 4 weeks vs tocilizumab 8 mg/kg plus placebo every 4 weeks	DB, PC, PG Patients ≥18 years of age with active RA with failure to respond to > 12 weeks of MTX treatment (stable dose >15 mg week for 6 weeks prior to study)	N=556 24 weeks	Primary: DAS 28 remission Secondary: DAS 28 low disease activity, ACR 20, ACR 50, ACR 70, ACR 90, and adverse events	Primary: DAS 28 remission rates at week 24 were 40.4% with the tocilizumab/MTX group vs 34.8% with tocilizumab monotherapy (P=0.19). Secondary: DAS 28 scored for low disease activity was significantly lower with combination therapy (tocilizumab/MTX) at week 24 that with the with tocilizumab monotherapy (61.7 vs 51.4%; P=0.029). ACR 20/50/70/90 was 71.5%/45.5%/24.5%/5.8% with tocilizumab/MTX. ACR 20/50/70/90 was 70.3%/40.2%/25.4%/5.1% with tocilizumab monotherapy. The differences between treatment groups were not considered significant. Adverse events noted were comparable in each treatment group with 6.1% of patients on tocilizumab/MTX reporting a serious adverse event while 5.8% reported a serious adverse event with tocilizumab monotherapy. Discontinuations and dose modifications occurred in 3.6% and 27.4% of tocilizumab/MTX patients and 2.5% and 18.5% of tocilizumab monotherapy patients, respectively. Increases in alanine aminotransferase elevations from normal at baseline to greater than upper limit of normal and to more than three times upper limit of normal at one or more time points during 24 weeks occurred in 48.8% and 7.8% on tocilizumab/MTX and in 27.6% and 1.2% of tocilizumab monotherapy patients, respectively.
Maxwell et al.[110] (2009) Abatacept 2 to 10 mg/kg alone or in	SR RCTs of patients ≥16 years of age with RA meeting the	N=2,908 (7 trials) ≥3 months	Primary: ACR 50 response and safety Secondary:	Primary: At three months, the ACR 50 response in the abatacept group was not significantly higher than the control group (RR, 2.50; 95% CI, 0.52 to 11.96). At six and 12 months, the ACR 50 response was significantly higher in the abatacept group compared to the control group (RR, 2.47;

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combination with DMARDs or biologics vs placebo or DMARDs or biologics	ACR 1987 revised criteria		ACR 20, ACR 70, components of ACR radiographic progression, DAS, EULAR response criteria, and changes in HAQ and SF-36	95% CI, 2.00 to 3.07 and RR, 2.21; 95% CI, 1.73 to 2.82, respectively). At one year the NNT in order to achieve ACR 50 was 5 (95% CI, 4 to 7). The RR for adverse events with abatacept compared to controls was 1.05 (95% CI, 1.01 to 1.08). There was a greater number of serious adverse infections with abatacept compared to controls (OR, 1.91; 95% CI, 1.07 to 3.42). However, after removing a study in which patients were treated with combination of etanercept and abatacept, the OR decreased to 1.82 (95% CI, 1.00 to 3.32). Abatacept treated patients had increased number of headaches and infusion reactions (RR, 1.45; 95% CI, 1.20 to 1.74 and RR, 1.30; 95% CI, 1.13 to 1.50). Secondary: ACR 20 response was achieved in significantly more patients treated with abatacept compared to controls at six and 12 months (RR, 1.79; 95% CI, 1.59 to 2.02 and RR, 1.79; 95% CI, 1.55 to 2.07, respectively) but not at three months (RR, 1.70; 95% CI, 0.93 to 3.12). More patients treated with abatacept achieved an ACR 70 at six and 12 months (RR, 3.53; 95% CI, 2.41 to 5.16 and RR, 4.02; 95% CI, 2.62 to 6.18) but not at three months (RR, 5.00; 95% CI, 0.25 to 100.20). There was a statistically significant reduction in the progression of joint damage at 12 months with abatacept (mean difference, -0.27; 95% CI, -0.42 to -0.12). The abatacept treated patients were significantly more likely to reach low DAS (DAS 28 <3.2) compared to controls at six and 12 months (RR, 3.36; 95% CI, 2.28 to 4.96 and RR, 4.33; 95% CI, 2.84 to 6.59), and a NNT of 4 (95% CI, 3 to 5). At 12 months, patients in the abatacept group were significantly more likely to achieve DAS remission (DAS 28 <2.6) with RR of 12.74 (95% CI, 4.76 to 34.15). For clinically meaningful improvement on the HAQ; RR, 1.69 (95% CI, 1.51 to 1.90) in favor of abatacept. There was an absolute difference of 24% (95% CI, 16 to 32) and a NNT to achieve HAQ >0.3 of 5 (95% CI, 4 to 7).

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				Improvement in the physical component of the SF-36 was significantly more likely in the abatacept group (RR, 1.90, 95% CI, 1.52 to 2.39). There was no significant difference between the groups in likelihood of scoring worse. The RR of scoring the same was 0.66 in favor of placebo (95% CI, 0.56 to 0.78). There were significantly fewer patients that scored worse on the mental component of the SF-36 (RR, 0.64; 95% CI, 0.44 to 0.94). Scoring the same was not significantly different between the groups. A score of better was significantly higher in the abatacept group (RR, 1.42; 95% CI, 1.14 to 1.76).
Navarro-Sarabia et al.[111] (2005) Adalimumab 20, 40, 80 mg every week to every other week, alone or in combination with DMARDs vs placebo or placebo plus DMARDs	SR RCTs of patients with confirmed RA (defined by ACR 1987 criteria), who had active disease and who either failed MTX or other DMARDs therapy, or DMARD naive	N=2,381 (6 trials) 12 to 52 weeks	Primary: ACR, EULAR responses, DAS 28, components of ACR responses, and radiographic data Secondary: Safety	Primary: Adalimumab 40 mg every other week was associated with a RR of 1.52 to 4.63 to attain an ACR 20 response at 24 weeks with a NNT of 1.9 to 5.4. The RR to achieve an ACR 50 response was 4.63 (95% CI, 3.04 to 7.05) and NNT was 3.0 (95% CI, 2.0 to 6.0). The RR to achieve an ACR 70 response was reported as 5.14 (95% CI, 3.14 to 8.41) and a NNT of 7 (95% CI, 5 to 13). At 52 weeks, the RRs were reported for ACR 20, ACR 50 and ACR 70 as 2.46 (95% CI, 1.87 to 3.22), 4.37 (95% CI, 2.77 to 6.91) and 5.15 (95% CI, 2.60 to 10.22) and NNTs were 2.9, 3.1 and 5.3, respectively. A significantly slower rate of radiological progression was detected with either adalimumab 40 mg every other week or 20 mg every week in combination with MTX compared to placebo plus MTX, at 52 weeks. Adalimumab monotherapy (40 mg every other week) was associated with a RR of 1.91 (95% CI, 1.17 to 3.10), 2.84 (95% CI, 1.58 to 5.12) and 7.33 (95% CI, 2.25 to 33.90) to achieve an ACR 20, ACR 50 and ACR 70 response, respectively, with NNTs of 5 (95% CI, 3 to 9), 7 (95% CI, 4 to 20) and 9 (95% CI, 3 to 38), respectively at 24 weeks. Secondary: Only one study demonstrated that adalimumab was associated with a significantly higher risk of developing serious infection (RR, 7.64; 95%

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				CI, 1.02 to 57.18; NNH, 30.2).
Mertens et al.[112] (2009) Anakinra 50 to 150 mg daily vs placebo	SR RCTs of patients >18 years of age with RA	N=2,876 (5 trials) 24 weeks	Primary: Patients achieving ACR 20 Secondary: Patients achieving ACR 50 and ACR 70, and safety	Primary: ACR 20 achievement was noted in significantly more participants taking anakinra (38%) compared to patients taking placebo (23%; RR, 1.61; 95% CI, 1.32 to 1.98). It was concluded that this 15% difference represented a modest yet clinically meaningful difference. Secondary: Both ACR 50 and ACR 70 were obtained at a significantly greater rate with anakinra as opposed to placebo (18 vs 7%; RR, 2.52; 95% CI, 1.56 to 4.03 and 7 vs 2%; RR, 3.71; 95% CI, 1.44 to 9.57, respectively). Anakinra was also associated with significant improvements in HAQ, visual analog score, Larsen radiographic scores and change in ESR compared to placebo. The number of withdrawals, deaths, adverse events and infections were not significantly different between active treatment and placebo. However, injection site reaction was significantly more prevalent in the anakinra group vs the placebo group (71 vs 28%).
Blumenauer et al.[113] (2003) Etanercept 10 mg or 25 mg twice weekly alone or in combination with MTX vs MTX or placebo	SR RCTs of patients ≥16 years of age meeting the ACR 1987 revised criteria for RA with evidence of active disease as demonstrated by ≥2 of the following: tender joint count, swollen joint count, duration of early morning stiffness >30 minutes, acute phase reactants such as Westergren	N=949 (3 trials) ≥6 months	Primary: ACR 20, ACR 50, ACR 70 responses, and erosion scores Secondary: Safety	Primary: At six months, 64% of individuals on etanercept 25 mg attained an ACR 20 response vs 15% of patients on control with either MTX alone or placebo (RR, 3.8; 95% CI, 2.5 to 6.0; NNT, 2). ACR 50 was achieved by 39% in the etanercept group compared to 4% in the control group (RR, 8.89; 95% CI, 3.61 to 21.89; NNT, 3). An ACR 70 response was reported in 15 and 1% of etanercept and control patients, respectively (RR, 11.31; 95% CI, 2.19 to 58.30; NNT, 7). Etanercept 10 mg was only associated with significant ACR 20 (51 vs 11% of controls; RR, 4.6; 95% CI, 2.4 to 8.8; NNT, 3) and ACR 50 responses (24 vs 5% of controls; RR, 4.74; 95% CI, 1.68 to 13.36; NNT, 5). Seventy-two percent of patients receiving etanercept had no increase in Sharp erosion score vs 60% of MTX patients. The Sharp erosion scores and JSN were not significantly reduced by either etanercept dose,

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	ESR or CRP			however etanercept 25 mg was associated with a significantly reduced total Sharp score (WMD, -10.50; 95% CI, -13.33 to -7.67). Secondary: Injection site reactions were reported in 34% of patients on etanercept 10 mg compared to 9% of controls (RR, 3.86; 95% CI, 2.59 to 5.77; NNH, 4) and 41% of patients receiving etanercept 25 mg vs 9% of controls (RR, 4.77; 95% CI, 3.26 to 6.97; NNH, 3.1). The number of withdrawals was reported less frequently in the etanercept 25 mg group (4%) compared to the control group (8%; RR, 0.50; 95% CI, 0.27 to 0.94) and no difference was found between the etanercept 10 mg group and control in the rate of discontinuation.
van Vollenhoven et al.[114] (2012) SWEFOT Infliximab 3 mg/kg at weeks zero, two and six then every eight weeks plus MTX 20 mg weekly (Group B) vs MTX 20 mg weekly plus SSZ 1,000 mg twice-daily plus hydroxychloroquine 400 mg daily (Group A)	MC, OL, PG, RCT Patients ≥18 years of age with RA (ACR) criteria, no previous DMARD treatment, no oral glucocorticoid treatment or stable glucocorticoid treatment for ≥4 weeks of at most 10 mg daily prednisolone (or equivalent), a DAS28 >3.2	N=487 24 months	Primary: Proportion of patients achieving a EULAR-define good response (a decrease of DAS28 by ≥1.2 and a resulting DAS28 ≤3.2 or less Secondary: EULAR and ACR responses at months 18 and 24, radiological outcomes at months 24	Primary: At month 18, there was no statistically significant difference in the proportion of patients achieving an EULAR-defined good response for patients treated with infliximab compared to conventional therapy (38 vs 29%, respectively; 95% CI, 0.93 to 1.85). Furthermore there was no statistically significant difference between the treatment groups at 24 months (38 vs 31%, respectively; P=0.204). Secondary: At 18 months, no statistically significant differences were reported between infliximab and conventional therapy with regard to ACR 20 (45 vs 34%, respectively; 95% CI, 0.99 to 1.82) ACR 70 (17 vs 11%, respectively; 95% CI, 0.86 to 2.98) or EULAR good or moderate response (58 vs 47%, respectively; 95% CI, 0.97 to 1.56). There was, however, a statistically significant difference favoring infliximab with regard to ACR 50 (30 vs 19%, respectively; 95% CI, 1.02 to 2.46). At 24 months there was no statistically significant difference between infliximab and conventional therapy with regard to ACR 20 response (40 vs 33%, respectively; P=0.259), ACR 50 (30 vs 22%; P=0.134), ACR 70 (16 vs 14%; P=0.566) or EULAR good to moderate response (59 vs 50%; P=0.166). Radiological outcomes were not statistically significant between

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				infliximab and conventional therapy at 24 months with regard to total score (P=0.118), erosion score (P=0.0730) or joint-space narrowing score (P=0.054).
Wiens et al.[115] (2009) Infliximab 3 mg/kg at weeks 0, 2 and 6 then every 8 weeks plus MTX vs placebo plus MTX	MA RCTs of adult patients with RA	N=2,129 (7 trials) ≥14 weeks	Primary: ACR 20, ACR 50, and ACR 70 response Secondary: Safety and discontinuation of therapy	Primary: Through 30 weeks, the proportion of patients achieving an ACR 20 was 59% in the infliximab group compared to the control group (RR, 1.87; 95% CI, 1.43 to 2.45). An ACR 50 was achieved in 33% of infliximab treated patients and 12% of controls (RR, 2.68; 95% CI, 1.79 to 3.99). The RR of achieving an ACR 70 was 2.68 (95% CI, 1.78 to 4.03) with 17 and 5% of infliximab and control groups achieving an ACR 70, respectively. After ≥1 year of treatment, 62% of patients in the infliximab group and 26% of controls achieved an ACR 20 (RR, 2.33; 95% CI, 1.90 to 2.87). An ACR 50 was achieved in 43% of the infliximab treated patients and 27% of controls (RR, 1.61; 95% CI, 1.14 to 2.27). The RR for reaching ACR 70 was 1.69 (95% CI, 0.87 to 3.28), and 29% of patients in the infliximab group compared to 17% of patients in the control group achieved an ACR 70. Secondary: There were no statistically significant differences in serious adverse events. There was a higher number of patients that withdrew due to adverse events in the infliximab group compared to the placebo group (7 vs 3%; RR, 2.05, 95% CI, 1.33 to 3.16); however, fewer patients in the infliximab group withdrew due to lack of efficacy compared to the control group (4 vs 12%; RR, 0.41; 95% CI, 0.18 to 0.95).
Nixon et al.[116] (2007) Adalimumab, anakinra, etanercept, or infliximab with or without MTX vs	MA RCTs of patients with a clinical diagnosis of RA	N=6,694 (13 trials) ≥6 months	Primary: ACR 20 response and ACR 50 response Secondary: Not reported	Primary: The OR for an ACR 20 response was 3.19 (95% CI, 1.97 to 5.48) with adalimumab, 1.70 (95% CI, 0.90 to 3.29) with anakinra, 3.58 (95% CI, 2.09 to 6.91) with etanercept and 3.47 (95% CI, 1.66 to 7.14) with infliximab, all compared to placebo. The OR to achieve an ACR 50 response with adalimumab was 3.97 (95% CI, 2.73 to 6.07), 2.13 (95% CI, 1.27 to 4.22) with anakinra, 4.21 (95% CI, 2.74 to 7.43) with etanercept and 4.14 (95% CI, 2.42 to 7.46) with infliximab, all compared to placebo.

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MTX or placebo				The addition of MTX to any of the agents was found to enhance the efficacy of each treatment. The TNF blockers in combination with MTX were associated with higher ACR 20 and ACR 50 responses than anakinra and MTX (OR, 6.35 vs 3.20 and OR, 8.53 vs 4.56, respectively). Further analysis of each agent against another was performed and no significant difference was determined between individual agents in obtaining an ACR 20 and ACR 50 response (adalimumab vs anakinra; OR, 1.88; 95% CI, 0.83 to 4.49 and OR, 1.84; 95% CI, 0.84 to 3.70; adalimumab vs etanercept; OR, 0.89; 95% CI, 0.42 to 1.79 and OR, 0.94; 95% CI, 0.50 to 1.62; adalimumab vs infliximab; OR, 0.92; 95% CI, 0.39 to 2.37 and OR, 0.96; 95% CI, 0.48 to 1.90; etanercept vs anakinra; OR, 2.11; 95% CI, 0.90 to 5.68 and OR, 1.94; 95% CI, 0.87 to 4.36; infliximab vs anakinra; OR, 2.05; 95% CI, 0.74 to 5.50 and OR, 1.93; 95% CI, 0.79 to 4.29; and infliximab vs etanercept; OR, 0.97; 95% CI, 0.34 to 2.33 and OR, 0.98; 95% CI, 0.45 to 1.93. However, the TNF blockers as a class showed a greater ACR 20 and ACR 50 response compared to anakinra (OR, 1.96; 95% CI, 1.03 to 4.01 and OR, 1.93; 95% CI, 1.05 to 3.50; P<0.05). Secondary: Not reported
Gabay et al.[117] (2013) ADACTA Tocilizumab 8 mg/kg vs adalimumab 40 mg every 2 weeks	DB, PG, RCT Patients ≥18 years of age with RA > 6 months, intolerant to MTX or were inappropriate for continued MTX treatment	N=326 24 weeks	Primary: DAS 28 improvement Secondary: Percentage of patients with: a remission response (DAS28 <2.6); low disease activity (DAS28 ≤ 3.2); improvements of at least 20%, 50%,	Primary: The change from baseline in DAS28 was significantly greater in the tocilizumab group (-3.3) than in the adalimumab group (-1.8) patients (difference -1.5; 95% CI, -1.8 to -1.1; P<0·0001). Secondary: DAS 28 remission rates at week 24 were achieved in 39.9% with tocilizumab and 10.5% in the adalimumab group (difference -1.5, 95% CI, -1.8 to -1.1; P<0·0001). The proportion of patients with low disease activity (DAS 28 ≤3.2) at 24 weeks was 51.5% in tocilizumab group and 19.8% in the adalimumab group (difference -1.5, 95% CI, -1.8 to -1.1; P<0.0001).

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			or 70% in ACR Score (ACR 20, ACR 50, and ACR 70); and with a EULAR good Response, and a EULAR good or moderate response	The proportion of patients on tocilizumab vs adalimumab with improvements of at least 20% in ACR score was 65.0 vs 49.4%, respectively, a 50% improvement was seen in 47.2 vs 27.8% respectively and a 70% improvement was observed in 32.5 vs 17.9%, respectively. The proportion of patients on tocilizumab vs adalimumab with a EULAR good response was 51.5 vs 19.8%, respectively, and percentage with a EULAR good or moderate was response 77.9 vs 54.9%, respectively.
Weinblatt et al.[118] (2013) Abatacept 125 mg subcutaneously once weekly and MTX vs adalimumab 40 mg subcutaneously every other week and MTX Patients were concomitantly treated with a stable dosage of MTX (15 to 25 mg weekly, or ≥7.5 mg weekly in patients with	MC, RCT Patients 18 years of age with a confirmed diagnosis of RA for ≤5 years, inadequate response to MTX, and who had not received previous biologic therapy	N=646 12 months	Primary: Noninferiority, assessed based on ACR20 at one year Secondary: ACR 50, ACR 70, DAS 28, remission response (DAS28 <2.6), low disease activity (DAS28 ≤ 3.2), and HAQ-DI	Primary: The proportions of patients achieving ACR 20 response were comparable between abatacept and adalimumab treatment groups (59.7 and 60.1%, respectively; difference 1.8%; 95% CI, -5.6 to 9.2%). Secondary: The proportions of patients achieving ACR 50 response were comparable between abatacept and adalimumab treatment groups (46.2 and 46%, respectively; 95% CI not reported). The proportions of patients achieving ACR 70 response were comparable between abatacept and adalimumab treatment groups (29.2 and 26%, respectively; 95% CI not reported). Mean improvements in DAS 28 were comparable between abatacept and adalimumab treatment groups (-2.30 and -2.27, respectively; 95% CI not reported). The proportions of patients achieving remission (DAS28 <2.6) were also comparable between abatacept and adalimumab treatment groups (43.3 and 41.9%, respectively; 95% CI not reported). In addition, the proportions of patients achieving low disease activity (DAS28 ≤3.2) were comparable between abatacept and adalimumab treatment groups (59.3 and 61.4%, respectively; 95% CI not reported). Improvements in the HAQ-DI score were comparable between abatacept and adalimumab treatment groups (60.4 and 57.0%, respectively; difference, 3.4%; 95% CI, -4.5 to 11.3%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
intolerance to higher doses). Concomitant treatment with SSZ, HCQ, NSAIDs and stable low-dose oral corticosteroids (≤10 mg/day prednisone equivalent) were allowed.				
Schiff et al.[119] (2013) AMPLE Abatacept 125 mg subcutaneously once weekly and MTX vs adalimumab 40 mg subcutaneously every other week and MTX Patients were concomitantly treated with a stable dosage of MTX (15 to 25 mg weekly, or ≥7.5 mg weekly in	MC, RCT Patients 18 years of age with a confirmed diagnosis of RA for ≤5 years, inadequate response to MTX, and who had not received previous biologic therapy	N=646 2 years	Primary: ACR20 at two years Secondary: ACR 50, ACR 70, DAS 28, remission response (DAS28 <2.6), low disease activity (DAS28 ≤3.2), HAQ-DI, and mTSS	Primary: The proportions of patients achieving ACR 20 response were comparable between abatacept and adalimumab treatment groups (59.7 and 60.1%, respectively; 95% CI not reported). Secondary: The proportions of patients achieving ACR 50 response were comparable between abatacept and adalimumab treatment groups (44.7 and 46.6%, respectively; 95% CI not reported). The proportions of patients achieving ACR 70 response were comparable between abatacept and adalimumab treatment groups (31.1 and 29.3%, respectively; 95% CI not reported). Mean improvements in DAS 28 were comparable between abatacept and adalimumab treatment groups (-2.35 and -2.33, respectively; 95% CI not reported). The proportions of patients achieving remission (DAS28 <2.6) were also comparable between abatacept and adalimumab treatment groups (50.6 and 53.3%, respectively; 95% CI not reported). In addition, the proportions of patients achieving low disease activity (DAS28 ≤3.2) were comparable between abatacept and adalimumab treatment groups (65.3 and 68.0%, respectively; 95% CI not reported). Improvements in the HAQ-DI score were comparable between abatacept and adalimumab treatment groups (54.1 and 48.8%, respectively; 95% CI not reported). The non-progression rate (change from baseline mTSS ≤smallest

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
patients with intolerance to higher doses). Concomitant treatment with SSZ, HCQ, NSAIDs and stable low-dose oral corticosteroids (≤10 mg/day prednisone equivalent) were allowed.				detectable change of 2.2) was 84.8% (95% CI, 80.4 to 89.2) vs 83.8% (95% CI, 79.4 to 88.3) in the abatacept and adalimumab groups, respectively.
Fleischmann et al.[120] (2012) ORAL Solo Tofacitinib 5 mg twice daily vs tofacitinib 10 mg twice daily vs placebo	DB, PC, PG, RCT Patients ≥18 years of age with a diagnosis of active RA (≥6 tender or painful joints [68 joint count] and ≥6 swollen joints [66 joint count] and either ESR>28 mm/hour or CRP>7 mg/L), and inadequate response or adverse reaction to at least one DMARD; all DMARDs except stable doses of antimalarial agents had to be discontinued; the use of NSAIDs and glucocorticoids (≤10 mg of a prednisone equivalent daily) was permitted	N=611 6 month	Primary: ACR20 response rate at month three, change from baseline in HAQ-DI at month three, and proportion of patients with DAS28-4(ESR) <2.6 at month three Secondary: ACR50, and ACR70 response rates, change from baseline in HAQ-DI score, DAS28-4(ESR) and DAS28-4(CRP), proportion of patients with DAS28-4(ESR) and DAS28-4(CRP) <2.6 and ≤3.2 at all visits up to month six, and	Primary: Greater proportions of patients receiving tofacitinib 5 mg and tofacitinib 10 mg twice daily met the criteria for an ACR20 response at month three than those receiving placebo (59.8 and 65.7 vs 26.7%; P<0.001 for both comparisons). Greater reductions from baseline in the HAQ-DI score were observed in patients receiving tofacitinib 5 and 10 mg twice daily at month three than those receiving placebo (least-squares mean changes from baseline, -0.50 and -0.57 vs -0.19; P<0.001 for both comparisons). Greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily achieved DAS28-4(ESR) <2.6 at month three than those receiving placebo (5.6 and 8.7 vs 4.4%; P=0.62 and P=0.10, respectively); however, improvement was not statistically significant. Secondary: Greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily met the criteria for an ACR50 response at month three than those receiving placebo (31.1 and 36.8 vs 12.5%; P<0.001 for both comparisons). Greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily met the criteria for an ACR70 response at month three than those receiving placebo (15.4 and 20.3 vs 5.8%; P=0.003 and P<0.001, respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			FACIT-F scores at month three	Proportions of patients receiving tofacitinib 5 and 10 mg twice daily who achieved DAS28-4(ESR) <2.6 at month six were 9.8 and 14.2%, respectively. Greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily achieved DAS28-4(ESR) ≤3.2 at month three than those receiving placebo (12.5 and 17.0 vs 5.3%; P=0.02 and P<0.001, respectively). Proportions of patients receiving tofacitinib 5 and 10 mg twice daily who achieved DAS28-4(ESR) ≤3.2 at month six were 22.0% and 28.0%, respectively. Greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily achieved DAS28-4(CRP) <2.6 at month three than those receiving placebo (18.7 and 24.4 vs 5.0%; P<0.001 for both comparisons). Proportions of patients receiving tofacitinib 5 and 10 mg twice daily who achieved DAS28-4(CRP) <2.6 at month six were 26.6 and 34.3%, respectively). Greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily achieved DAS28-4(CRP) ≤3.2 at month three than those receiving placebo (28.2 and 36.8 vs 6.7%; P<0.001 for both comparisons). Proportions of patients receiving tofacitinib 5 and 10 mg twice daily who achieved DAS28-4(CRP) ≤3.2 at month six were 43.6 and 50.8%, respectively. The least-squares mean changes from baseline at month three in FACIT-F scores were 6.7 points with the tofacitinib 5 mg and 8.0 points with the tofacitinib 10 mg doses, as compared to 2.8 points with placebo (P<0.001).
van Vollenhoven et al.[121] (2012) ORAL Standard	DB, PG, RCT Patients ≥18 years of age with a diagnosis of active	N=717 12 month	Primary: ACR20 response rate at month six, change in HAQ-DI at month three,	Primary: Greater proportions of patients receiving tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily and adalimumab met the criteria for an ACR20 response at month six than those receiving placebo (51.5, 52.6, and 47.2 vs 28.3%; P<0.001 for all comparisons).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Tofacitinib 5 mg twice daily vs tofacitinib 10 mg twice daily vs adalimumab 40 mg once every 2 weeks vs placebo Patients were also receiving MTX 7.5 to 25 mg weekly with an incomplete response.	RA (≥6 tender or painful joints [68 joint count] and ≥6 swollen joints [66 joint count] and either ESR>28 mm/hour or CRP>7 mg/L)		and proportion of patients with DAS28-4(ESR) <2.6 at month six Secondary: ACR20, ACR50, and ACR70 response rates, change from baseline in HAQ-DI, and DAS28-4(ESR) over time	Greater reductions from baseline in the HAQ-DI score were observed in patients receiving tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily and adalimumab at month three than those receiving placebo (least-squares mean changes from baseline: -0.55, -0.61 and -0.49 vs -0.24; P≤0.001 for all comparisons). Greater proportions of patients receiving tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily and adalimumab achieved DAS28-4(ESR) <2.6 at month six than those receiving placebo (6.2, 12.5, and 6.7 vs 1.1%; P≤0.05, P≤0.001, and P≤0.05, respectively). Secondary: Compared to placebo, significantly greater proportions of patient receiving active treatments achieved ACR50 and ACR70 responses and the changes from baseline in DAS28-4(ESR) and HAQ-DI scores over time (P≤0.05 for all comparisons). A significant difference in ACR20 and ACR50 responses with each tofacitinib treatment as compared to placebo was noted after one month (P≤0.001 for all comparisons). Data on comparison between adalimumab and placebo was not reported.
Burmester et al.[122] (2013) ORAL Step Tofacitinib 5 mg twice daily vs tofacitinib 10 mg twice daily vs placebo for 3	DB, MC, PG, RCT Patients ≥18 years of age with a diagnosis of moderate to severe active RA (≥6 tender or painful joints [68 joint count] and ≥6 swollen joints [66 joint count] and either ESR>28 mm/hour or CRP>7 mg/L) and	N=399 6 month	Primary: ACR20 response rate at month three, change from baseline in HAQ-DI score at month three, and proportion of patients with DAS28-4(ESR) <2.6 at month three Secondary: ACR20, ACR50,	Primary: Greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily met the criteria for an ACR20 response at month three than those receiving placebo (41.7 and 48.1 vs 24.4%; P=0.0024 and P<0.0001, respectively). Greater reductions from baseline in the HAQ-DI score were observed in patients receiving tofacitinib 5 mg and 10 mg twice daily at month three than those receiving placebo (least-squares mean changes from baseline: -0.43 and -0.46 vs -0.18; P<0.0001 for both comparisons). Greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily achieved DAS28-4(ESR) <2.6 at month three than those receiving placebo (6.7 and 8.8 vs 1.7%; P=0.0496 and P=0.0105, respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
months, followed by tofacitinib 5 mg or 10 mg twice daily Patients were also receiving oral or parenteral MTX continuously for ≥4 months at a stable dose of 7.5 to 25 mg weekly for ≥6 weeks. Stable background doses of antimalarial agents (≥8 weeks) were permitted.	inadequate response or intolerance to ≥1 TNF-blocking agents		and ACR70 response rates, change from baseline in HAQ-DI score, changes in DAS28-4(ESR) and DAS28-3(CRP), rates of DAS28-4(ESR) and DAS28-3(CRP) <2.6 and ≤3.2, patient's assessment of arthritis pain, and FACIT-F at all visits	Secondary: Compared to placebo, significantly greater proportions of patients in the tofacitinib 5 mg and 10 mg twice daily met the criteria for an ACR20 response at all visits through month three (P≤0.05 for all visits, except P<0.0001 for 10 mg group vs placebo at month three). Compared to placebo, significantly greater proportion of patients in the tofacitinib 5 mg twice daily group achieved ACR50 at all visits through month three (P≤0.05 at two week and one month visits and P<0.0001 at three month visit). Compared to placebo, significantly greater proportion of patients in the tofacitinib 10 mg twice daily group achieved the ACR50 at three month study visit (P<0.0001); however, responses at two week and at one month visits were not significantly different (P values not reported). Compared to placebo, significantly greater proportions of patients in the tofacitinib 5 mg and 10 mg twice daily groups achieved ACR70 at one month and three months visits (P≤0.05 for all visits, except P<0.001 for 5 mg group vs placebo at month three). The responses between both active treatment groups and placebo at two week visit were not significantly different (P values not reported). Compared to placebo, significantly greater reductions from baseline in the HAQ-DI score were observed in patients receiving tofacitinib 10 mg twice daily at all visits through month three (P≤0.05 for all comparisons, except P<0.0001 at month three). Compared to placebo, significantly greater reductions from baseline in the HAQ-DI score were also observed at three month visit in patients receiving tofacitinib 5 mg twice daily (P<0.0001); however, the changes at two week and one month visits were not significantly different (P values not reported). Compared to placebo, changes from baseline in DAS28-4(ESR) were greater in patients receiving tofacitinib 5 and 10 mg twice daily at all visits through month three (P=0.01 for both comparisons; P values not reported for all other visits). Compared to placebo, significantly greater changes from baseline in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				DAS28-3(CRP) were observed in patients receiving tofacitinib 5 and 10 mg twice daily at all visits through month three (P<0.0001 for all comparisons). Compared to placebo, significantly greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily achieved DAS28-4(ESR) <2.6 at month three (P=0.0496 and P=0.0105, respectively; P values not reported for all other visits). Compared to placebo, significantly greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily achieved DAS28-3(CRP) <2.6 at month three (P<0.0001 for both comparisons; P values not reported for all other visits). Compared to placebo, significantly greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily achieved DAS28-4(ESR) ≤3.2 at month three (P≤0.05 and P<0.0001, respectively; P values not reported for all other visits). Compared to placebo, significantly greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily achieved DAS28-3(CRP) ≤3.2 at month three (P<0.0001 for both comparisons; P values not reported for all other visits). Changes from baseline in patient's assessment of arthritis pain at month three were greater in tofacitinib 5 and 10 mg twice daily treatment groups than in those receiving placebo (−27.2 and −25.0 vs −8.3; P<0.0001 for both comparisons; P values not reported for all other visits). Improvements in FACIT-F at month three were greater in patients receiving tofacitinib 5 and 10 mg twice daily than in those receiving placebo (6.3 and 4.6 vs 1.1; P<0·0001 and P=0.0043, respectively; P values not reported for all other visits).
Van der Heijde et al.[123] (2013) ORAL Scan	DB, MC, PG, RCT Patients ≥18 years of age with a	N=797 12 month	Primary: ACR20 response rate at month six, mean change from	Primary: Greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily met the criteria for an ACR20 response at month six than those receiving placebo (51.5 and 61.8% vs 25.3%; P=0.0001 for both

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Tofacitinib 5 mg twice daily vs tofacitinib 10 mg twice daily vs placebo Patients receiving placebo and not achieving ≥20% improvement in swollen and tender joint counts after 3 months were switched to a predetermined dose of tofacitinib 5 mg or 10 mg twice daily. All patients continuing to receive placebo were switched in a blinded manner to tofacitinib after 6 months. Patients were also receiving stable doses of MTX (15	diagnosis of active RA (≥6 tender or painful joints [68 joint count] and ≥6 swollen joints [66 joint count] and either ESR>28 mm/hour or CRP>7 mg/L) and evidence of ≥3 joint erosions on posteroanterior hand and wrist radiographs or anteroposterior foot radiographs (if radiographic evidence of joint erosions was unavailable, presence of IgM rheumatoid factor positivity or antibodies to cyclic citrullinated peptide).		baseline in mTSS at month six, change from baseline in HAQ-DI score at month three, and proportion of patients with DAS28-4(ESR) <2.6 at month six Secondary: ACR20, ACR50, and ACR70 response rates, DAS28-4(ESR) at all visits, changes from baseline in the ACR code disease activity measures at month six, rates of nonprogressors (≤0.5 unit change from baseline in mTSS or erosion score) at months six, 12, and 24, changes from baseline in mTSS (at months 12 and 24), changes from baseline in erosion score and JSN score (at months six, 12,	comparisons). The least squares mean changes in mTSS at month six were 0.12 and 0.06 for patients receiving tofacitinib 5 and 10 mg twice daily, respectively, vs 0.47 for placebo (P=0.0792 and P≤0.05, respectively). The least squares mean changes in the HAQ-DI score at month three for tofacitinib at 5 and 10 mg twice daily were -0.40 and -0.54, respectively, vs -0.15 for placebo (P value not reported and P<0.0001, respectively). Proportions of patients achieving DAS28-ESR <2.6 at month six were 7.2% and 16.0% for tofacitinib at 5 and 10 mg twice daily, respectively, vs 1.6% for placebo (P value not reported and P<0.0001, respectively). Secondary: Compared to placebo at month six, significantly greater proportions of patients in the tofacitinib 5 mg and 10 mg twice daily groups achieved ACR50 (32.4 and 43.7 vs 8.4%; P<0.0001 for both comparisons) and ACR70 (14.6 and 22.3 vs 1.3%; P<0.0001 for both comparisons). At month 12, ACR20, ACR50, and ACR70 response rates were 48.5, 32.7, and 18.8%, respectively, for tofacitinib 5 mg and 57.0, 41.1, and 27.5%, respectively, for tofacitinib 10 mg. At month 12, the proportions of patients with DAS28-ESR <2.6 were 10.6 and 15.2% in the groups receiving tofacitinib 5 and 10 mg twice daily, respectively. At month six, the proportions of patients with DAS28-ESR ≤3.2 were 14.3 and 28.4% in the groups receiving tofacitinib 5 and 10 mg twice daily, respectively, compared to 3.1% of patients receiving placebo (P<0.0001 for both comparisons). At month 12, the rates of DAS28-ESR <3.2 for patients receiving tofacitinib at 5 and 10 mg twice daily increased to 23.4 and 30.7%, respectively. At month six, least squares mean changes from baseline in DAS28-ESR were greater for tofacitinib 5 and 10 mg twice daily compared to placebo (-2.1 and -2.5 vs -1.3; P<0.0001 for both comparisons); at month 12, least squares mean changes from baseline in DAS28-ESR were -2.3 and -2.5 for tofacitinib 5 and 10 mg twice daily, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
to 25 mg weekly or <15 mg if there were safety issues at higher doses) for ≥6 weeks. Stable doses of low-dose corticosteroids (≤10 mg daily prednisone or equivalent) and NSAIDs were permitted. Prior use of biologic or nonbiologic DMARDs was permitted.			and 24), change from baseline in HAQ-DI score, the FACIT-F, and the patient's assessment of arthritis pain	Compared to placebo a month six, statistically significant improvements from baseline were observed in all ACR core components in both tofacitinib 5 and 10 mg twice daily groups, including improvements in tender or painful joint count (P≤0.05 and P<0.01, respectively), swollen joint count (P<0.01 and P<0.0001, respectively), CRP (P<0.0001 for both comparisons), patient's global assessment of disease activity (P<0.0001 for both comparisons), physician's global assessment of disease activity (P<0.0001 for both comparisons), patient's assessment of pain (P<0.01 and P<0.0001, respectively), and HAQ-DI (P<0.0001 for both comparisons). The proportion of patients with no radiographic progression (≤0.5 unit increase from baseline in mTSS) at months six and 12 was similar in both tofacitinib treatment groups and significantly greater than in the placebo treatment group (P≤0.05 for both). At month six, the proportion of patients with no progression in erosion score (≤0.5 unit increase from baseline) was numerically greater, but not statistically significantly different, in the tofacitinib treatment groups compared to the placebo-treated group (P>0.05). The proportion of patients with no progression in erosion score at month 12 was significantly greater in both tofacitinib treatment groups compared to the placebo-treated group (P≤0.05). The plots of changes from baseline in mTSS, JSN score, and erosion score at months six and 12 for both tofacitinib-treated groups were very similar and were different from the plot for the placebo-treated group (P values not reported). Compared to placebo, greater reductions from baseline in the HAQ-DI score were observed in patients receiving tofacitinib 5 and 10 mg twice daily at all visits (P<0.001 for all comparisons, except P<0.01 for tofacitinib 5 mg vs placebo at one month visit). Improvements in FACIT-F from baseline to month six were greater in patients receiving tofacitinib 5 and 10 mg twice daily than in those receiving placebo (5.6 and 6.9 vs 2.1; P<0.001 and P<0.0001, respectively; P values not reported for all other visits).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Changes from baseline in patient's assessment of arthritis pain at month six were greater in 5 and 10 mg twice daily treatment groups than in those receiving placebo (-26.4 and -29.7 vs -15.70; P<0.01 and P<0.0001, respectively; P values not reported for all other visits).
Kremer et al.[124] (2013) ORAL Sync Tofacitinib 5 mg twice daily vs tofacitinib 10 mg twice daily vs placebo Patients receiving placebo and not achieving ≥20% improvement in swollen and tender joint counts after 3 months were switched to a predetermined dose of tofacitinib 5 or 10 mg twice daily. All patients continuing to receive placebo were switched in a blinded manner to	DB, MC, PG, RCT Patients ≥18 years of age with a diagnosis of active RA (≥4 tender or painful joints [68 joint count] and ≥4 swollen joints [66 joint count] and either ESR>28 mm/hour or CRP>7 mg/L) and inadequate response to ≥1 stably dosed nonbiologic or biologic DMARDs	N=792 12 month	Primary: ACR20 response rate at month six, change from baseline in HAQ-DI score at month three, and proportion of patients with DAS28-4(ESR) <2.6 at month six Secondary: ACR20, ACR50, and ACR70 response rates, change from baseline in HAQ-DI score, changes in DAS28-4(ESR), and FACIT-F score over time	Primary: Greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily met the criteria for an ACR20 response at month six than those receiving placebo (52.1 and 56.6 vs 30.8%; P<0.001 for both comparisons). Greater reductions from baseline in the HAQ-DI score were observed in patients receiving tofacitinib 5 and 10 mg twice daily at month three than those receiving placebo (least-squares mean changes from baseline: -0.44 and -0.53 vs -0.16; P<0.001 for both comparisons). Greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily achieved DAS28-4(ESR) <2.6 at month six than those receiving placebo (8.5 and 12.5 vs 2.6%; P=0.005 and P<0.001, respectively). Secondary: Over time, statistically significant response rates were observed for ACR20 and ACR50 by week two in both tofacitinib groups compared to placebo (P≤0.001 for all comparisons) and for ACR70 by week two in the tofacitinib 10 mg group (P≤0.05 at week two and P≤0.001 at all visits thereafter) and one month in the tofacitinib 5 mg group (P≤0.001 for all comparisons). Mean treatment differences in changes from baseline in HAQ-DI, DAS28- 4(ESR), and FACIT-F response rates for both tofacitinib groups compared to placebo were statistically significant over time (P≤0.001 for all).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
tofacitinib after 6 months. Patients were also receiving ≥1 nonbiologic DMARDs. Patients receiving MTX ≤25 mg weekly required ≥4 months of therapy at a stable dose for ≥6 weeks. Stable doses of low-dose corticosteroids (≤10 mg daily prednisone or equivalent) were permitted.				
He et al.[125] (2013) Tofacitinib 1, 3, 5, 10, or 15 mg twice daily vs adalimumab 40 mg once every 2 weeks vs placebo	MA, SR RCTs including patients ≥18 years of age with a diagnosis of RA	N=3,791 (8 trials) 12 to 24 weeks	Primary: ACR20 and ACR50 response rate at month three and six Secondary: Incidence of infections, immunological or hematological adverse events, incidence of withdrawal from the trials, changes in neutrophil count, hemoglobin and serum	Primary: At month three, the differences in ACR20 response rates between tofacitinib 1 mg twice daily and placebo groups did not reach statistical significance (RR, 1.83; 95% CI, 1.00 to 3.32). Greater proportions of patients receiving tofacitinib 3 mg twice daily met the criteria for an ACR20 response at month three than those receiving placebo (RR, 2.20; 95% CI, 1.20 to 4.04). Greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily met the criteria for an ACR20 response at month three than those receiving placebo (RR, 2.20; 95% CI, 1.58 to 3.07) and (RR, 2.38; 95% CI, 1.81 to 3.14), respectively. The effect was maintained at month six for both 5 mg twice daily (RR, 1.94; 95% CI, 1.55 to 2.44) and 10 mg twice daily (RR, 2.20; 95% CI, 1.76 to 2.75) treatment groups. Greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily met the criteria for an ACR50 response at month three than those

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			creatinine levels, incidence of ALT and AST more than one times upper limit of the normal range, and mean percentage changes of LDL and HDL	receiving placebo (RR, 2.91; 95% CI, 2.03 to 4.16) and (RR, 3.32; 95% CI, 2.33 to 4.72), respectively. Greater proportions of patients receiving tofacitinib 15 mg twice daily met the criteria for an ACR20 response at month three than those receiving placebo (RR, 2.29; 95% CI, 1.19 to 4.41). Greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily met the criteria for an ACR20 response at month three than those receiving adalimumab (RR, 1.65; 95% CI, 1.08 to 2.53) and (RR, 1.97; 95% CI, 1.32 to 2.92), respectively. At month six, there were no significant differences in ACR20 response rates in patients receiving tofacitinib vs adalimumab (P values not reported). Greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily met the criteria for an ACR50 response at month three than those receiving adalimumab (RR, 1.95; 95% CI, 1.00 to 3.80) and (RR, 2.35; 95% CI, 1.26 to 4.38), respectively. Secondary: Compared to placebo, there were no statistically significant differences in the incidences of infections, neutropenia and withdrawal due to adverse events in patients receiving tofacitinib (P values not reported). However, significantly fewer patients withdrew from tofacitinib than placebo (RR, 0.60; 95% CI, 0.45 to 0.78). The withdrawal rate due to lack of efficacy was significantly lower in the patients receiving tofacitinib than placebo (RR, 0.18; 95% CI, 0.09 to 0.35). Compared to placebo, the mean neutrophil count significantly declined in patients receiving tofacitinib (P value not reported). The mean hemoglobin level was not significantly different in tofacitinib group compared to placebo group (P value not reported). Compared to placebo, the mean serum creatinine was found to be significantly higher for tofacitinib 10 mg twice daily (P value not reported). The risk ratios of the mean changes of ALT or AST exceeding one times upper limit of the normal range were statistically significant (P values not reported). Compared to placebo, the mean percentage change of HDL and LDL was

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				significant higher in patients receiving tofacitinib (P values not reported).
Berhan et al.[126] (2013) Tofacitinib 3, 5, 10, or 15 mg twice daily (with or without MTX) vs placebo	MA DB, RCT including patients with a diagnosis of active RA for ≥6 months who were on at least one of nonbiologic or biologic DMARD	N=3,260 (8 trials) 12 to 24 weeks	Primary: ACR20 response rate, change from baseline in HAQ-DI score Secondary: Safety	Primary: Compared to placebo, tofacitinib treated patients had higher odds of meeting the criteria for an ACR20 response (OR, 4.15; 95% CI, 3.23 to 5.32). With the exception of one study, ACR20 response rates for patients receiving tofacitinib dosages ≥3 mg twice daily was significantly greater than those who received placebo (P value not reported). The subgroup odds ratios in the subgroups of tofacitinib 10 mg twice daily (OR, 4.3; 95% CI, 3.023 to 6.376) and 15 mg twice daily (OR, 6.06; 95% CI, 2.383 to 15.428) was higher than 3 mg twice daily (OR, 4.06; 95% CI, 1.340 to 12.305) and 5 mg twice daily (OR, 3.55; 95% CI, 2.435 to 5.169) treated groups. A statistically significant improvement in HAQ-DI scores were seen in patients receiving tofacitinib than placebo treated patients (SMD, −0.62; 95% CI, -0.735 to -0.506). Patients treated with tofacitinib dosages ≥5 mg twice daily have shown a statistically significant reduction in HAQ-DI scores (P value not reported). Secondary: The proportion of infections was higher in the tofacitinib treated groups than in the placebo groups (SMD, 1.96, 95% CI, 1.428 to 2.676). In contrast to the subgroups of tofacitinib 10 mg (SMD, 3.08; 95% CI, 1.694 to 5.570) and 15 mg (SMD, 1.97; 95% CI, 1.088 to 3.558), the proportion of infections in the subgroups of tofacitinib 3 mg (SMD, 1.64; 95% CI, 0.858 to 3.142) and 5 mg (SMD, 1.52; 95% CI, 0.644 to 3.594) were not significantly different from placebo. There were significant increases from baseline in tofacitinib treated groups in the mean hemoglobin level (SMD, 0.11; 95% CI, 0.130 to 0.210), mean serum creatinine (SMD, 0.24; 95% CI, 0.112 to 0.372), HDL (SMD, 1.01; 95% CI, 0.332 to 1.682), and LDL (SMD, 0.95; 95% CI, 0.337 to 1.555).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				A significant number of patients with ALT (OR, 1.7; 95% CI, 1.29 to 2.46) and AST (OR, 2.19; 95% CI, 1.50 to 3.19) exceeding one times upper limit of the normal range were reported among tofacitinib treated groups. The rate of tofacitinib discontinuation due to adverse events was not significantly different from placebo (SMD, 1.27; 95% CI, 0.949 to 1.700).
Ulcerative Colitis				
Rutgeerts et al.[127] (2005) ACT 1 and ACT 2 Infliximab 5 to 10 mg/kg at weeks 0, 2, 6 and then every 8 weeks vs placebo	DB, MC, PC, RCT Adult patients with endoscopy confirmed active ulcerative colitis (Mayo score 6 to 12) and moderate to severe active disease on sigmoidoscopy despite concurrent treatment with corticosteroids alone or in combination with azathioprine or mercaptopurine (ACT 1) or despite concurrent treatment with corticosteroids alone or mercaptopurine and medications containing 5-aminosalicylates (ACT 2)	N=364 (ACT 1) N=364 (ACT 2) 30 weeks (ACT 2) 54 weeks (ACT1)	Primary: Clinical response at week eight Secondary: Clinical response or clinical remission with discontinuation of corticosteroids at week 30 (ACT 1 and ACT 2) and week 54 (ACT 1), clinical remission and mucosal healing at weeks eight and 30 (ACT 1 and ACT 2) and week 54 (ACT 1), and clinical response at week eight in patients with a history of corticosteroid refractory disease	Primary: At week eight in ACT 1, the proportion of patients with clinical response was significantly higher in the infliximab 5 and 10 mg/kg groups (69.4 and 61.5%) compared to the placebo group (37.2%; P<0.001 for both). In ACT 2 at week eight, the proportion of patients with clinical response was significantly higher in the infliximab 5 and 10 mg/kg groups (64.5 and 69.2%) compared to the placebo group (29.3%; P<0.001 for both). Secondary: In ACT 1, the proportion of patients with clinical response at week 30 was significantly higher in the infliximab 5 and 10 mg/kg groups (52.1 and 50.8%) compared to the placebo group (29.8%; P<0.001 and P=0.002, respectively). In ACT 2 at week 30, the proportion of patients with clinical response was significantly higher in the infliximab 5 and 10 mg/kg groups (47.1 and 60.0%) compared to the placebo group (26.0%; P<0.001 for both). In ACT 1 at week 54, the clinical response rate was significantly higher in the infliximab 5 and 10 mg/kg groups compared to the placebo group (45.5 and 44.3 vs 19.8%; P<0.001 for both). In ACT 1, the proportion of patients with clinical remission at week eight was significantly higher in the infliximab 5 and 10 mg/kg groups (38.8 and 32.0%) compared to the placebo group (14.9%; P<0.001 and P=0.002, respectively). In ACT 2 at week eight, the proportion of patients with clinical remission was significantly higher in the infliximab 5 and 10 mg/kg groups (33.9 and 27.5%) compared to the placebo group (5.7%; P<0.001 for both). In ACT 1, the proportion of patients with clinical remission at week 30 was significantly higher in the infliximab 5 and 10 mg/kg groups (33.9 and 36.9%) compared to the placebo group (15.7%; P=0.001 and P<0.001, respectively). In ACT 2 at week 30, the proportion

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				of patients with clinical remission was significantly higher in the infliximab 5 and 10 mg/kg groups (25.6 and 35.8%) compared to the placebo group (10.6%; P=0.003 and P<0.001, respectively). In ACT 1 at week 54, the clinical remission rate was significantly higher in the infliximab 5 and 10 mg/kg groups compared to the placebo group (34.7 and 34.4 vs 16.5%; P=0.001 for both). In ACT 1 at week eight, the proportion of patients refractory to corticosteroids that had a clinical response was significantly higher in the infliximab 5 and 10 mg/kg groups compared to the placebo group (77.4 and 67.7 vs 35.3%; P<0.001 and P=0.010, respectively). In ACT 2 at week eight when compared to the placebo group (37.5%), the proportion of patients refractory to corticosteroids that had a clinical response was significantly higher in the infliximab 10 mg/kg (65.5%; P=0.011), but not 5 mg/kg group (63.3%; P=0.053). In ACT 1, the proportion of patients with mucosal healing at week eight was significantly higher in the infliximab 5 and 10 mg/kg groups (62.0 and 59.0%) compared to the placebo group (33.9%; P<0.001 for both). In ACT 2 at week eight, the proportion of patients with mucosal healing was significantly higher in the infliximab 5 and 10 mg/kg groups (60.3 and 61.7%) compared to the placebo group (30.9%; P<0.001 for both). In ACT 1, the proportion of patients with mucosal healing at week 30 was significantly higher in the infliximab 5 and 10 mg/kg groups (50.4 and 49.2%) compared to the placebo group (24.8; P<0.001 for both). In ACT 2 at week 30, the proportion of patients with mucosal healing was significantly higher in the infliximab 5 and 10 mg/kg groups (46.3 and 56.7%) compared to the placebo group (30.1%; P=0.009 and P<0.001, respectively). In ACT 1 at week 54, the mucosal healing rate was significantly higher in the infliximab 5 and 10 mg/kg groups compared to the placebo group (45.5 and 46.7 vs 18.2%; P=0.001 for both).
Hyams et al.[128] (2011) (abstract) Infliximab 5 mg/kg at weeks 0, 2 and 6	MC, OL, R Patients 6 to 17 years of age with active ulcerative colitis (Mayo score	N=60 54 weeks	Primary: Clinical response at week eight (decrease from baseline in Mayo score ≥30% and	Primary: At week eight, 73.3% of patients had a clinical response with infliximab (95% CI, 62.1 to 84.5). Clinical remission by Mayo score was achieved in 33.3% of patients. At week 54, there was a greater proportion of patients achieving clinical

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
then 5 mg/kg every 8 weeks through week 46 vs infliximab 5 mg/kg at weeks 0, 2 and 6 then 5 mg/kg every 12 weeks through week 42	6 to 12, including endoscopic subscore ≥2) who failed to respond to or tolerate treatment with mercaptopurine, azathioprine, corticosteroids, and/or 5-aminosalicylates		≥3 points, with a decrease in rectal bleeding subscore of 0/1) compared to baseline Secondary: Not reported	remission with infliximab 5 mg/kg every eight weeks compared to infliximab 5 mg/kg every 12 weeks; though, this difference was not significant (P=0.146). Secondary: Not reported
Reinisch et al.[129] (2011) Adalimumab 160 mg at week 0, 80 mg at week 2, 40 mg at weeks 4 and 6 (ADA 160/80 group) vs Adalimumab 80 mg at week 0, 40 mg at weeks 2, 4 and 6 (ADA 80/40 group) vs placebo	DB, MC, PC, RCT Adult patients with moderate to severe active ulcerative colitis, (Mayo score of 6 to 12 with an endoscopy subscore of 2–3) who failed concurrent and stable treatment with oral corticosteroids and/or immunomodulators	N=390 8 weeks	Primary: Proportion of patients in remission (Mayo score ≤2 and no subscore >1) compared to baseline Secondary: Proportion of patients with a clinical response (decrease in Mayo Score ≥3 points and ≥30% from baseline plus decrease in rectal bleeding subscore ≥1 or an absolute rectal bleeding subscore of 0 or 1); proportion of patients with mucosal healing (endoscopy	Primary: At week eight, 18.5% of patients in the ADA 160/80 group (P=0.031 vs placebo) and 10.0% in the ADA 80/40 group (P=0.833 vs placebo) were in remission compared to placebo (9.2%). Secondary: At week eight, 54.6% of patients in the ADA 160/80 group (P vs placebo not reported), 51.5% in the ADA 80/40 group (P vs placebo not reported) and 44.6% in the placebo group had a clinical response. At week eight, 46.9% of patients in the ADA 160/80 group (P vs placebo not reported), 37.7% in the ADA 80/40 group (P vs placebo not reported) and 41.5% in the placebo group had mucosal healing. At week eight, 77.7% of patients in the ADA 160/80 group (P=0.038 vs placebo), 70.0% in the ADA 80/40 group (P vs placebo not reported) and 66.2% in the placebo group had a rectal bleeding subscore of ≤ 1. At week eight, 60.0% of patients in the ADA 160/80 group (P=0.035 vs placebo), 53.8% in the ADA 80/40 group (P vs placebo not reported) and 46.9% in the placebo group had a PGA subscore of ≤ 1 At week eight, 48.5% of patients in the ADA 160/80 group (P vs placebo not reported), 36.2% in the ADA 80/40 group (P vs placebo not reported) and 37.7% in the placebo group had a stool frequency subscore of ≤ 1

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			subscore of 0 or 1); proportion of patients with rectal bleeding subscore ≤1, PGA subscore ≤1, or stool frequency subscore ≤1	
Sandborn et al.[130] (2012) Adalimumab 160 mg at week 0, 80 mg at week 2, then 40 mg every other week vs placebo	DB, MC, PC, RCT Adult patients with moderate to severe active ulcerative colitis >3 months, (Mayo score of 6 to 12 with an endoscopy subscore >2) despite concurrent treatment with oral corticosteroids and/or azathioprine or 6-mercaptopurine.	N=494 52 weeks	Primary: Proportion of patients in remission (Mayo score ≤2 and no subscore >1) at week 8 and 52 Secondary: Proportion of patients in remission at week 8 and 52; proportion of patients with a clinical response (decrease in Mayo Score ≥3 points and ≥30% from baseline plus decrease in rectal bleeding subscore ≥1 or an absolute rectal bleeding subscore of 0 or 1); proportion of patients with mucosal healing (endoscopy	Primary: At week 8, 16.5% of patients in the adalimumab group were in remission compared to placebo (9.3%; P=0.019; 95% CI, 1.2 to 12.9). At week 52, 17.3% of patients in the adalimumab group were in remission compared to placebo (8.5%; P=0.004; 95% CI, 2.8 to 14.5). Secondary: At week 8 and 52, 8.5% of patients in the adalimumab group (P=0.47 vs placebo) and 4.1% in the placebo group were in sustained remission. At week 8, 50.4% of patients in the adalimumab group (P<0.001 vs placebo) and 34.6% in the placebo group had a clinical response. At week 52, 30.2% of patients in the adalimumab group and 18.3% in the placebo group had a clinical response. (P=0.002). At week 8 and 52, 23.8% of patients in the adalimumab group (P<0.001 vs placebo) and 12.2% in the placebo group were in sustained remission. Mucosal healing was achieved at week 8 in 41.1% of patients in the adalimumab group and 31.7% of patients receiving placebo (P=0.032). At week 52, 25% of patients in the adalimumab group and 15.4% of patients receiving placebo (P=0.009) had mucosal healing. Mucosal healing at week 8 and 52, 18.5% of patients in the adalimumab group (P<0.013 vs placebo) and 10.6% in the placebo group. At week 8, 46.0% of patients in the adalimumab group (P=0.028 vs placebo) and 37.4% in the placebo group had a PGA subscore of ≤ 1. At week 8, 37.9% of patients in the adalimumab group (P=0.058 vs

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			subscore of 0 or 1); proportion of patients who discontinued corticosteroid; proportion of patients with rectal bleeding subscore ≤1, PGA subscore ≤1, or stool frequency subscore ≤1	placebo) and 28.5% in the placebo group had a stool frequency subscore of ≤ 1. At week 8, 70.2% of patients in the adalimumab group (P=0.006 vs placebo) and 58.1% in the placebo group had a rectal bleeding subscore of ≤ 1. Proportion of patients that discontinued corticosteroid use before week 52 and achieved remission at week 52 was13.3% of patients in the adalimumab group (P=0.35 vs placebo) and 5.7% in the placebo group. Proportion of patients that for ≥90 days before week 52 and achieved remission at week 52 was 13.3% of patients in the adalimumab group (P=0.35 vs placebo) and 5.7% in the placebo group.
Sandborn et al.[131] (2013) PURSUIT-SC Phase 2 (dose-finding): Golimumab 400 mg subcutaneously at week 0 and 200 mg subcutaneously at week 2 (400 mg/200 mg) vs golimumab 200 mg subcutaneously at week 0 and 100 mg subcutaneously at week 2 (200 mg/100 mg) vs	2 DB, MC, PC, RCT Patients ≥18 years of age with moderate to severe active ulcerative colitis (Mayo score of 6 to 12 with an endoscopy subscore ≥2) despite treatment with ≥1 conventional therapy (oral mesalamine, oral corticosteroids, azathioprine or 6-mercaptopurine) or corticosteroid dependent	Phase 2 N=169 Phase 3 N=774 6 weeks	Primary: Phase 2: Change in Mayo score from baseline to week six Phase 3: Clinical response at week six defined as a decrease from baseline in the Mayo score ≥30% and ≥3 points with either a rectal bleeding subscore of 0 to 1 or a decrease from baseline in the rectal bleeding subscore ≥1 Secondary: Phase 2: Not	Primary: In phase 2, median changes from baseline in the Mayo score were -3.0, -2.0, and -3.0 in the 100 mg/50 mg, 200 mg/100 mg, and 400 mg/200 mg golimumab treatment groups, respectively, compared to -0.1 in the placebo group (P=0.038, P=0.332 and P=0.038, respectively). In phase 3, the proportion of patients with clinical response at week six was greater for patients treated with golimumab 200 mg/100 mg and 400 mg/200 mg compared to placebo (51.0 and 54.9 vs 30.3%; P≤0.0001 for both comparisons). Secondary: In phase 3, the proportion of patients in clinical remission at week six was greater for patients treated with golimumab 200 mg/100 mg and 400 mg/200 mg compared to placebo (17.8 and 17.9 vs 6.4%; P≤0.0001 for both comparisons). In phase 3, the proportion of patients achieving mucosal healing at week six was greater for patients treated with golimumab 200 mg/100 mg and 400 mg/200 mg compared to placebo (42.3 and 45.1 vs 28.7%; P=0.0014 and P≤0.0001, respectively). In phase 3, the improvements from baseline in IBDQ score at week six

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
golimumab 100 mg subcutaneously at week 0 and 50 mg subcutaneously at week 2 (100 mg/50 mg) vs placebo Phase 3 (dose-confirming): Golimumab 400 mg subcutaneously at week 0 and 200 mg subcutaneously at week 2 (400 mg/200 mg) vs golimumab 200 mg subcutaneously at week 0 and 100 mg subcutaneously at week 2 (200 mg/100 mg) vs placebo Patients were required to maintain			reported Phase 3: Clinical remission defined as Mayo score ≤2 points, with no individual subscore >1, mucosal healing defined as a Mayo endoscopy subscore of 0 or 1, and IBDQ change from baseline, all at week 6	were greater in patients treated with golimumab 200 mg/100 mg and 400 mg/200 mg compared to placebo (mean 27.0±33.72 and 26.9±34.28 vs 14.8±31.25%; P<0.0001 for both comparisons).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
stable doses of concurrent oral aminosalicylates, oral corticosteroids (<40 mg/day), azathioprine, 6-mercaptopurine, and/or MTX.				
Sandborn et al.[132] (2013) PURSUIT-M Golimumab 50 mg SC every four weeks vs golimumab 100 mg SC every four weeks vs placebo Patients were required to maintain stable doses of concurrent oral aminosalicylates, oral corticosteroids (<40 mg/day), azathioprine, 6-mercaptopurine, and/or MTX. After induction, patients in	DB, MC, PC, RCT Patients ≥18 years of age with moderate to severe active ulcerative colitis (Mayo score of 6 to 12 with an endoscopy subscore ≥2) despite treatment with ≥1 conventional therapy (oral mesalamine, oral corticosteroids, azathioprine or 6-mercaptopurine) or corticosteroid dependent who completed PURSUIT-IV or PURSUIT-SC studies	N=464 54 weeks	Primary: Clinical response through week 54 among golimumab-induction responders Secondary: Clinical remission at weeks 30 and 54, mucosal healing at weeks 30 and 54, clinical remission at both weeks 30 and 54 among patients who had clinical remission at baseline, and corticosteroid-free clinical remission at week 54 among patients receiving concomitant corticosteroids at baseline	Primary: The proportion of patients who maintained a clinical response through week 54 was greater for patients treated with golimumab 100 mg and 50 mg compared to placebo (49.7 and 47.0 vs 31.2%; P<0.001 and P=0.010, respectively). Secondary: The proportion of patients in clinical remission at both weeks 30 and 54 was greater for patients treated with golimumab 100 mg and 50 mg compared to placebo (27.8 and 23.2 vs 15.6%; P=0.004 and P=0.091, respectively); however, the difference was only statistically significant for golimumab 100 mg treatment group. The proportion of patients with mucosal healing at both weeks 30 and 54 was significantly greater for patients receiving golimumab 100 mg compared to placebo (42.4 vs 26.6%; P=0.002). The mucosal healing rate for patients receiving golimumab 50 mg was 41.7% (P value not reported). Greater proportions of patients who received golimumab 100 mg or 50 mg maintained clinical remission compared to placebo (40.4 and 36.5 vs 24.1%; P=0.073 and P=0.365, respectively); however, the differences were not statistically significant. Greater proportions of patients who received golimumab 100 mg or 50 mg were in corticosteroid-free clinical remission at week 54 compared to placebo (22.9 and 27.8 vs 18.4%; P=0.464 and P=0.299, respectively) ; however, the differences were not statistically significant.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
clinical response and receiving concomitant corticosteroids at baseline were required to taper corticosteroids (for dose of >20 mg/day prednisone or equivalent: taper daily dose by 5 mg/week; for dose of ≤20 mg/day prednisone or equivalent: taper daily dose by 2.5 mg/week) beginning at baseline.				
Neonatal-Onset Multisystem Inflammatory Disease				
Sibley et al.[133] (2012) Anakinra 1 to 5 mg/kg/day	OL Patients with NOMID with at least 2 of the following clinical manifestations: urticaria-like rash, CNS involvement (papilledema, cerebrospinal fluid CSF pleocytosis, or sensorineural hearing loss), or epiphyseal and/or patellar overgrowth on radiographs	N=43 60 months	Primary: Sustained improvements in diary scores, parent's/patient's and physician's global scores of disease activity, CHAQ scores, parent's/patient's pain scores, and inflammatory markers (CRP level, ESR, and SAA) Secondary: Reduction or	Primary: Scores for daily diaries, parent's and physician's global assessment of disease activity, parent's assessment of pain, and C-HAQ decreased significantly from baseline to 36 months (P=0.0016 for C-HAQ and P<0.001 for all other assessments). These parameters did not show significant change from month 36 to month 60. Significant decreases in inflammatory markers (CRP level, ESR, and SAA) were observed from baseline to 12 months and from baseline to 36 months (all P<0.001). These parameters did not show significant change from month 36 to month 60. Secondary: CNS inflammation, including CSF leukocyte count and elevated opening pressure, decreased significantly at the study end points 36 and 60 months compared to baseline (P=0.0026 and P=0.0076, respectively, for CSF WBC count and P=0.0012 and P<0.001, respectively, for opening pressure). These parameters did not show significant change from month

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			elimination CNS organ inflammation and damage and the absence of leptomeningeal enhancement on MRI, and in the eyes as the absence of eye inflammation on examination. Other endpoints include improvements in hearing, vision, bone lesions and growth, and safety.	36 to month 60. The number of patients with leptomeningeal enhancement decreased to three of 26 patients at 36 months (P=0.039) and one of 20 patients at 60 months (P=0.016). Improvement in hearing occurred in 30% of ears, and progression of hearing loss was halted in the majority of the patients. Visual acuity and peripheral vision improved or stabilized in most patients over five years. One patient had worsening of visual acuity, and two other patients had worsening of peripheral vision in the absence of clinically detectable intraocular inflammation. (Note-All three of these patients had severely atrophic nerves at baseline). Bony overgrowth was present in 10 of 26 patients, and during the study period the volume of the bony lesions increased significantly; however, no new bone lesions developed in patients while they were receiving anakinra therapy. No dose-limiting toxicity was observed during the study. Upper respiratory infections (58 to 62%), rash (27 to 32%), malaise (17 to 19%) gastroenteritis (11 to 12%), and urinary tract infections (4 to 12%), nausea/vomiting (10 to 11%) injection site reactions (1 to 10%) were frequently observed.

*Not currently available in the United States.
Study abbreviations: CI=confidence interval, DB=double-blind, DD=double dummy, ES=extension study, HR=hazard ratio, MA=meta-analysis, MC=multicenter, NNH=number needed to harm, NNT=number needed to treat, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel group, PRO=prospective, R=randomized, RCT=randomized controlled trial, RD=risk difference, RR=relative risk, SD=standard deviation, SR=systematic review, WMD=weighted mean difference
Miscellaneous abbreviations: ACR=American College of Rheumatology, ACR-N=numeric index of the ACR response, ACR pedi 30=American College of Rheumatology pediatric 30% improvement criteria, ALT=alanine transaminase, AS=ankylosing spondylitis, ASAS=Assessment of Spondyloarthritis International Society criteria, AST=aspartate aminotransferase, AUC=area under the curve, BASDAI=Bath Ankylosing Spondylitis Disease Activity Index, BASFI=Bath Ankylosing Spondylitis Functional Index, BASMI=Bath Ankylosing Spondylitis Metrology Index, BSA=body surface area, CCP=cyclic citrullinated protein CD=Crohn's disease, CDAI=Crohn's disease activity index, CDAI-100=Crohn's disease activity index decrease of ≥100 points from baseline, CHAQ=Childhood Health Assessment Questionnaire, CNS=central nervous system, COX=cyclooxygenase, CR-70=clinical remission, CR-100=clinical remission 100, CRP=C-reactive protein, CSF=cerebrospinal fluid, CT=computed tomography, DAS 28=Disease Activity Score in 28 joints, DLQI=Dermatology Life Quality Index, DMARD=disease-modifying antirheumatic drug, DOI=definition of improvement, ECL=electrogenerated chemiluminescence, EIM=extra-intestinal manifestations, ELISA=enzyme-linked immunosorbent assay, ESR=erythrocyte sedimentation rate, EULAR=European League Against Rheumatism Response criteria, FACIT-F=Functional Assessment of Chronic Illness Therapy-Fatigue, HAQ=health assessment questionnaire, HAQ-DI=health assessment questionnaire–disability index, HBI=Harvey-Bradshaw index, HCQ=hydroxychloroquine, HDL=high density lipoprotein, IBDQ=inflammatory bowel disease questionnaire, IOIBD=international organization for the study of inflammatory bowel disease, ITT=intent to treat, JIA=juvenile idiopathic arthritis, JRA=juvenile rheumatoid arthritis, JSN=joint space narrowing, LDL=low density lipoprotein, MCR=major clinical response, MRE=magnetic resonance enterography, MRI=magnetic resonance imaging, mTSS=modified Total Sharp Scores, MTX=methotrexate, NOMID=neonatal-onset multisystem inflammatory disease,

NSAIDs=nonsteroidal anti-inflammatory drugs, PASI=psoriasis area and severity index, PCDAI=pediatric Crohn's disease activity index, PGA=physician global assessment, PsA=psoriatic arthritis, PsARC=psoriatic arthritis response criteria, PSSI=psoriasis scalp severity index, SIAQ=Self-Injection Assessment Questionnaire, RA=rheumatic arthritis, RF=rheumatoid factor, SF-36=short form-36, SF-36 MCS=short form-36-mental component, SF-36 PCS=short form-36-physical component, SAA=serum amyloid A, SMD=standardized mean differences, SSZ=sulfasalazine, TB=tuberculosis, TNF=tumor necrosis factor, VAS=visual analog scale

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 14. Relative Cost of the Disease-Modifying Antirheumatic Agents

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Abatacept	injection	Orencia®	$$$$$	N/A
Adalimumab	injection	Humira®	$$$$$	N/A
Anakinra	injection	Kineret®	$$$$$	N/A
Apremilast	tablet	Otezla®	$$$$$	N/A
Certolizumab pegol	injection	Cimzia®	$$$$$	N/A
Etanercept	injection	Enbrel®	$$$$$	N/A
Golimumab	injection	Simponi®, Simponi Aria®	$$$$$	N/A
Infliximab	injection	Remicade®	$$$$$	N/A
Leflunomide	tablet	Arava®*	$$$$	$$$$
Tocilizumab	injection	Actemra®	$$$$$	N/A
Tofacitinib	tablet	Xeljanz®	$$$$$	N/A

*Generic is available in at least one dosage form or strength.
N/A=Not available

X. Conclusions

The disease-modifying antirheumatic drugs (DMARDs) are used for a variety of inflammatory and immunologic conditions which include: rheumatoid arthritis, neonatal-onset multisystem inflammatory disease, psoriatic

arthritis, plaque psoriasis, juvenile idiopathic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, and hidradenitis suppurativa.[1-13] Leflunomide is the only product available in a generic formulation.

Current clinical guidelines support the use of the DMARDs with respect to their Food and Drug Administration (FDA)-approved indications, particularly in conditions where patients were unresponsive or refractory to traditional treatments, which usually include nonsteroidal anti-inflammatory drugs (NSAIDs) and/or methotrexate depending on the disease state.[17-36] As more recent guidelines are published, the recommendations for use tumor necrosis factor (TNF)-α inhibitors earlier in therapy is becoming a more common occurance.[26,27,30] The adverse event profiles are similar across the TNF-α inhibitors; however, routes of administration and dosing frequency may vary. In general, no one TNF-α inhibitor is preferred over another.[17-36] Leflunomide is FDA-approved for use in rheumatoid arthritis. Guidelines for rheumatoid arthritis, psoriatic arthritis, and juvenile idiopathic arthritis recommend leflunomide as an alternative treatment to methotrexate.[13,23-25,32] Clinical trials directly comparing methotrexate and leflunomide have shown mixed results.[97,99,101,102]

Humira® (adalimumab) was granted orphan drug designation for the treatment of moderate to severe hidradenitis suppurativa (Hurley Stage II and Hurley Stage III disease), a chronic inflammatory skin disease which affects fewer than 200,000 patients in the United States.[2,36] Current literature supports topical or oral antibiotics, intralesional steroids, retinoids, zinc, anti-androgens or laser surgery for mild (stage I) disease. Stage II disease should generally be treated similar to Stage I with the addition of rifampin plus clindamycin, dapsone, and prednisone. Stage III disease is treated with similar measures as Stages I and II; however, the use of anti-inflammatory agents is recommended, with TNF-α inhibitors, adalimumab and infliximab, having the most positive data.[36]

Most research with these agents is for rheumatoid arthritis. In these trials, the DMARD was compared directly to placebo or methotrexate, either as monotherapy or in combination with methotrexate. Consistently, DMARDs have shown greater improvement in symptoms over the comparator.[82-126] To date, the majority of trials conducted have been placebo-controlled, with very few trials directly comparing two DMARDs head-to-head for any of the FDA-approved indications.[38-134] In those that have been conducted, most have shown comparable results.[117-119] In one trial in rheumatoid arthritis patients who were either intolerant or were not candidates for methotrexate treatment, significantly greater improvements were observed in patients treated with tocilizumab compared to adalimumab.[117] In another trial in rheumatoid arthritis patients with inadequate response to methotrexate, similar responses were observed in patients treated with abatacept and adalimumab.[118,119] The inclusion of adalimumab arm in one phase 3 trial of tofacitinib allowed establishing relative safety and efficacy of tofacitinib; however, formal noninferiority comparison was not performed.[120] The few direct head-to-head trials available prevent clearly determining superiority of one agent over another. Recently anakinra was FDA-approved for neonatal-onset multisystem inflammatory disease, the only agent FDA-approved for this indication. The approval was based on the results of a single trial demonstrating sustained improvements in affected patients over 60 months.[133]

There is insufficient evidence to support that one brand disease-modifying antirheumatic agent is safer or more efficacious than another within its FDA-approved indication(s). The drugs in this AHFS class are used in a specific patient population. Because these agents have narrow indications with limited usage and serious adverse events, these agents should be managed through the medical justification portion of the prior authorization process.

Therefore, all disease-modifying antirheumatic agents within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand disease-modifying antirheumatic agent is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

1. Orencia® [package insert]. Princeton (NJ): Bristol-Myers Squibb; 2015 Jun.
2. Humira® [package insert]. North Chicago (IL): Abbvie Inc; 2015 Sep.
3. Kineret® [package insert]. Stockholm (Sweden): Swedish Orphan Biovitrum AB; 2013 Nov.
4. Otezla® [package insert]. Summit (NJ): Celgene Corporation; 2015 Dec.
5. Cimzia® [package insert]. Smyrna (GA): UCB, Inc.; 2013 Oct.
6. Enbrel® [package insert]. Thousand Oaks (CA): Immunex Corporation; 2015 Mar.
7. Simponi® [package insert]. Horsham (PA): Janssen Biotech, Inc.; 2015 Jun.
8. Simponi Aria® [package insert]. Horsham (PA): Janssen Biotech, Inc.; 2015 Mar.
9. Remicade® [package insert]. Horsham (PA): Janssen Biotech, Inc; 2015 Jan.
10. Arava® [package insert]. Bridgewater (NJ): sanofi-aventis U.S. LLC; 2015 Aug.
11. Actemra® [package insert]. South San Francisco (CA): Genetech, Inc.; 2014 Nov.
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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
New Drug Pharmacotherapy Review of Kitabis®
Aminoglycosides: AHFS Class 081202
May 11, 2016

I. Overview

The parenteral aminoglycosides are used empirically as monotherapy or in combination with other antibacterial agents to treat serious infections, such as septicemia, respiratory tract infections, and complicated urinary tract infections.[1-2] Once susceptibility tests are available and a pathogen has been identified, the aminoglycosides are often discontinued so that treatment with a less toxic agent can be initiated.[3] Tobramycin inhalation solution and inhalation powder are approved to improve respiratory symptoms in cystic fibrosis patients colonized with *Pseudomonas aeruginosa*.[4-7]

The antibacterial properties of aminoglycosides result from both the inhibition of bacterial protein synthesis and the creation of fissures in the outer membrane of the bacterial cell membrane. Irreversible binding to bacterial ribosomes and disruption of the cell membrane results in leakage of intracellular contents and accounts for most of the bactericidal activity.[3,8,9] The aminoglycosides display concentration-dependent bactericidal activity and a prolonged post-antibiotic effect. They act synergistically when administered with other antibacterial agents.[9] Resistance to the aminoglycosides has been reported infrequently.

Currently, there are five inhaled tobramycin agents available on the market. TOBI® (tobramycin solution for inhalation) was the first available agent in 1997, followed by Bethkis® (tobramycin solution for inhalation) in early 2013, TOBI® Podhaler (tobramycin inhalation powder) in June 2013, generic tobramycin inhalation solution in November 2013, and lastly a new preparation, Kitabis® Pak (tobramycin solution for inhalation), in December 2014. All of these products have the same FDA-approved indication of management of cystic fibrosis adults and pediatric patients six years of age and older with *Pseudomonas aeruginosa*.[4-7] The most recently approved agent, Kitabis® Pak (tobramycin solution for inhalation), was FDA approved using the same clinical trial data as TOBI® (tobramycin solution for inhalation).[4] This is the only agent that co-packages the generic tobramycin inhalation solution with a reusable nebulizer (PARI LC Plus™).[10] There are several minor differences between all of these agents, the most notable being that the TOBI® Podhaler (tobramycin inhalation powder) does not require a nebulizer and does not need to be stored in a refrigerator. In addition, the time to administer these agents does vary between products from two to seven minutes for the TOBI® Podhaler (tobramycin inhalation powder) and approximately 15 minutes for the remainder of the tobramycin agents.[2,4-7]

The tobramycin products included in this review are listed in Table 1. Kitabis® is not available in a generic formulation.

Table 1. Products Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Tobramycin	inhalation solution	Kitabis®	none

PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current clinical guidelines are summarized in Table 2.

Table 2. Treatment Guidelines Using Tobramycin Inhalation Solution

Clinical Guideline	Recommendation(s)
Cystic Fibrosis Foundation: **Cystic Fibrosis Pulmonary Guidelines (2013)**[11]	Aerosolized antibiotics • For patients with cystic fibrosis, six years of age and older, who have moderate to severe lung disease with *Pseudomonas aeruginosa* persistently present in cultures of the airways, the chronic use of inhaled tobramycin to improve lung function, improve quality of life, and reduce exacerbations is strongly

Clinical Guideline	Recommendation(s)
	recommended. • For patients with cystic fibrosis, six years of age or older, who have mild lung disease, and with *Pseudomonas aeruginosa* persistently present in cultures of the airways, chronic use of inhaled tobramycin to reduce exacerbations is recommended. • For patients with cystic fibrosis, six years of age and older, who have moderate to severe lung disease with *Pseudomonas aeruginosa* persistently present in cultures of the airways, the chronic use of inhaled aztreonam to improve lung function and quality of life is strongly recommended. • For patients with cystic fibrosis, six years of age or older, who have mild lung disease, and with *Pseudomonas aeruginosa* persistently present in cultures of the airways, chronic use of inhaled aztreonam to improve lung function and quality of life is recommended. • For patients with cystic fibrosis, six years of age or older, with *Pseudomonas aeruginosa* persistently present in cultures of the airways, there is insufficient evidence to recommend for or against routinely providing other chronically inhaled antibiotics (i.e., carbenicillin, ceftazidime, colistin, gentamicin) to improve lung function, improve quality of life, or reduce exacerbations. <u>Anti-inflammatory agents</u> • For patients with cystic fibrosis, six years of age or older, without asthma or allergic bronchopulmonary aspergillosis, routine use of inhaled corticosteroids to improve lung function, quality of life and reduce pulmonary exacerbations is not recommended. • For patients with cystic fibrosis, six years of age or older, without asthma or allergic bronchopulmonary aspergillosis, chronic use of oral corticosteroids to improve lung function, quality of life or reduce exacerbations is not recommended. • For patients with cystic fibrosis, between six and 17 years of age, with an forced expiratory volume in one second greater than or equal to 60% predicted, the chronic use of oral ibuprofen, at a peak plasma concentration of 50 to 100 µg/mL, to slow the loss of lung function is recommended. • For patients with cystic fibrosis, 18 years of age and older, the evidence is insufficient to recommend for or against the chronic use of oral ibuprofen to slow the loss of lung function or reduce exacerbations. • For patients with cystic fibrosis, six years of age or older, there is insufficient evidence to recommend for or against routinely providing the chronic use of leukotriene modifiers to improve lung function, quality of life, or reduce exacerbations. <u>Antipseudomonal antibiotics</u> • For patients with cystic fibrosis, six years of age and older, with *Pseudomonas aeruginosa* persistently present in cultures of the airways, there is insufficient evidence to recommend for or against routinely providing the chronic use of oral antipseudomonal antibiotics to improve lung function, quality of life, or reduce exacerbations. <u>Antistaphylococcal antibiotics</u> • For patients with cystic fibrosis, six years of age or older, with *Staphylococcus aureus* persistently present in cultures of the airways, there is insufficient evidence to recommend for or against the chronic use of oral antistaphylococcal antibiotics to improve lung function and quality of life or reduce exacerbations. • For patients with cystic fibrosis, prophylactic use of oral antistaphylococcal antibiotics to improve lung function and quality of life or to reduce exacerbations is not recommended.

Clinical Guideline	Recommendation(s)
	Bronchodilators • For patients with cystic fibrosis, six years of age or older, there is insufficient evidence to recommend for or against chronic use of inhaled β_2-adrenergic receptor agonists to improve lung function and quality of life or reduce exacerbations. • For patients with cystic fibrosis, six years of age or older, there is insufficient evidence to recommend for or against routinely providing the chronic use of inhaled anticholinergic bronchodilators to improve lung function and quality of life or reduce exacerbations. • For patients with cystic fibrosis, six years of age or older, there is insufficient evidence to recommend for or against routinely providing chronic use of inhaled or oral N-acetylcysteine or inhaled glutathione to improve lung function, quality of life or reduce exacerbations. Hypertonic saline • For patients with cystic fibrosis, six years of age or older, chronic use of inhaled hypertonic saline to improve lung function, improve quality of life, and to reduce exacerbations is recommended. Ivacaftor • For patients with cystic fibrosis, six years of age or older, with at least one G551D CFTR mutation, the chronic use of ivacaftor to improve lung function, quality of life, and to reduce exacerbations is strongly recommended. Macrolide antibiotics • For patients with cystic fibrosis, six years of age or older, and with *Pseudomonas aeruginosa* persistently present in cultures of the airways, chronic use of azithromycin to improve lung function and to reduce exacerbations is recommended. • For patients with cystic fibrosis, six years of age or older, without *Pseudomonas aeruginosa* persistently present in cultures of the airways, chronic use of azithromycin to reduce exacerbations is recommended. Recombinant human DNase • For patients with cystic fibrosis, six years of age or older, with moderate to severe lung disease, chronic use of dornase alfa to improve lung function, improve quality of life, and reduce exacerbations is strongly recommended. • For patients with cystic fibrosis, six years of age or older, and asymptomatic or with mild lung disease, chronic use of dornase alfa to improve lung function and reduce exacerbations is recommended.

III. Indications

The Food and Drug Administration (FDA)-approved indications for tobramycin inhalation solution are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for Tobramycin Inhalation Solution[1]

Indication	Kitabis®
Management of cystic fibrosis in patients six years of age and older with *Pseudomonas aeruginosa**	✔

*Safety and efficacy have not been demonstrated in patients under the age of 6 years, patients with FEV_1 <25% or >75% predicted, or patients colonized with *Burkholderia cepacia*.

IV. Pharmacokinetics

The pharmacokinetic parameters of tobramycin inhalation solution are listed in Table 4.

Table 4. Pharmacokinetic Parameters of Kitabis®[2]

Generic Name(s)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Tobramycin	0 to 30	Not reported	Renal (60 to 85)	1.6 to 3.0

V. Drug Interactions

Major drug interactions with the aminoglycosides are listed in Table 5.

Table 5. Major Drug Interactions with the Aminoglycosides[2]

Generic Name(s)	Interaction	Mechanism
Aminoglycosides (tobramycin)	Nondepolarizing muscle relaxants	Aminoglycosides may increase the neuromuscular blocking effects of non-depolarizing muscle relaxants. Prolonged respiratory depression and apnea may occur.
Aminoglycosides (tobramycin)	Diuretics	Some diuretics can enhance aminoglycoside toxicity by altering aminoglycoside concentrations in serum and tissue.
Aminoglycosides (tobramycin)	Succinylcholine	Neuromuscular blocking effects of succinylcholine may be increased by aminoglycosides. Prolonged respiratory depression with extended periods of apnea may occur.

VI. Adverse Drug Events

The most common adverse drug events reported with tobramycin inhalation solution are listed in Table 6.

Table 6. Adverse Drug Events (%) Reported with Tobramycin Inhalation Solution[1,4]

Adverse Event	Kitabis®
Cough Increased	46.1
Dyspnea	33.7
Hemoptysis	19.4
Laryngitis	≤5
Lung Function Decreased	16.3
Myalgia	≤5
Pharyngitis	38.0
Rash	5.4
Sputum Increased	37.6
Taste Perversion	6.6
Tinnitus	3
Voice Alteration	12.8

✔ Percent not specified.
- Event not reported.

VII. Dosing and Administration

The usual dosing regimens for tobramycin inhalation solution are listed in Table 7.

Table 7. Usual Dosing Regimens for Tobramycin Inhalation Solution[1]

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Tobramycin	Management of cystic fibrosis patients with *Pseudomonas aeruginosa*: Inhalation solution: 300 mg administered twice daily for 28 days; after 28 days of therapy, patients should stop tobramycin therapy for the next 28 days, and then resume therapy for the next "28 days on/28 days off" cycle	Management of cystic fibrosis patients with *Pseudomonas aeruginosa* in patients ≥6 years of age: Inhalation solution: 300 mg administered twice daily for 28 days; after 28 days of therapy, patients should stop tobramycin therapy for the next 28 days, and then resume therapy for the next "28 days on/28 days off" cycle	Inhalation solution: 300 mg/5 mL

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of tobramycin inhalation solution are summarized in Table 8. No new clinical studies were conducted for the approval of Kitabis® Pak.

Table 8. Comparative Clinical Trials with Tobramycin Inhalation Solution

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ramsey et al.[12] (1999) Tobramycin inhalation solution 300 mg BID for three cycles (each cycle consisting of 28 days during which the medication was administered and 28 days during which it was not administered) vs placebo	DB, MC, PC Patients at least six years of age with cystic fibrosis, a respiratory tract culture positive for *Pseudomonas aeruginosa*, ability to perform pulmonary function tests, and FEV_1 25 to 75% of predicted value	N=520 24 weeks	Primary: FEV_1 and the density of *Pseudomonas aeruginosa* in sputum at 20 weeks Secondary: Hospitalization and treatment with IV antipseudomonal antibiotics	Primary: At the end of 20 weeks, patients treated with tobramycin inhalation solution had an average 10% increase in FEV_1, as compared to 2% decline for the patients receiving placebo (P<0.001). At the end of 20 weeks, patients treated with tobramycin inhalation solution had an average reduction of 0.8 log_{10} colony forming unit per gram of sputum, as compared to the value at 0 weeks, whereas the density in the placebo group had increased by 0.3 log_{10} colony forming unit per gram (P<0.001). Secondary: Patients receiving tobramycin were 26% less likely to be hospitalized and 36% less likely to require IV antipseudomonal antibiotics.
Murphy et al.[13] (2004) Tobramycin inhalation solution 300 mg BID for seven cycles (each cycle consisting of 28 days during which the medication was administered and	MC, OL, PG, RCT Patients six to 10 years of age with cystic fibrosis and chronic *Pseudomonas aeruginosa*, FEV_1 $\geq$70% and $\leq$110% of predicted value; patients 11 to 15 years of age with	N=184 56 weeks	Primary: Rate of lung function decline, FEV_1, rates of hospitalization, and concomitant antibiotic use Secondary: Not reported	Primary: Patients treated with tobramycin inhalation solution trended toward improvement in percent predicted FEV_1 over control group at weeks 20 and 32, but the improvement was not statistically significant. Significantly fewer tobramycin inhalation solution patients were hospitalized for worsening of respiratory symptoms (11.0 vs 25.6%; P<0.011), and fewer tobramycin inhalation solution patients were hospitalized overall (16.5 vs 27.8%; P<0.065). Fewer tobramycin inhalation solution patients received antibiotics other than the study drug (78.0 vs 95.6%), and significantly fewer patients

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
28 days during which it was not administered) vs placebo	cystic fibrosis and FEV_1 >70% and <90% of predicted value			received oral antibiotics (76.9 vs 91.1%; P<0.009). Secondary: Not reported
Quittner et al.[14] (2002) Tobramycin inhalation solution 300 mg BID for 28 days for three cycles vs placebo	RETRO Patients greater than six years of age with cystic fibrosis who were infected with *Pseudomonas aeruginosa* and had an FEV_1 25 to 75% of predicted values	N=520 24 weeks	Primary: Improvement in quality of life Secondary: Not reported	Primary: Patients treated with tobramycin inhalation solution were more likely to report improvement in quality of life than those receiving placebo (P<0.005). Secondary: Not reported
Moss et al.[15] (2002) Tobramycin inhalation solution 300 mg BID for 28 days for three cycles vs placebo	OL Patients 13 to 17 years of age with cystic fibrosis who were infected with *Pseudomonas aeruginosa* and had an FEV_1 ≥25 and ≤75% of predicted values	N=128 2 years	Primary: Pulmonary function, *Pseudomonas aeruginosa* colony-forming unit density, incidence of hospitalization and IV antibiotic use, weight gain Secondary: Not reported	Primary: Patients originally randomized to tobramycin inhalation solution and placebo treatments exhibited improvements in FEV_1 percent predicted of 13.5 and 9.4%, respectively. Improvement in pulmonary function was significantly correlated with reduction in *Pseudomonas aeruginosa* colony forming unit density (P=0.0001). The average number of hospitalizations and IV antibiotic courses did not increase over time. Secondary: Not reported
Bowman[16] (2002) Tobramycin	OL Patients at least six years of age with	N=396 48 weeks	Primary: Pulmonary function and antibiotic use	Primary: At the start of the OL study period, the patients who had been receiving tobramycin inhalation solution continued to show mean FEV_1 values that remained above their baseline values. The patients who were crossed over

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
inhalation solution 300 mg BID for nine cycles (each cycle consisting of 28 days during which the study drug was administered and 28 days during which it was not administered)	cystic fibrosis who were infected with *Pseudomonas aeruginosa* and had an FEV_1 ≥25 and ≤75% of predicted values		Secondary: Not reported	from placebo to OL tobramycin inhalation solution had a marked improvement in their pulmonary function. However, mean FEV_1 in the placebo group did not reach the levels seen in patients who had received with tobramycin inhalation solution in the initial, DB phase. By the end of the 12th treatment cycle, the mean FEV_1 in the tobramycin inhalation solution-only group was 4.7% above the baseline value at the start of the study. Mean FEV_1 at endpoint in patients in the placebo-tobramycin inhalation solution XO group was slightly less than the baseline level, but was still greater than it had been at the end of the placebo phase (week 24). In addition to improvement in the FEV_1, patients who were treated with tobramycin inhalation solution had a significant reduction in the number of courses of IV anti-pseudomonal antibiotic use per year. The patients receiving placebo required 1.9 courses of anti-pseudomonal antibiotics per patient per year, while the patients receiving tobramycin inhalation solution (both the randomized and the OL portions of the trial, regardless of initial study group assignment) required approximately 1.25 courses per patient per year. A subgroup analysis was performed evaluating the change in FEV_1 for patients aged 13 to 17 years. The adolescent patients treated with tobramycin inhalation solution from the beginning had a marked improvement of approximately 15% in their FEV_1 over the first three cycles of treatment. This contrasts with an approximately 8% decline in FEV_1 for the adolescent patients treated with placebo. The patients who continued tobramycin inhalation solution maintained their level of improvement over the next nine cycles, ending with an FEV_1 that was still an average of 14.3% above their week 0 baseline after 12 cycles of tobramycin inhalation solution. The group of adolescent patients who crossed over from the conventional therapy with placebo aerosol to receive tobramycin inhalation solution in the OL phase showed a marked improvement during subsequent cycles. This degree of improvement was similar to that seen in the group who started on tobramycin inhalation solution in the DB study. The mean FEV_1

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				values of this XO group after nine cycles (72 weeks) of tobramycin inhalation solution were maintained at levels above those at the start of the OL part of the study. Secondary: Not reported
Briesacher et al.[17] (2011) Tobramycin inhalation solution	RETRO Patients with cystic fibrosis with at least one claim for tobramycin inhalation solution	N=804 Variable duration	Primary: Adherence and hospitalization Secondary: Not reported	Primary: Chronic use of tobramycin inhalation solution was low in patients with *Pseudomonas aeruginosa* as only 6% were dispensed four or more cycles per year. Tobramycin inhalation solution usage was similar for patients with and without the diagnosis of *Pseudomonas aeruginosa*. In comparison to patients with high utilization of tobramycin inhalation solution, those using less than four cycles a year were more likely to be hospitalized. High use of tobramycin inhalation solution was associated with a decreased risk of hospitalization relative to low use (AOR, 0.40; 95% CI, 0.19 to 0.84). A higher than average comorbidity risk (AOR, 7.53; 95% CI, 5.20 to 10.90), a coded diagnosis of *Pseudomonas aeruginosa* (AOR, 3.0; 95% CI, 2.13 to 4.32), and a coded diagnosis of failure to thrive/growth failure (AOR, 2.8; 95% CI, 1.09 to 7.14) were all independently associated with an increased risk of hospitalization. Secondary: Not reported
O'Sullivan et al.[18] (2011) Tobramycin inhalation solution	RETRO Patients at least six years of age with cystic fibrosis and pulmonary infections	N=1,064 1 year	Primary: Health care utilization Secondary: Not reported	Primary: A higher percentage of children had at least one cystic fibrosis-related office visit (P=0.0046), cystic fibrosis-related outpatient hospital visit (P<0.0001), outpatient hospital visit for any reason (P=0.0016), and cystic fibrosis-related emergency room visit (P=0.0159) compared to adults. Adults with cystic fibrosis averaged about 12 office visits per year for any diagnosis, compared to about 10 visits per year among children (P=0.0067). Children had more cystic fibrosis-related outpatient hospital visits

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(P=0.004) as well as prescriptions for than tobramycin inhalation solution (P=0.0007) and dornase alfa (P<0.0001) compared to adult patients. Adults had more frequent inpatient stays for any diagnosis (P=0.0021) and numbers of prescriptions for antibiotics other than tobramycin inhalation solution and azithromycin compared to children (P=0.0009). Adults had an average of 43 prescriptions per year compared to 39 prescriptions per year for children (P=0.03). Secondary: Not reported
Ratjen et al.[19] (2010) Tobramycin inhalation solution for an additional 28 days vs discontinuation of tobramycin	MC, OL, RCT Patients at least six months with cystic fibrosis and early *Pseudomonas aeruginosa* infection who had already received 28 days of treatment with tobramycin inhalation solution	N=123 56 days	Primary: Median time to recurrence of any strain of *Pseudomonas aeruginosa* Secondary: Proportion of patients free of *Pseudomonas aeruginosa* one month after the end of treatment; time to recurrence of any strain of *Pseudomonas aeruginosa*; number of patients with the same genotype of *Pseudomonas aeruginosa* at baseline and recurrence or a	Primary: The median time to recurrence of *Pseudomonas aeruginosa* was 26.12 and 25.82 months following than tobramycin inhalation solution for 28 and 56 days, respectively (P=0.593). At the time of each patient's final study visit, 66% of patients remained free of *Pseudomonas aeruginosa* in the 28-day than tobramycin inhalation solution group and 69% remained free of *Pseudomonas aeruginosa* in the 56-day than tobramycin inhalation solution group. Secondary: The proportion of patients free of *Pseudomonas aeruginosa* at day 28 and one month after the end of treatment was comparable in both groups. The proportion of patients free of *Pseudomonas aeruginosa* one month after the end of treatment was similar in sputum producers and non-sputum producers. Paired samples (baseline and recurrence) were available in 21 patients, of which 12 had the same genotype at baseline and at recurrence. For the remaining patients (n=9), paired samples were of a different genotype. Two patients (5.3%) in the 56-day than tobramycin inhalation solution group were hospitalized on one occasion, each for a pulmonary exacerbation during the study.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			new genotype at recurrence; proportion of patients free of *Pseudomonas aeruginosa* one month after the end of treatment for sputum and non-sputum producers and by baseline characteristics, lung function and infection status; number and length of hospital admissions for respiratory indications	No major short- or long-term changes in spirometric parameters were observed during the study period.
Hodson et al.[20] (2002) Tobramycin inhalation solution 300 mg BID vs colistin nebulized solution 80 mg inhaled BID	RCT Patients older than six years of age with cystic fibrosis, FEV_1>25%; *Pseudomonas aeruginosa* positive sputum culture	N=115 4 weeks	Primary: Mean change from baseline to week four in FEV_1 percent predicted Secondary: Change in sputum *Pseudomonas aeruginosa* density, tobramycin/colistin MICs, and safety assessment	Primary: Tobramycin inhalation solution produced a mean 6.7% improvement in lung function (P=0.006), while there was no significant improvement in the colistin-treated patients (mean change 0.37%). Secondary: Both nebulized antibiotic regimens produced a significant decrease in the sputum *Pseudomonas aeruginosa* density, and there was no development of highly resistant strains over the course of the study. No significant difference was detected between groups with respect to incidence of adverse events.
Berlana et al.[21] (2011)	OBS, PRO Adult patients with	N=81 4 years	Primary: Frequency and duration of	Primary: Significant differences were observed in the mean yearly rates for hospitalizations, duration of hospitalization, and duration of antibiotic use

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Tobramycin inhalation solution vs colistin inhalation solution vs tobramycin inhalation solution plus colistin inhalation solution	cystic fibrosis who received inhaled colistin, inhaled tobramycin or both to treat *Pseudomonas aeruginosa* bronchial colonization, a history of chronic *Pseudomonas aeruginosa* bronchial colonization, a diagnosis of bronchiectasis or chronic obstructive pulmonary disease, and who were receiving long-term treatment (≥12 weeks) of outpatient inhaled antibiotic therapy		hospitalizations for respiratory exacerbations Secondary: Emergence of bacterial resistance, antibiotic use during admission, emergence of other opportunistic microorganisms, achievement of sustained *Pseudomonas aeruginosa* eradication in the airways, mortality, safety, and changes in respiratory function	between the tobramycin and colistin plus tobramycin groups. No significant differences were found in hospitalizations, hospitalization days, or days of antibiotic use between tobramycin and colistin treatment. Secondary: Of the 93 microbiologically assessable antibiotic courses, 10 episodes of *Pseudomonas aeruginosa* were classified as eradicated, 20 reduced, 17 maintained negative, and 46 no response. Antimicrobial resistance was assessable in 72 episodes. The frequency of emergence of resistant strains differed significantly according to the antibiotic received (48% for tobramycin and 8% for colistin). The highest rate of emergence of other microorganisms was seen in the colistin plus tobramycin group. Only one patient was treated to control persistent isolation of *Aspergillus* species. Neither *Pseudomonas aeruginosa* eradication nor emergence of other microorganisms was linked to the inhaled antibiotic treatment received. No significant differences were found in the mean change/year in pulmonary function tests between the treatment groups. The overall frequency of patients experiencing an adverse event was 40%. A total of 12 patients (14.8%) died during the study, all for respiratory causes. There were no significant differences in mortality between the study groups, and FEV_1 percent was linked to mortality (HR, 0.93; 95% CI, 0.86 to 0.98).
Smyth et al.[22] (2005) Tobramycin 10 mg/kg/day IV administered TID for 14 days plus ceftazidime	DB, RCT Patients older than five years of age with cystic fibrosis who had a pulmonary exacerbation	N=244 14 days	Primary: Change in FEV_1 over 14 days of treatment, mean change in baseline FEV_1 Secondary: Change in serum	Primary: The mean change in FEV_1 (percent predicted) over 14 days was similar between the two regimens (10.4% [once daily] vs 10.0% [TID] (adjusted mean difference, 0.4%; 95% CI, –3.3 to 4.1). Mean % change in FEV_1 from baseline was also similar in both treatments (21.9 vs 22.1%; –0.1%; –8.0 to 7.9). Secondary: There was no significant difference in percent change in creatinine from

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs tobramycin 10 mg/kg/day IV once daily for 14 days plus ceftazidime IV			creatinine	baseline (–1.5% [once daily] vs 1.7% [TID]). In children, once-daily treatment was significantly less nephrotoxic than TID treatment (mean percent change in creatine, –4.5% [once daily] vs 3.7% [TID] (adjusted mean difference, –8.0%; 95% CI, –15.7 to –0.4; P=0.04).
Konstan et al.[23] (2011) Tobramycin inhalation powder 112 µg via T-326 inhaler BID for three treatment cycles (28 days on-drug, 28 days off-drug) vs tobramycin inhalation solution 300 mg/5 mL via PARI LC PLUS nebulizer BID for three treatment cycles (28 days on-drug, 28 days off-drug)	OL, RCT Patients ages six years and older with cystic fibrosis with *Pseudomonas aeruginosa* infection with FEV_1 ≥25 to ≤75% predicted	N=553 24 weeks	Primary: Safety assessments; relative chance in FEV_1 percent predicted from baseline, change in sputum *Pseudomonas aeruginosa* density, tobramycin susceptibility to *Pseudomonas aeruginosa* using MIC, antipseudomonal antibiotic use, respiratory-related hospitalizations Secondary: Not reported	Primary: More patients in the tobramycin inhalation powder group reported adverse events compared to tobramycin inhalation solution group (90.3 vs 84.2%; P<0.05). The percentage of adverse events was highest in cycle 1, 77.9% with tobramycin inhalation powder group and 66.5% with tobramycin inhalation solution group and decreased with cycles 2 and 3 (cycle 2: 67.0 vs 66.3%; cycle 3: 65.8 vs 58.5%, respectively). The most frequently reported adverse event was cough during the study period (tobramycin inhalation powder: 48.4% vs tobramycin inhalation solution: 31.1%). The rate of cough suspected to be study drug related was higher in tobramycin inhalation powder group (25.3 vs 4.3%). Twelve out of 308 (4%) tobramycin inhalation powder-treated patients discontinued due to cough vs 1% (2/209) of tobramycin inhalation solution-treated patients. Dysphonia (13.6 vs 3.8%) and dysgeusia (3.9 vs 0.5%) were also more commonly reported in the tobramycin inhalation powder group. The incidence of serious adverse events was similar in both groups. Both treatment groups had similar increases in FEV_1 percent predicted from baseline to day 28 of cycle 3 (least squares mean difference, 1.1% relative change [standard error, 1.75]). On day 28 of cycle 3, 11.6% tobramycin inhalation powder-treated patients and 9.9% tobramycin inhalation solution-treated patients had negative *Pseudomonas aeruginosa* cultures. The proportion of patients requiring any new antipseudomonal antibiotic was significantly higher with tobramycin inhalation powder group (64.9 vs

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				54.5%; P=0.0148). The number of patients hospitalized for respiratory-related events was similar in the tobramycin inhalation powder group vs tobramycin inhalation solution group (24.4 vs 22.0%). Administration time was significantly less for tobramycin inhalation powder compared to the solution formulation (mean, 5.6 vs 19.7 minutes; P<0.0001). Secondary: Not reported
Mazurek et al.[24] (2014) Tobramycin nebulization solution 300 mg/4 mL (28 days on-drug, 28 days off-drug) vs tobramycin nebulization solution 300 mg/5 mL (28 days on-drug, 28 days off-drug) Subset of patients continued receiving tobramycin nebulization solution 300 mg/4 mL only.	MC, OL, RCT (core phase) SA (extension phase) Patients ages six years and older with cystic fibrosis with *Pseudomonas aeruginosa* infection with FEV_1 ≥40 and ≤80% predicted	N=321 (N=321: core phase; N=209: extension phase) 56 weeks (8 weeks: core phase; 48 weeks: extension phase)	Primary: Core phase: absolute change in FEV_1 percent predicted from baseline to week four; extension phase: long term safety of tobramycin nebulization solution 300 mg/4 mL; both phases: microbiological assessments, adverse events, and audiometry findings Secondary: Not reported	Primary: In the core phase, FEV_1 percent predicted increased similarly from baseline (absolute change) following a single on-treatment cycle for both groups: tobramycin nebulization solution 300 mg/4 mL, 7.0% vs tobramycin nebulization solution 300 mg/5 mL, 7.5% (difference between treatments, -0.5; 95% CI, -2.6 to 1.6). The baseline- and country-adjusted mean of absolute change from baseline to week four in FEV_1 percent predicted was 4.7 and 5.2% for 4 and 5 mL solution, respectively, with a significant (P<0.001) improvement vs baseline for both groups. These improvements were maintained throughout the extension phase. *Pseudomonas aeruginosa* sputum count reductions ranged between 0.6 (95% CI, 0.2 to 0.9) to 2.3 (95% CI, 2.0 to 2.6) log_{10} colony forming unit/g throughout the 56 weeks. No remarkable safety issues were identified throughout both study phases, with similar percentages of patients reporting adverse events in the two treatment groups during the core phase (4 mL, 31.4%; 5 mL, 28.0%; P=0.579). The adverse events that were judged to be related to the drug were also similar between the two groups (4 mL, 6.4%; 5 mL, 6.0%; P=1.000). Cough, rhinitis, pharyngitis, and pulmonary exacerbations were the most commonly reported adverse events, proportionally similar between the two groups. Serious adverse events occurred in six (3.8%) and two (1.2%) of patients treated with 4 and 5 mL solution, respectively (Fisher's test, P=0.161). During the extension phase, adverse events were reported by 148 patients (70.8%). Similar to the core phase, the most commonly reported adverse events included pulmonary exacerbation (24.9%), rhinitis (12.4%), cough

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(11%), pyrexia (7.7%), and bronchitis (7.2%). Bronchospasm and death was not reported in either core or extension phase. Secondary: Not reported
Galeva et al.[25] (2013) Tobramycin inhalation powder 112 µg, as capsules administered via dry powder inhaler, BID vs placebo	DB, MC, PC, Phase 3, RCT Patients six to 21 years of age with cystic fibrosis with FEV_1 ≥25 and ≤80% and a positive sputum or throat culture for *Pseudomonas aeruginosa* within six months of screening and a positive sputum culture for *Pseudomonas aeruginosa* at the screening visit	N=62 Duration not specified	Primary: Relative change in FEV_1 percent predicted from baseline to day 29 Secondary: Relative change in forced vital capacity percent predicted and forced expiratory flow 25 to 75% predicted from baseline to day 29; change from baseline in sputum density of *Pseudomonas aeruginosa*; rates of antipseudomonal antibiotic use and hospitalizations due to respiratory events; safety assessments: the incidence and severity of all adverse events and serious adverse events and	Primary: Mean treatment difference was 5.9% (95% CI, -2.2 to 14.0; P=0.148) for relative change in FEV_1 percent predicted. Secondary: Mean treatment difference was 4.4% (95% CI, 0.0 to 8.8; P<0.05) for absolute change in FEV_1 percent predicted. Tobramycin inhalation powder significantly reduced sputum *Pseudomonas aeruginosa* density by -1.2 $\log_{10}$ colony forming unit (P=0.002). The tobramycin group had higher clearance rate for *Pseudomonas aeruginosa* compared to placebo (41.4 vs 0% at day 29). Antipseudomonal antibiotic use was reported to be used in three patients in each of the treatment groups. Hospitalization due to respiratory events occurred in one patient in the placebo group. Adverse events were mild to moderate in severity and they occurred in 26.7% patients in the tobramycin group compared to 34.4% patients in the placebo group. Drug-related adverse events occurred in five (16.7%) tobramycin-treated patients compared to two (6.3%) patients in the placebo group; the difference was due to adverse event of cough that was reported in three patients in the tobramycin group to be drug-related. There was no difference between the groups in serious adverse events. There were no major differences that were observed between the groups in any hematology, renal or biochemistry variables, or acuity.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			regular monitoring of hematology, blood chemistry and urine protein, vital signs, physical condition, and bodyweight	
Chuchalin et al.[26] [abstract] (2007) Tobramycin inhalation solution 300 mg/4 mL vs placebo Four-week treatment periods ('on' cycles) were followed by four-week periods without treatment ('off' cycles)	DB, MC, PC Patients with cystic fibrosis with chronic *Pseudomonas aeruginosa* infection	N=247 24 weeks Endpoint time assessment was at week 20	Primary: FEV_1 percent predicted normal Secondary: Forced vital capacity, forced expiratory flow at 25 to 75% of forced vital capacity, *Pseudomonas aeruginosa* susceptibility, MIC required to inhibit 90% of strains, rates of *Pseudomonas aeruginosa* -negative culture, *P. aeruginosa* persistence and superinfection, need for hospitalization and parenteral antipseudomonal antibiotics, loss of school/working days due to the	Primary: FEV_1 was significantly increased in the tobramycin group and the adjusted mean difference between groups in the intention-to-treat population was statistically significant (P<0.001). Secondary: Tobramycin group had clinically relevant improvements in forced vital capacity (P=0.022) and forced expiratory flow at 25 to 75% of forced vital capacity (P=0.001). The microbiologic outcomes at the end of the last 'on' cycle period were better in the tobramycin group than the placebo group (P=0.024). There was a concomitant trend toward an increase in the minimum concentration required to inhibit 90% of strains of isolated *Pseudomonas aeruginosa* strains. Tobramycin group had a lower percentage of patients hospitalized (P=0.002) and had a lower need for parenteral antipseudomonal antibiotics (P=0.009) compared to the placebo group. Tobramycin group patients had fewer lost school/working days due to the disease (P<0.001). Compared to placebo, there was a favorable effect of tobramycin in terms of an increase in bodyweight and body mass index at all time points (P<0.01 and P<0.001, respectively). There were no significant changes in serum creatinine and auditory function. The proportion of patients with drug-related adverse events was 15% in both treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			disease, and nutritional status (bodyweight and body mass index); safety parameters including adverse events, audiometry, and renal function	
Lenoir et al.[27] (2007) Tobramycin inhalation solution 300 mg/4 mL BID for four weeks vs placebo BID	DB, MC, PC, PG, PRO, RCT Patients six years of age and older with cystic fibrosis with a FEV_1 ≥40 and ≤80% of predicted normal with *Pseudomonas aeruginosa* infection	N=59 8 weeks	Primary: Pulmonary function as measured by FEV_1, forced vital capacity, and forced expiratory flow at the midportion of vital capacity, *Pseudomonas aeruginosa* susceptibility, microbiologic results, and in vitro MIC for 90% of strains; safety as monitored by the recording of adverse events, audiometry (bone conduction at 250 to 8,000 Hz frequency), laboratory tests, physical examination, and	Primary: The tobramycin group had a significant increase in FEV_1 from baseline compared to the placebo group: the absolute difference between groups (intent-to-treat population) of predicted normal was 13.2% at week two (95% CI, 4.88 to 21.54; P=0.002) and 13.3% at week four (95% CI, 4.74 to 21.81; P=0.003). The forced vital capacity and forced expiratory flow at the midportion of vital capacity also increased in the tobramycin group compared to the placebo group: the estimated differences at week four visit were 10.65% (95% CI, 1.94 to 19.37; P=0.017) and 15.78% (95% CI, 5.24 to 26.32; P=0.004) for the two variables, respectively. There was no significant effects in terms of maintenance of *Pseudomonas aeruginosa* negative cultures at the end of the run-out phase in the tobramycin group (P=0.202 between-group comparison). There was no differences between treatments in the mean changes from baseline of MIC for 90% at the end of week four in patients with persistent *Pseudomonas aeruginosa* (P=0.780). There was no difference between the treatment groups in terms of drug-related adverse events (P=0.184). Results of audiometric tests did not show statistically significant differences between groups. There were no differences between treatment groups in increase in serum creatinine levels (P=0.850). There were no clinically significant changes in heart rate and blood pressure in either group at any time.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			general health condition Secondary: Not reported	Secondary: Not reported

Drug regimen abbreviations: BID=twice daily, IM=intramuscular, IV=intravenous, TID=three times daily.
Study abbreviations: AOR=adjusted odds ratio, CI=confidence interval, DB=double-blind, HR=hazard ratio, MA=meta-analysis, MC=multicenter, OBS=observational, OL=open-label, OR=odds ratio, PC=placebo- controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, RR=risk ratio, SA=single arm, SEM=standard error of the mean.
Miscellaneous abbreviations: FEV_1=forced expiratory volume in one second, MIC=minimum inhibitory concentration

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 9. Relative Cost of Tobramycin Inhalation Solution

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Tobramycin	inhalation solution	Kitabis®	$$$$$	N/A

N/A=Not available

X. Conclusions

Kitabis® is the newest inhaled tobramycin agent, and it is approved for management of cystic fibrosis adults and pediatric patients six years of age and older with *Pseudomonas aeruginosa*.[4] This is the only agent that co-packages the generic tobramycin inhalation solution with a reusable nebulizer (PARI LC Plus™).[4,10]

The chronic use of inhaled tobramycin is recommended for patients six years of age and older with cystic fibrosis colonized with *Pseudomonas aeruginosa* regardless of the severity of lung disease.[11] Kitabis® was FDA approved using the same clinical trial data as TOBI® (tobramycin solution for inhalation).[4] Treatment with tobramycin has been associated with improvements in pulmonary function, improved quality of life, decreased requirement for intravenous anti-pseudomonal antibiotics, and a decrease in hospitalizations compared to placebo.[12-16,26-27] Open-label studies following patients for up to two years have also demonstrated continued benefit over time.[15-16] There is no clinical evidence of differences in efficacy with the various inhaled tobramycin formulations, and the Cystic Fibrosis Foundation guidelines do not give preference to one inhaled tobramycin formulation over another.[11,23-34]

Therefore, all brand aminoglycosides products within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use. Tobramycin inhalation solution and inhalation powder has been shown to improve lung function and reduce exacerbations in cystic fibrosis patients colonized with *Pseudomonas aeruginosa*. Therefore, these patients should be allowed approval for inhalation solution and inhalation powder through the medical justification portion of the prior authorization process.

XI. Recommendations

No brand tobramycin inhalation product is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Update of Opiate Agonists
AHFS Class 280808
May 11, 2016

I. Update

Opioid abuse, misuse, dependence, and overdose are significant health problems in the United States.[1,2] In response to this growing issue, many organizations have released strategies for mitigating prescription drug abuse, with the Food and Drug Administration (FDA), Centers for Medicare and Medicaid Services (CMS), and Centers for Disease Control and Prevention (CDC) all addressing opioid use in recent communications.[1-3]

The FDA has developed an action plan to take steps toward reducing the impact of opioid abuse on American families and communities. These actions include expanding the use of advisory committees, developing warnings and safety information for labeling of immediate-release (IR) opioids, strengthening postmarket requirements, updating the scope of the existing Risk Evaluation and Mitigation Strategy (REMS) program, expanding access to abuse-deterrent formulations to discourage abuse, supporting improved overdose and pain treatments, and reassessing the risk-benefit approval framework for opioid use.[1] Class-wide labeling changes for all extended-release and long-acting (ER/LA) opioid analgesics occurred in April 2014, addressing the risks of misuse, abuse, hyperalgesia, addiction, overdose, death, and neonatal opioid withdrawal syndrome.[4] On March 22, 2016 the FDA announced required class-wide safety labeling changes for IR opioid pain medications. Among the changes, the FDA requires a new boxed warning about the serious risks of misuse and abuse, which can lead to addiction, overdose, and death.[5]

In January 2016, CMS released an informational bulletin addressing prescription opioid overdoses, misuse, and addiction. The purpose of the bulletin was to highlight strategies for preventing opioid-related harms.[2] CMS emphasizes that methadone accounts for a disproportionate share of opioid-related overdoses and deaths, and encourages states to consider additional steps to reduce the use of methadone prescribed for pain relief. The pharmacokinetic and pharmacodynamic parameters of methadone make it a complex medication to prescribe for pain relief.[2] Of note, its elimination half-life is longer than its duration of analgesic action, there is high interpatient variability in absorption, metabolism, and relative analgesic potency, it is retained in the liver with repeat dosing, and it has a narrow therapeutic index.[6,7] CMS recommends removing methadone from preferred drug lists and limiting its use only to patients for whom treatment with other pain medications is ineffective.[2]

On March 18, 2016 the CDC published guidelines for prescribing opioids for chronic pain. This guideline provides recommendations for primary care clinicians who are prescribing opioids for chronic pain outside of active cancer treatment, palliative care, and/or end-of-life care.[3] This guideline states that nonpharmacologic and nonopioid pharmacologic therapies are preferred for chronic pain. When opioid therapy is initiated for chronic pain, IR opioids should be used before ER/LA agents. ER/LA opioids should be reserved for severe, continuous pain and should be considered only for patients who have received IR opioids daily for at least a one-week duration. The guideline states that methadone has been associated with disproportionate numbers of overdose deaths relative to the frequency with which it is prescribed for chronic pain. Methadone should not be the first choice for an ER/LA opioid.[3]

A summary of the 2016 CDC Guideline for Prescribing Opioids for Chronic Pain, as well as the previous February 2016 review of opiate agonists have been included in the appendix below.

There is insufficient evidence to support that one brand opiate agonist is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process. Methadone should be managed through the medical justification portion of the prior authorization process due to the potential risk of abuse and overdose, the known complexities with appropriately prescribing this medication, and the guideline recommendations for not using this medication as a first-line agent.

Therefore, all brand opiate agonists within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

II. Recommendations

No brand opiate agonist is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

Methadone should not be placed in preferred status regardless of cost.

III. References

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Appendix

Centers for Disease Control and Prevention: **CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016 (2016)**[3]	This guideline provides recommendations for primary care clinicians who are prescribing opioids for chronic pain outside of active cancer treatment, palliative care, and end-of-life care.
	
	Determining when to initiate or continue opioids for chronic pain
	• Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain. Clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patient. If opioids are used, they should be combined with nonpharmacologic and nonopioid pharmacologic therapies, as appropriate.
	  o Several nonopioid pharmacologic therapies (including acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), and selected antidepressants and anticonvulsants) are effective for chronic pain.
	  o In particular, acetaminophen and NSAIDs can be useful for arthritis and low back pain. Selected anticonvulsants such as pregabalin and gabapentin can improve pain in diabetic neuropathy and post-herpetic neuralgia. Pregabalin, gabapentin, and carbamazepine are FDA-approved for treatment of certain neuropathic pain conditions, and pregabalin is FDA-approved for fibromyalgia management.
	• Before starting opioid therapy for chronic pain, clinicians should establish treatment goals with all patients, including realistic goals for pain and function, and should consider how therapy will be discontinued if benefits do not outweigh risks. Clinicians should continue opioid therapy only if there is clinically meaningful improvement in pain and function that outweighs risks to patient safety.
	• Before starting and periodically during opioid therapy, clinicians should discuss with patients the known risks and realistic benefits of opioid therapy as well as patient and clinician responsibilities for managing therapy.
	
	Opioid selection, dosage, duration, follow-up, and discontinuation
	• When starting opioid therapy for chronic pain, clinicians should prescribe immediate-release (IR) opioids instead of extended-release/long-acting (ER/LA) opioids.
	  o ER/LA opioids include methadone, transdermal fentanyl, and extended-release versions of opioids such as oxycodone, oxymorphone, hydrocodone, and morphine.
	  o Recommendations cannot be offered at this time related to use of abuse-deterrent formulations.
	  o Methadone has been associated with a disproportionate number of overdose deaths relative to the frequency with which it is prescribed for chronic pain. Methadone should not be a first-line agent for an ER/LA opioid for pain management.
	  o ER/LA opioids should be reserved for severe, continuous pain and should be considered only for patients who have received IR opioids daily for at least one week.
	• When opioids are initiated, clinicians should prescribe the lowest effective dosage. Clinicians should use caution when prescribing opioids at any dose, should carefully reassess evidence of individual benefits and risks when increasing doses to ≥50 morphine milligram equivalents (MME)/day, and should avoid increasing doses to ≥90 MME/day or carefully justify a decision to titrate doses to ≥90 MME/day.
	• Long-term opioid use often begins with treatment of acute pain. When opioids

	are used for acute pain, clinicians should prescribe the lowest effective dose of IR opioids and should not prescribe a quantity greater than needed for the expected duration of pain considered severe enough to require opioids. Three days or less is often sufficient; more than seven days is rarely be needed. • Clinicians should evaluate benefits and harms with patients within one to four weeks of starting opioid therapy for chronic pain or a dose escalation. Clinicians should evaluate the benefits and harms of continued therapy with patients every three months or more frequently, as clinically warranted. If the benefits do not outweigh the harms of continued opioid therapy, clinicians should optimize other therapies and work with patients to taper opioids to lower doses or taper and discontinue opioids. <u>Assessing risk and addressing harms of opioid use</u> • Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk factors for opioid-related harms. Clinicians should incorporate strategies into the management plan to mitigate risks, including the consideration of naloxone prescribing when factors that increase the risk for opioid overdose are present (e.g., a history of overdose, history of substance use disorder, higher opioid doses (≥50 MME/day), or concurrent benzodiazepine use). • Clinicians should review the patient's history of controlled substance prescriptions using state prescription drug monitoring program (PDMP) data to determine whether the patient is receiving other opioid doses or dangerous combinations that may put him or her at high risk for overdose. Clinicians should review PDMP data when initiating opioid therapy for chronic pain and periodically during opioid therapy for chronic pain, ranging from every prescription to every three months. • When prescribing opioids for chronic pain, clinicians should use urine drug testing before starting opioid therapy and consider urine drug testing at least annually to assess for prescribed medications as well as other controlled prescription drugs and illicit drug use. • Clinicians should avoid prescribing opioid pain medications and benzodiazepines concurrently whenever possible. • Clinicians should offer or arrange evidence-based treatment options (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for patients with opioid use disorder.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Opiate Agonists
AHFS Class 280808
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I. Overview

The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of damage." Chronic pain is further defined as "pain which persists past the normal time of healing," generally lasting ≥3 months.[1] Pain is a subjective experience that is unique to the individual.[2] There are numerous etiologies of pain and successful pain management can be difficult to achieve.

Opioids exert their effect by binding to receptors are widely distributed within the brain, spinal cord, and gastrointestinal tract. Binding and activation of the mu opioid receptor produces a variety of pharmacologic effects, including analgesia, euphoria, dysphoria, respiratory depression, somnolence, decreased gastrointestinal motility, histamine release, and physical dependence.[3] In addition to binding to the mu receptor, tapentadol inhibits norepinephrine reuptake, while tramadol inhibits both norepinephrine and serotonin reuptake.[4-6] The opiate agonists have no ceiling to their analgesic effect; the degree of analgesia is only limited by dose-related adverse events.[4-7] They are available in a variety of dosage forms as single entity agents, as well as in combination with acetaminophen, aspirin, butalbital, caffeine, and ibuprofen. Acetaminophen, aspirin, and ibuprofen are non-opiate analgesics. Butalbital is a barbiturate, which has anxiolytic and muscle relaxant properties. Caffeine is an analgesic adjuvant, as well as a central nervous system stimulant.[4-6]

Opioid dependence is a significant health problem in the United States. Interventions for opioid-related conditions (dependence, abuse, intoxication, and withdrawal) include both psychosocial and pharmacotherapy treatments.[8] Methadone, buprenorphine (with or without naloxone), and naltrexone are Food and Drug Administration (FDA)-approved for the detoxification and maintenance treatment of opioid dependence.[4-6] The use of methadone is restricted to federally approved Opioid Treatment Programs (OTPs). Qualified office-based physicians may prescribe buprenorphine-containing products for the treatment of opioid dependence, which has significantly expanded access to treatment. Since methadone is a full agonist at the mu receptor, the potential for abuse, misuse, and diversion exists.[8,9] Patients may also experience withdrawal symptoms when a dose is missed. In addition, there is no ceiling to its effects and an overdose can be fatal. Compared to full agonists, buprenorphine (partial agonist) has a lower potential for abuse and is safer in an overdose situation.[9]

In May 2010, the FDA notified healthcare providers about an increased risk of suicide with tramadol. Deaths have occurred in patients with previous histories of emotional disturbances or suicidal ideation or attempts, as well as histories of misuse of tranquilizers, alcohol, and other central nervous system-active drugs.[10] An additional safety communication regarding the risks of using tramadol in children aged 17 years and younger was released in September 2015. The FDA is reviewing available information on the rare but serious risk of slowed or difficult breathing and will communicate final conclusions when the review is complete.[11] In November 2010, the FDA recommended against the continued prescribing and use of propoxyphene-containing products and asked manufacturers to voluntarily remove these products from the United States market. The decision was based on the results of a new study, which showed that when propoxyphene was taken at therapeutic doses, there were significant changes to the electrical activity of the heart (prolonged QT, PR, and QRS intervals).[12] In January 2011, the FDA also asked manufacturers to limit the amount of acetaminophen in prescription drug products (which are predominantly combinations of acetaminophen and opioids) to 325 mg per dosage form to make these products safer for patient to use.[13] In January 2014 the FDA recommended health care professionals discontinue prescribing and dispensing prescription combination drug products that contain more than 325 mg of acetaminophen. More than half of manufacturers have voluntarily complied with the initial 2011 FDA request. However, some prescription combination drug products containing more than 325 mg of acetaminophen per dosage unit remain available.[14] Over the last several years, the FDA has made great efforts to curb the rapidly-escalating problem of misuse and abuse of extended-release and long-acting opioids. Emphasis has been placed on the development of abuse-deterrent opioid formulations, and a Risk Evaluation and Mitigation Strategy

(REMS) has been implemented to educate prescribers on the dangerous risks associated with the prescription and utilization of opioid medications.[15]

In September 2013, the FDA announced labeling changes for all extended-release and long-acting opioids, and the changes were finalized in April 2014. Safety labeling across the class now includes an updated indication stating that these agents are indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or otherwise inadequate. The FDA requires a new boxed warning regarding the risk of neonatal opioid withdrawal syndrome when these agents are used during pregnancy, and also requires the manufacturers of extended-release and long-acting opioids to conduct postmarket studies further assessing the known risks of misuse, abuse, hyperalgesia, addiction, overdose, and death. These changes are incorporated into the aforementioned REMS program.[16]

Another regulatory change regarding hydrocodone and acetaminophen combination products occurred on October 6, 2014, as the DEA re-scheduled hydrocodone and acetaminophen combination products from schedule III to schedule II.[17]

The opiate agonists that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. All of the products are available in a generic formulation, with the exception of remifentanil and tapentadol. This class was last reviewed in November 2013. The sustained-release opiate agonists, with the exception of fentanyl transdermal patch, morphine sustained-release, tapentadol extended-release, and tramadol extended-release, are not included in this review; the remaining sustained-release agents are included in the Alabama Medicaid Prior Authorization Program, which is outside of the Preferred Drug Program.

Table 1. Opiate Agonists Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Alfentanil	injection^	Alfenta®*	alfentanil
Codeine	tablet	N/A	codeine
Fentanyl	buccal lozenge, buccal tablet, injection, nasal spray, sublingual spray, sublingual tablet, transdermal patch	Abstral®, Actiq®*, Duragesic®*, Fentora®, Lazanda®, Sublimaze®*, Subsys®	fentanyl
Hydromorphone	injection, liquid, rectal suppository, tablet	Dilaudid®*	hydromorphone
Levorphanol	tablet	N/A	levorphanol
Meperidine	injection, solution, tablet	Demerol®*	meperidine
Methadone	injection, oral concentrate, solution, tablet	Dolophine®*, Methadose®*	methadone
Morphine	epidural, injection, rectal suppository, solution, tablet	Astramorph-PF®, Duramorph®, Infumorph®	morphine
Oxycodone	capsule, oral concentrate, solution, tablet	Oxecta®, Roxicodone®*	oxycodone
Oxymorphone	injection, tablet	Opana®*	oxymorphone
Remifentanil	injection^	Ultiva®	none
Sufentanil	injection^	Sufenta®*	sufentanil
Tapentadol	extended-release tablet, tablet	Nucynta®, Nucynta ER®	none
Tramadol	extended-release capsule, extended-release tablet, tablet	Conzip ER®*, Ultram®*, Ultram ER®*	tramadol
Combination Products			
Codeine and acetaminophen	elixir, suspension, tablet	Capital w/Codeine®, Tylenol-Codeine No.3®*, Tylenol-	codeine and acetaminophen

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
		Codeine No.4®*	
Codeine, butalbital, acetaminophen, and caffeine	capsule	Fioricet With Codeine®*	codeine, butalbital, acetaminophen, and caffeine
Codeine, butalbital, aspirin, and caffeine	capsule	Fiorinal With Codeine®*	codeine, butalbital, aspirin, and caffeine
Dihydrocodeine, acetaminophen, and caffeine	capsule	N/A	dihydrocodeine, acetaminophen, and caffeine
Dihydrocodeine, aspirin, and caffeine	capsule	Synalgos-DC®*	dihydrocodeine, aspirin, and caffeine
Hydrocodone and acetaminophen	solution, tablet	Hycet®*, Lorcet HD®*, Lorcet Plus®*, Lortab®*, Norco®*, Verdrocet®*, Vicodin®*, Vicodin ES®*, Vicodin HP®*, Xodol®*, Zamicet®*	hydrocodone and acetaminophen
Hydrocodone and ibuprofen	tablet	Ibudone®*, Reprexain®*, Vicoprofen®*, Xylon®*	hydrocodone and ibuprofen
Opium and belladonna	rectal suppository	N/A	opium and belladonna
Oxycodone and acetaminophen	extended-release tablet, solution, tablet	Percocet®*, Primlev®, Xartemis XR®	oxycodone and acetaminophen
Oxycodone and aspirin	tablet	Percodan®*	oxycodone and aspirin
Oxycodone and ibuprofen	tablet	N/A	oxycodone and ibuprofen
Tramadol and acetaminophen	tablet	Ultracet®*	tramadol and acetaminophen

*Generic is available in at least one dosage form or strength.
^Product is primarily administered in an institution.
PDL=Preferred Drug List
N/A=Not available

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the opiate agonists are summarized in Table 2.

Table 2. Treatment Guidelines Using the Opiate Agonists

Clinical Guideline	Recommendation(s)
National Comprehensive Cancer Network: **Adult Cancer Pain (2015)**[18]	• The most widely accepted algorithm for the treatment of cancer pain was developed by the World Health Organization (WHO) which suggests that patients with pain be started on acetaminophen or a nonsteroidal anti-inflammatory drug (NSAID). If sufficient pain relief is not achieved, patients should be escalated to a "weak opioid," such as codeine, and then to a "strong opioid," such as morphine. • The pain management algorithm distinguishes three levels of pain intensity, based on a 0 to 10 numerical rating scale: severe pain (7 to 10), moderate pain (4 to 6) and mild pain (1 to 3). • Pain associated with oncology emergency should be addressed while treating the underlying condition. <u>General principles of opioid treatment</u> • The appropriate dose is that which relieves the patient's pain throughout the dosing interval without causing unmanageable adverse effects. • Titrate with caution in patients with risk factors such as decreased renal/hepatic function, chronic lung disease, upper airway compromise, sleep

Clinical Guideline	Recommendation(s)
	apnea, and poor performance status. • According to Food and Drug Administration (FDA) guidelines, when higher doses of analgesic are needed, switch from preparations of opioid combined with other medications (such as aspirin and acetaminophen) to a pure opioid preparation to provide adequate pain relief while avoiding the toxicities of the non-opioid component. • Monitor for aberrant drug-taking behaviors. • Risk Evaluation and Mitigation Strategies (REMS) programs are currently in place for all transmucosal fentanyl products; long-acting, extended-release formulations of opioids (e.g. hydrocodone ER, hydromorphone ER, morphine ER, oxycodone ER, oxymorphone ER, tapentadol ER); methadone tablets and solutions indicated for use as analgesics; and fentanyl or buprenorphine-containing transdermal systems. <u>Principles of maintenance opioid therapy</u> • For continuous pain, it is appropriate to give pain medication on a regular schedule with supplemental doses for breakthrough pain. • Add extended-release or long-acting formulation to provide background analgesia for control of chronic persistent pain controlled on stable doses of short-acting opioids. • When possible, use the same opioid for short-acting and extended-release forms. • Increase the dose of extended-release opioid if patient persistently needs doses of as-needed opioids or when dose of around-the-clock opioid fails to relieve pain at peak effect or at end of dose. • Allow rescue use of short-acting opioids at doses of 10 to 20% of the 24-hour total of long-acting or regularly scheduled oral opioid dose up to every one hour as needed. <u>Management of pain in opioid-naïve patients</u> • Opioid-naïve patients (those not chronically receiving opioid therapy on a daily basis) should be provided with non-opioid adjuvant analgesics as indicated, prophylactic bowel regimen, psychosocial support, as well as patient and family education. • Opioid-naïve patients experiencing severe pain should receive rapid titration of short-acting opioids. • For opioid-naïve patients whose pain intensity is moderate at presentation, the pathways are quite similar to those for severe pain, with slower titration of short-acting opioids. • Opioid-naïve patients experiencing mild pain intensity should receive nonopioid analgesics, such as NSAIDs or acetaminophen, or treatment with consideration of slower titration of short-acting opioids. • Patients with chronic persistent pain controlled by stable doses of short-acting opioids should be provided with round-the-clock extended-release or long-acting formulations of opioids with provision of a ‘rescue dose’ to manage break-through or transient exacerbations of pain. Opioids with rapid onset and short duration are preferred as rescue doses. The repeated need for rescue doses per day may indicate the necessity to adjust the baseline treatment. <u>Management of pain in opioid-tolerant patients</u> • Opioid-tolerant patients are those chronically taking opioids for pain relief. According to the FDA, opioid-tolerant patients “are those who are taking at least 60 mg oral morphine/day, 25 µg transdermal fentanyl/hour, 30 mg oral oxycodone/day, or an equianalgesic dose of another opioid for one week or longer.”

Clinical Guideline	Recommendation(s)
	• In order to achieve adequate analgesia in opioid-tolerant patients who are experiencing breakthrough pain of intensity greater than or equal to 4, or a pain intensity less than 4 without meeting goals for pain control and function, the previous 24-hour total oral or intravenous opioid requirement must be calculated and the new "rescue" dose must be increased by an opioid dose equivalent to 10 to 20% of the total opioid taken in the previous 24 hours. • Efficacy and adverse effects should be assessed every 60 minutes for orally administered opioids and every 15 minutes for intravenous opioids to determine a subsequent dose. Upon assessment, if the pain score remains unchanged or is increased, administration of 50 to 100% of the previous rescue dose is recommended. <u>Selecting an appropriate opioid</u> • Optimal analgesic selection will depend on the patient's pain intensity, any current analgesic therapy, and concomitant medical illness(es). An individual approach should be used to determine opioid starting dose, frequency, and titration in order to achieve a balance between pain relief and medication adverse effects. • In a patient who has not been exposed to opioids in the past, morphine is generally considered the standard starting drug of choice. • Morphine and hydromorphone should be used with caution in patients with fluctuating renal function due to potential accumulation of renally cleared metabolites that may cause neurologic toxicity. • Pure agonists (such as codeine, fentanyl, oxycodone, and oxymorphone) are the most commonly used medications in the management of cancer pain. Opioid agonists with a short half-life are preferred and include fentanyl, hydromorphone, morphine, and oxycodone. • Transdermal fentanyl is not indicated for rapid opioid titration and only should be recommended after pain is controlled by other opioids in opioid-tolerant patients. It is usually the drug of choice for patients who are unable to swallow, patients with poor tolerance to morphine, and patients with poor compliance. • Individual variations in methadone pharmacokinetics make using this agent in cancer pain difficult. Methadone should be started at lower-than-anticipated doses and slowly titrated upwards with provision of adequate short acting breakthrough pain medications during the titration period. • Meperidine, mixed agonist-antagonists (e.g., butorphanol, pentazocine), and placebos are not recommended for cancer patients. Meperidine is contraindicated for chronic pain, especially in patients with impaired renal function or dehydration. • The least invasive, easiest and safest route of administration should be provided to ensure adequate analgesia. Oral administration is preferred for chronic opioid therapy. The oral route should be considered first in patients who can take oral medications unless a rapid onset of analgesia is required or the patient experiences adverse events associated with the oral administration. Continuous parenteral infusion, intravenous or subcutaneous, is recommended for patients who cannot swallow or absorb opioids enterally. Opioids, given parenterally, may produce fast and effective plasma concentrations in comparison with oral or transdermal opioids. Intravenous route is considered for faster analgesia because of the short lag-time between injection and effect in comparison with oral dosing. • The methods of administering analgesics that are widely accepted within clinical practice include "around the clock", "as needed", and "patient-controlled analgesia." • "Around the clock" dosing is provided to chronic pain patients for continuous

Clinical Guideline	Recommendation(s)
	pain relief. A "rescue dose" should also be provided as a subsequent treatment for patients receiving "around the clock" doses. Rescue doses of short acting opioids should be provided for pain that is not relieved by regularly scheduled, "around the clock" doses. Opioids administered on an "as needed" basis are for patients who have intermittent pain with pain-free intervals. The "as needed" method is also used when rapid dose titration is required. The patient-controlled analgesia technique allows a patient to control a device that delivers a bolus of analgesic "on demand". • No single opioid is optimal for all patients. When considering opioid rotation, defined as changing to an equivalent dose of an alternative opioid to avoid adverse effects, it is important to consider relative effectiveness when switching between oral and parenteral routes to avoid subsequent overdosing or under-dosing. • Subsequent treatment is based upon the patient's continued pain rating score. All approaches for all pain intensity levels must include administering regular doses of opioids with rescue doses as needed, management of constipation, and psychosocial support and education for patients and their families. • Although pain intensity ratings will be obtained frequently to evaluate opioid dose increases, a formal re-evaluation to evaluate patient's goals of comfort and function is mandated at each contact. • If adequate comfort and function has been achieved, and 24-hour opioid requirement is stable, the patients should be converted to an extended-release oral medication (if feasible) or another extended-release formulation (i.e., transdermal fentanyl) or long-acting agent (i.e., methadone). The subsequent treatment is based upon the patients' continued pain rating score. Rescue doses of the short acting formulation of the same long acting drug may be provided during maintenance therapy for the management of pain in cancer patients not relieved by extended-release opioids. • Procedure-related pain represents an acute short-lived experience which may be accompanied by a great deal of anxiety. • Interventions to manage procedure-related pain should take into account the type of procedure, the anticipated level of pain, other individual characteristics of the patient such as age, and physical condition. • Opioids alone may not provide the optimal therapy, but when used in conjunction with nonopioid analgesics, such as an NSAID or adjuvant, and psychological and physical approaches, they can help to improve patient outcomes. • Addition of adjuvant analgesics should be re-evaluated to either enhance the analgesic effect of the opioids or, in some cases, to counter the adverse events associated with opioids. • The term adjuvant refers to medications that are coadministered to manage an adverse event of an opioid or to adjuvant analgesics that are added to enhance analgesia. Adjuvant may also include drugs for neuropathic pain. Clinically, adjuvant analgesics consist of anticonvulsants (e.g., gabapentin, pregabalin), antidepressants (e.g., tricyclic antidepressants), corticosteroids, and local anesthetics (e.g., topical lidocaine patch). • Adjuvant analgesics are commonly used to help manage bone pain, neuropathic pain, visceral pain, and to reduce systemic opioid requirement, and are particularly important in treating neuropathic pain that is resistant to opioids. • Acetaminophen and NSAIDs are recommended non-opioid analgesics that can be used in the management of adult cancer pain. Non-pharmacological specialty consultations for physical modalities and cognitive modalities may be beneficial adjuncts to pharmacologic interventions. Attentions should be focused on psychosocial support and providing education to patients and families.

Clinical Guideline	Recommendation(s)
American Society of Interventional Pain Physicians: **Guidelines for Responsible Opioid Prescribing in Chronic Non-Cancer Pain (2012)**[19]	• Once medical necessity is established, opioid therapy may be initiated with low doses and short-acting drugs with appropriate monitoring to provide effective relief and avoid side effects. • Up to 40 mg of morphine equivalent is considered as a low dose, 41 to 90 mg of morphine equivalent as a moderate dose, and greater than 91 mg of morphine equivalent as a high dose. • In reference to long-acting opioids, titration must be carried out with caution, and overdose and misuse must be avoided. • The long-acting opioids in high doses are recommended only in specific circumstances with severe intractable pain that is not amendable to short-acting or moderate doses of long-acting opioids, as there is no significant difference between long-acting and short-acting opioids for their effectiveness or adverse effects. • Methadone and buprenorphine are recommended for use in late stages after failure of other opioid therapy and only by clinicians with specific training in the risks and uses. • It is essential to monitor for side effects and manage them appropriately, including discontinuation of opioids if indicated. • A trial of opioid rotation may be considered for patients experiencing intolerable adverse events or inadequate benefit despite dose increases. • Chronic opioid therapy may be continued, with continuous adherence monitoring, in well-selected populations, in conjunction with or after failure of other modalities of treatments with improvement in physical and functional status and minimal adverse effects.

European Society for Medical Oncology: **Management of Cancer Pain (2012)**[20]	• Treatment of mild pain (WHO Step 1 analgesics):
	  o Acetaminophen or NSAIDs.
	• Treatment of moderate pain (WHO Step 2 analgesics):
	  o Acetaminophen, aspirin, or an NSAID plus a weak immediate-release opioid such as codeine, dihydrocodeine, tramadol, or propoxyphene or a strong opioid at low doses such as morphine or oxycodone.
	  o New opioid formulations may improve drug administration for patients with moderate pain. These include controlled release formulations of codeine, dihydrocodeine, tramadol, morphine and oxycodone in dosages appropriate for moderate pain.
	  o Additional options include low-dose formulations of transdermal fentanyl and of transdermal buprenorphine.
	• Treatment of severe pain (WHO Step III analgesics):
	  o Morphine is most commonly used in severe pain and oral administration is the preferred route.
	  o Hydromorphone and oxycodone are an alternative to oral morphine.
	  o Transdermal fentanyl and transdermal buprenorphine should be reserved for patients whose opioid requirements are stable. They are usually the treatment of choice for patients who are unable to swallow, patients with poor tolerance to morphine and patients with poor compliance.
	  o Methadone is an alternative treatment option, but may be more complicated to use because of its pharmacokinetic parameters. Methadone should be initiated by physicians with experience and expertise in its use.
	  o Strong opioids may be combined with a nonopioid analgesic (step 1).
	  o Patients with severe pain that need urgent relief should be treated with parenteral opioids
	• Opioid doses should be titrated to effect as rapidly as possible, with around-

Clinical Guideline	Recommendation(s)
	the-clock dosing and an as-needed 'breakthrough dose' (usually=10% of total daily dose) to manage transient pain exacerbations. If more than four 'breakthrough doses' per day are necessary, opioid treatment with a slow-release formulation should be initiated. • Reduction in opioid dose may be achieved by using a co-analgesic, such an antidepressant, neuroleptic psychoactive drug or anticonvulsant. Such combinations may also alleviate refractory side effects such as constipation, nausea, vomiting and central nervous system toxicity. Other strategies include the continued use of anti-emetics, laxatives, major tranquilizers, and psychostimulants; also, switching to another opioid agonist and/or another route may allow titration to adequate analgesia without the same disabling effects. • Neuropathic pain may not be adequately controlled by opioids alone; combination with co-analgesics may improve pain control. Steroids should be considered in case of nerve compression. There is sufficient evidence for use of bisphosphonates for refractory bone pain, but not for general use as first-line therapy of bone pain.

National Opioid Use Guideline Group: **Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain (2010)**[21]	<u>Conducting an opioid trial</u>
	• During an opioid trial, select the most appropriate opioid for trial therapy using a stepped approach, and consider safety.
	• Mild-to-moderate pain:
	  o First-line therapy: codeine or tramadol. There is a lower risk of overdose and addiction with these agents than stronger opioids. Tramadol is associated with seizures in patients at high seizure risk, or when combined with medications that increase serotonin levels (e.g., selective serotonin reuptake inhibitors).
	  o Second-line therapy: morphine, oxycodone or hydromorphone.
	• Severe pain:
	  o First-line therapy: morphine, oxycodone or hydromorphone. Oxycodone, hydromorphone and hydrocodone may have a higher abuse liability than morphine.
	  o Second-line therapy: fentanyl. Before starting fentanyl, ensure the patient is fully opioid tolerant.
	  o Third-line therapy: methadone. Titration of methadone is hazardous due to its very long half life leading to drug accumulation.
	• Start with a low dosage, increase dosage gradually and monitor opioid effectiveness until optimal dose is attained.
	• Chronic non-cancer pain can be managed effectively in most patients with dosages at or below 200 mg/day of morphine or equivalent.
	• When initiating opioid therapy for patients at higher risk for misuse, prescribe only for well-defined somatic or neuropathic pain conditions, start with lower doses and titrate in small-dose increments, and monitor closely for signs of drug-related behaviors.
	• Meperidine is not recommended for use in chronic non-cancer pain. Oral meperidine has poor bioavailability and is less effective than codeine. Normeperidine can accumulate with frequent use of parenteral doses of meperidine, causing seizures and delirium.
	• Use acetaminophen-opioid combinations with caution to avoid acetaminophen toxicity.
	• Titrate controlled-release formulations with caution to avoid overdose and misuse. Each controlled-release tablet can contain a much higher opioid dose than immediate-release formulations, and can easily be converted to immediate release by biting or crushing the tablet.
	• Parenteral opioids are not recommended for use in chronic non-cancer pain. The parenteral route has higher risk of overdose, abuse and addiction, and

Clinical Guideline	Recommendation(s)

	infection.
	
	<u>Monitoring long-term opioid therapy</u>
	• For patients experiencing unacceptable adverse effects or insufficient opioid effectiveness from one particular opioid, try prescribing a different opioid or discontinuing therapy.
	• For patients receiving opioids for a prolonged period who may not have had an appropriate trial of therapy, take steps to ensure that long-term therapy is warranted and dose is optimal.
	
	<u>Treating specific populations with long-term opioid therapy</u>
	• Opioid therapy in elderly patients can be safe and effective. They cause less organ toxicity than NSAIDs and appear to cause less cognitive impairment than benzodiazepines. Among strong opioids, oxycodone and hydromorphone may be preferred over oral morphine because they are less likely to cause constipation and sedation. Controlled-release formulations are recommended due to compliance. There is no evidence controlled-release formulations are more effective than immediate-release formulations. For breakthrough pain or activity-related pain, immediate release formulations can be used.
	• A trial of opioid therapy may be considered for adolescent patients with well-defined somatic or neuropathic pain conditions when non-opioid alternatives have failed, risk of opioid misuse is assessed as low, close monitoring is available, and consultation, if feasible, is included in the treatment plan.
	• Pregnant patients taking long-term opioid therapy should be tapered to the lowest effective dose slowly enough to avoid withdrawal symptoms, and then therapy should be discontinued if possible.
	• Patients with a psychiatric diagnosis are at greater risk for adverse effects from opioid treatment. Usually in these patients, opioids should be reserved for well-defined somatic or neuropathic pain conditions. Titrate more slowly and monitor closely; seek consultation where feasible.
	
	<u>Managing opioid misuse and addiction in chronic non-cancer pain patients</u>
	• For patients with chronic non-cancer pain who are addicted to opioids, three treatment options should be considered: methadone or buprenorphine treatment, structured opioid therapy, or abstinence-based treatment.
	• Indications for methadone treatment are any of the following:
	  o Failed trial of structured opioid therapy.
	  o Using opioids by injection, snorting, or crushing tablets.
	  o Accessing opioids from multiple physicians or from the “street”.
	  o Addiction to opioids and to other drugs/substances.
	• Indications for buprenorphine treatment are similar to those for methadone treatment. Buprenorphine could be preferred over methadone for:
	  o Patients who are at higher risk of methadone toxicity.
	  o Adolescents and young adults.
	  o Patients in communities where methadone treatment is unavailable.
	• An ideal candidate for a structured opioid therapy trial would be an opioid-addicted patient with chronic non-cancer pain who:
	  o Has a well-defined somatic or neuropathic pain condition for which opioids have been shown to be effective.
	  o Is well-known to the physician.
	  o Is not currently addicted to cocaine, alcohol or other drugs.
	  o Is not accessing opioids.
	• Abstinence-based treatment can be a patient preference or used when methadone or buprenorphine treatment is not available.

American Society of	• Pharmacologic management of chronic pain includes anticonvulsants,

Clinical Guideline	Recommendation(s)
Anesthesiologists/ American Society of Regional Anesthesia and Pain Medicine: **Practice Guidelines for Chronic Pain Management (2010)**[22]	antidepressants, benzodiazepines, N-methyl-D-aspartate (NMDA) receptor antagonists, NSAIDs, opioid therapy, skeletal muscle relaxants, and topical agents. • Anticonvulsants should be used as part of a multimodal strategy for patients with neuropathic pain. • Tricyclic antidepressants should be used as part of a multimodal strategy for patients with chronic pain. • Serotonin–norepinephrine reuptake inhibitors should be used as part of a multimodal strategy for a variety of chronic pain patients. • Selective serotonin reuptake inhibitors may be considered specifically for patients with diabetic neuropathy. • As part of a multimodal pain management strategy, extended-release oral opioids should be used for neuropathic or back pain patients, and transdermal, sublingual, and immediate-release oral opioids may be used. • For selected patients, NMDA receptor antagonists (e.g., neuropathic pain), NSAIDs (e.g., back pain), and topical agents (e.g., peripheral neuropathic pain) may be used; benzodiazepines and skeletal muscle relaxants may be considered. • A strategy for monitoring and managing side effects, adverse effects, and compliance should be considered for all patients undergoing any long-term pharmacologic therapy.

Veterans Health Administration, Department of Defense: **Clinical Practice Guideline for the Management of Opioid Therapy for Chronic Pain (2010)**[23]	<u>General considerations</u>
	• A trial of opioid therapy is indicated for a patient with chronic pain who meets all of the following criteria:
	  o Moderate to severe pain that has failed to adequately respond to non-opioid and non-drug therapeutic interventions.
	  o The potential benefits of opioid therapy are likely to outweigh the risks.
	  o The patient is fully informed and consents to the therapy.
	  o Clear and measurable treatment goals are established.
	
	<u>Initiation phase</u>
	• There is no evidence to recommend for or against the selection of any specific opioid:
	  o Select a specific opioid formulation that matches the individual's needs and specific medical conditions.
	  o Consider patient preference, and agent that allows administration by the least in visual analogue scale route.
	  o Consider the ease of drug administration, patient's prior experience with, and level of tolerance to opioid medications, potential risk for misuse, and abuse patterns.
	  o Transdermal fentanyl should be avoided in opioid naïve patients.
	• Start the opioid therapy trial with a low dose and with one medication at a time.
	• For continuous chronic pain, an agent with a long duration of action, such as controlled-release morphine or methadone is recommended. Short-acting opioids can be started, and later converted to long acting opioids.
	• Treatment of continuous chronic pain should be initiated with opioids on a defined and scheduled basis.
	• For episodic chronic pain, consider short-acting opioids (such as morphine, oxycodone, or hydrocodone), trying one medication at a time on an as needed basis. Long-acting opioids should not be used on an as needed basis.
	
	<u>Titration phase</u>
	• Titration should be individualized according to the patient's age, health status,

Clinical Guideline	Recommendation(s)

	previous exposure to opioids, level of pain, comorbidities, potential drug interactions, opioid formulation, level of care, attainment of therapeutic goals, and predicted or observed harms.
	• The daily dose may be increased by 25 to 100% at a time. Smaller increments are appropriate for elderly patients, those with likely low opioid tolerance, and patients experiencing unsatisfactory pain relief in the presence of some adverse effects. Larger increments may be used in patients with severe uncontrolled pain or likely high level of opioid tolerance.
	• To ensure that the full effect from a dosage change has been manifested, and to avoid potential toxicity due to rapid accumulation of a drug, do not increase the dose more frequently than every five half-lives.
	• Methadone dosage titration should not occur more frequently than every seven days or longer (e.g., every one to two months), and only if there is no problem with daytime sedation.
	• If possible, titrate one drug at a time while observing the patient for additive effects. Maintain patients on as few medications as possible to minimize drug interactions and adverse events.
	• Discontinue medications, especially adjuvant medications, which do not add substantially to patient function or comfort.
	• If a medication provides less than satisfactory pain reduction despite increasing the dose as tolerated to a reasonable level (<200 mg/day morphine equivalent), evaluate for potential causes such as nonadherence and drug interactions, and consider changing to an alternate opioid medication.
	• During the titration phase, reasonable supplemental doses of a short acting opioid may be considered.
	• Consider one or more of the following adjustments in therapy when there is an apparent loss of analgesic effect:
	  o Further optimize adjuvant therapies.
	  o Re-titrate the dose.
	  o Rotate to another opioid.
	  o Refer or consult with advanced pain care specialist.
	  o Discontinue opioid therapy.
	
	<u>Maintenance phase</u>
	• Maintain the lowest effective and well-tolerated dose. The optimal opioid dose is the one that achieves the goals of pain reduction and/or improvement in functional status and patient satisfaction with tolerable adverse effects.
	
	<u>Supplemental therapy</u>
	• Supplemental short- acting opioids may be considered in specific situations but their routine use in chronic pain is controversial.
	• This guideline supports the use of long-acting opioids in a scheduled manner for chronic pain, rather than the use of supplemental or as-needed opioids for exacerbations.
	• Evaluate worsening or new pain symptoms to determine the cause and the best treatment approach.
	• Encourage the use of nonpharmacologic treatments.
	• Evaluate the potential benefits, side effects, and risks when considering supplemental opioids. Consider supplemental short-acting opioid, non-opioid, or a combination of both agents on an as needed basis.
	• Avoid the use of rapid-onset opioids as supplemental opioid therapy in chronic pain, unless the time course of action of the preparation matches the temporal pattern of pain intensity fluctuation.
	• Avoid use of long-acting agents for acute pain or on an as-needed basis in an outpatient setting.

Clinical Guideline	Recommendation(s)
	• When using combination products, do not exceed maximum recommended daily doses of acetaminophen, aspirin, or ibuprofen. • Avoid the use of mixed agonist-antagonist opioids, as these agents may precipitate withdrawal in patients who have physical opioid dependence. • Whenever possible, use the same opioid for supplemental therapy as the long-acting opioid to avoid confusion about the cause of any adverse effects that may develop. • When using short-acting pure agonist opioids (alone or in combination with non-opioid analgesics) for supplemental therapy, give opioid doses equivalent to about 10 to 15%, the every four hourly equivalent, or 1/6th of the total daily opioid dose, as needed. • Use rescue short-acting opioids to assist with pain management during the titration process and to help determine the long-term daily opioid dose. • Do not use breakthrough pain therapy routinely for chronic pain. If necessary, use breakthrough pain therapy sparingly. • Consider adjusting the long-acting opioid regimen if pain exacerbations are interfering with patient function due to severity, frequency, or diurnal variations in pain intensity. • Consider providing preemptive analgesia for preventing incident pain.
American Pain Society/ American Academy of Pain Medicine: **Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain (2009)**[24]	• Consider a trial of chronic opioid therapy if chronic noncancer pain is moderate or severe, pain is having an adverse impact on function or quality of life, and potential therapeutic benefits outweigh or are likely to outweigh potential harms. • Opioid selection, initial dosing, and titration should be individualized according to the patient's health status, previous exposure to opioids, attainment of therapeutic goals, and predicted or observed harms. • There is insufficient evidence to recommend short-acting vs long-acting opioids, or as-needed vs around-the-clock dosing of opioids. • Methadone is characterized by complicated and variable pharmacokinetics and pharmacodynamics and should be initiated and titrated cautiously by clinicians familiar with its use and risks. • When repeated dose escalations occur in patients on chronic opioid therapy, evaluate potential causes and reassess benefits relative to harms. • In patients who require relatively high doses of chronic opioid therapy, evaluate for unique opioid-related adverse effects, changes in health status, and adherence to the chronic opioid therapy treatment plan on an ongoing basis, and consider more frequent follow-up visits. • Consider opioid rotation when patients on chronic opioid therapy experience intolerable adverse effects or inadequate benefit despite dose increases. • Taper or wean patients off of chronic opioid therapy who engage in repeated aberrant drug-related behaviors or drug abuse/diversion, experience no progress toward meeting therapeutic goals, or experience intolerable adverse effects. • In patients on around-the-clock chronic opioid therapy with breakthrough pain, consider as-needed opioids based upon an initial and ongoing analysis of therapeutic benefit vs risk.
Veterans Health Administration, Department of Defense: **Clinical Practice Guideline for Management of Substance Use Disorders (2009)**[25]	General considerations • Opioid agonist treatment is the first-line treatment for chronic opioid dependence. • Provide access to opioid agonist treatment for all opioid dependent patients, under appropriate medical supervision and with concurrent addition-focused psychosocial treatment. • Strongly recommend methadone or sublingual buprenorphine/naloxone maintenance as first-line therapy. Buprenorphine monotherapy is preferred in pregnancy.

Clinical Guideline	Recommendation(s)
	• By administering an opioid to prevent withdrawal, reduce craving, and reduce the effects of illicit opioids, the opioid-dependent patient is able to focus more readily on recovery activities. <u>Opioid agonist treatment program and office-based opioid treatment</u> • Opioid agonist treatment should be administered in an opioid agonist treatment program or office-based opioid treatment. • Doses should be adjusted to maintain a therapeutic range between signs/symptoms of overmedication and opioid withdrawal. • The usual dosage range for optimal effects is 60 to 120 mg/day. • Buprenorphine target dose is generally up to 16 mg/day; doses >32 mg are rarely indicated. • In all cases (except pregnancy), the combination product of buprenorphine/naloxone should be used. <u>Methadone therapy</u> • Methadone for the treatment of opioid dependence may only be prescribed out of an accredited opioid agonist treatment program as it is a schedule II agent. It is illegal to prescribe methadone for the treatment of opioid dependence out of an office-based practice. • For newly admitted patients, the initial dose of methadone should not exceed 30 mg and the total dose for the first day should not exceed 40 mg, without provider documentation that 40 mg did not suppress opioid withdrawal symptoms. • Under usual practices, a stable, target dose is greater than 60 mg/day and most patients will require considerably higher doses in order to achieve a pharmacological blockade of reinforcing effects of exogenously administered opioids. <u>Buprenorphine therapy</u> • Office-based treatment with sublingual buprenorphine for opioid dependence can only be provided by physicians who have received a waiver from the Substance Abuse and Mental Health Services Administration (SAMHSA) and have a special Drug Enforcement Agency (DEA) number. • Buprenorphine induction (~1 week) involves helping a patient in the process of switching from the opioids of abuse to buprenorphine. • In all cases (except pregnancy), the combination product of buprenorphine/naloxone should be used. • The initial dose of buprenorphine/naloxone combination is between 2/0.5 mg to 4/1 mg, which can be repeated after two hours. The amount of buprenorphine administered in the first day should not exceed 8 mg. • The daily buprenorphine/naloxone dose is the equivalent to the total amount of buprenorphine/naloxone (or buprenorphine) that was administered on day one. Doses may be increased as needed for symptomatic relief, with a target dose of 12/3 mg to 16/4 mg per day to be achieved within the first week.
American Psychiatric Association: **Practice Guideline for Treatment of Patients with Substance Use Disorders (2006)**[26]	<u>Treating dependence and abuse</u> • Goals of therapy are to identify stable maintenance dose of opioid agonist and facilitate rehabilitation. • The choice of treatment for opioid dependence is based on patient preference, past response to treatment, probability of achieving and maintaining abstinence, and assessment of the short- and long-term effects of continued use of illicit opioids on the patient's life adjustment and overall health status. • Maintenance treatment with methadone or buprenorphine is appropriate for patients with ≥ 1 year history of opioid dependence. Maintenance therapy with naltrexone is an alternative strategy.

Clinical Guideline	Recommendation(s)

	• Methadone is a full mu agonist opioid, and is the most thoroughly studied and widely used agent for opioid dependence.
	• Methadone maintenance treatment for opioid-dependent individuals has generally been shown to be effective in:
	  o Decreasing illicit opioid use.
	  o Decreasing psychosocial and medical morbidity.
	  o Improving overall health status.
	  o Decreasing mortality.
	  o Decreasing criminal activity.
	  o Improving social functioning.
	  o Reducing the spread of Human Immunodeficiency Virus infection among intravenous drug users.
	• Maintenance on methadone is generally safe; however, one key issue is determining a dose sufficient to suppress the patient's opioid withdrawal and craving, as no single dose is optimal for all patients.
	• Methadone can be diverted for abuse, as can other opiates that have agonist effects at the mu receptor.
	• Buprenorphine produces a partial agonist effect at the mu receptor and an antagonistic effect at the kappa receptor.
	• Buprenorphine enters the systemic circulation more slowly through the sublingual route than with parenteral administration and has less abuse potential compared to the parenterally delivered form.
	• The combination of buprenorphine and naloxone significantly reduces the risk of diversion because naloxone will exert a potent opioid antagonist effect if the combination tablet is crushed and administered intravenous by an opioid-dependent person. Naloxone has poor sublingual bioavailability.
	• Buprenorphine is generally safe. Overdose with buprenorphine generally does not produce significant respiratory depression
	
	<u>Treating intoxication</u>
	• Mild to moderate opioid intoxication usually does not require specific therapy.
	• Severe opioid toxicity, marked by respiratory depression, is a medical emergency. Naloxone will reverse respiratory depression and other overdose manifestations.
	
	<u>Treating withdrawal</u>
	• Treatment of withdrawal is directed at safely decreasing acute symptoms and easing transition into a long-term treatment program.
	• Effective strategies include:
	  o Substitution of opioid with methadone or buprenorphine.
	  o Abrupt discontinuation of opioids, with use of clonidine to suppress withdrawal symptoms.
	  o Clonidine-naltrexone detoxification.

Center for Substance Abuse Treatment: **Medication-Assisted Treatment For Opioid Addiction in Opioid Treatment Programs (TIP 43) (2005)**[27]	• To be considered for buprenorphine maintenance, patients should have a diagnosis of opioid dependence. • It is recommended that buprenorphine and naloxone be used for induction treatment (and for stabilization and maintenance) for most patients. • The initial induction doses should be administered as observed treatment; further doses may be provided via prescription thereafter. • To minimize the chances of precipitated withdrawal, patients who are transferring from long-acting opioids to buprenorphine should be inducted using buprenorphine monotherapy, but switched to buprenorphine and naloxone soon thereafter. • The longest period that a patient is on buprenorphine is the maintenance

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	phase. This period may be indefinite. • Buprenorphine can be used for the medically supervised withdrawal of patients from both self-administered opioids and from opioid agonist treatment with methadone or levo-alpha-acetyl-methadol. • The goal of using buprenorphine for medically supervised withdrawal from opioids is to provide a transition from the state of physical dependence on opioids to an opioid-free state, while minimizing withdrawal symptoms. • It is recommended that patients dependent on short-acting opioids who will be receiving medically supervised withdrawal be inducted directly onto buprenorphine and naloxone tablets. • The use of buprenorphine or buprenorphine and naloxone to taper off long-acting opioids should be considered only for those patients who have evidence of sustained medical and psychosocial stability, and should be undertaken in conjunction and in coordination with patients' opioid treatment programs.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the opiate agonists are noted in Tables 3 to 6. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Single Agent Opiate Agonists (Drugs A-M)[4-6]

Indication	Codeine	Fentanyl	Hydromorphone	Levorphanol	Meperidine	Methadone	Morphine
Analgesia							
For obstetrical analgesia					✔ ‡		
Management of breakthrough pain in patients with cancer who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain		✔ *»^					
Management of moderate to severe pain in patients where an opioid analgesic is appropriate			✔	✔			✔
Management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time						✔ ‖	✔ #
Management of persistent, moderate to severe chronic pain in opioid-tolerant patients when a continuous, around-the-clock opioid analgesic is required for an extended period of time, and the patient cannot be managed by other means such as non-steroidal analgesics, opioid combination products, or immediate-release opioids		✔ †					
Relief of mild to moderate pain	✔						
Relief of moderate to severe pain					✔ ‡§	✔ ‡	
Treatment of pain following major surgery							✔ **
Anesthesia							
For analgesic action of short duration during the anesthetic periods, premedication, induction and maintenance, and in the immediate postoperative period as the need arises		✔ ‡					
Narcotic analgesic supplement in general or regional anesthesia		✔ ‡					
For administration with a neuroleptic as an anesthetic premedication, for the induction of anesthesia and as an adjunct in the maintenance of general and regional anesthesia		✔ ‡					
For use as an anesthetic agent with oxygen in selected high risk patients, such as those undergoing open heart surgery or certain complicated neurological or orthopedic procedures		✔ ‡					
Preoperative medication					✔ ‡		
Support of anesthesia					✔ ‡		
Detoxification/Dependence							
For detoxification treatment of opioid addiction (heroin or other						✔ ¶	

Indication	Codeine	Fentanyl	Hydromorphone	Levorphanol	Meperidine	Methadone	Morphine
morphine-like drugs)							
For maintenance treatment of opioid addiction (heroin or other morphine-like drugs), in conjunction with appropriate social and medical services						✔ ¶	
For use in temporary treatment of opioid dependence in patients unable to take oral medication						✔ ‡	

*Buccal formulation.
^Intranasal formulation.
»Sublingual formulation.
†Transdermal formulation.
‡Injection formulation.
§Oral formulations.
‖ Oral solution and tablet formulations (5 to 10 mg only).
¶ Oral concentrate, oral solution, and tablet formulations.
# Sustained-release tablet.
**Epidural formulation.

Table 4. FDA-Approved Indications for the Single Agent Opiate Agonists (Drugs N-Z)[4-6]

Indication	Oxycodone	Oxymorphone	Tapentadol	Tramadol
Analgesia				
For obstetrical analgesia		✔ *		
Management of moderate to moderately severe chronic pain in adults who require around-the-clock treatment of their pain for an extended period of time				✔ †
Management of moderate to severe chronic pain or neuropathic pain associated with diabetic peripheral neuropathy in adults when a continuous, around-the-clock opioid analgesic is needed for an extended period of time			✔ †	
Management of moderate to severe pain in patients where an opioid analgesic is appropriate	✔	✔		
Relief of moderate to moderately severe pain				✔
Relief of moderate to severe pain			✔	
Anesthesia				
Preoperative medication		✔ *		
Support of anesthesia		✔ *		
Miscellaneous				
Relief of anxiety in patients with dyspnea associated with pulmonary edema secondary to acute left ventricular dysfunction		✔ *		

*Injection formulation.
†Extended-release formulation.

Table 5. FDA-Approved Indications for the Combination Opiate Agonists (Drugs A-H)[4-6]

Indication	Codeine and Acetaminophen	Codeine, Butalbital, Acetaminophen and Caffeine	Codeine, Butalbital, Aspirin and Caffeine	Dihydrocodeine, Acetaminophen and Caffeine	Dihydrocodeine, Aspirin and Caffeine	Hydrocodone and Acetaminophen	Hydrocodone and Ibuprofen
Analgesia							
Relief of mild to moderate pain	✔						
Relief of moderate to moderately severe pain				✔	✔	✔	
Short-term (≤10 days) management of acute pain							✔
Headache							
Relief of tension or muscle contraction headache		✔	✔				

Table 6. FDA-Approved Indications for the Combination Opiate Agonists (Drugs I-Z)[4-6]

Indication	Opium and Belladonna	Oxycodone and Acetaminophen	Oxycodone and Aspirin	Oxycodone and Ibuprofen	Tramadol and Acetaminophen
Analgesia					
Relief of moderate to moderately severe pain		✔	✔		
Relief of moderate to severe pain associated with ureteral spasms not responsive to nonopioid analgesics and to space intervals between injections of opiates	✔				
Short-term (≤5 days) management of acute pain					✔
Short-term (≤7 days) management of acute, moderate to severe pain				✔	

IV. Pharmacokinetics

The pharmacokinetic parameters of the opiate agonists are listed in Table 7. Pharmacokinetic properties of the combination products not listed in the table below would be in line with the properties of their individuals components listed in the table below.

Table 7. Pharmacokinetic Parameters of the Opiate Agonists[4-6]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Single Entity Agents/Components					
Codeine	Oral: well absorbed	7	Liver (24 to 89)	Renal (11)	2.5 to 3.5
Dihydrocodeine	21	Not reported	Not reported	Not reported	3.3 to 4.5
Fentanyl	Buccal: 50 to 76 SL: 54 TD: 92	80 to 86	Liver	Renal (10)	Buccal: 2.6 to 12.0 Injection: <4 SL: 5 to 13.5 TD: 17
Hydrocodone	Not reported	Not reported	Liver	Renal (6 to 20)	3.8 to 4.5
Hydromorphone	24	8 to 27	Liver (95)	Renal (1 to 13)	2.5
Levorphanol	Rapid	40 to 50	Liver	Not reported	11
Meperidine	Oral: variable	65 to 80	Liver	Renal (0.5 to 2)	3.2 to 3.7
Methadone	Oral: 85	71 to 88	Liver	Renal (21)	23
Morphine	Buccal: 50 Oral: 20 to 40 TD: 75	20 to 36	Liver	Renal (9)	1.5 to 2.0
Oxycodone	60 to 87	45	Liver	Renal (19)	3.2
Oxymorphone	10	10 to 12	Liver	Renal (1 to 2)	Injection: 1.3 Oral: 7 to 9
Tapentadol	32	20	Liver (97)	Renal (99)	4
Tramadol	IR: 75 ER: 85 to 95	20	Liver	Renal (30)	IR: 6.3 ER: 7.9
Combination Products					
Opium and belladonna	Not reported	Not reported	Not reported	Not reported	Not reported

ER=extended-release, IR=immediate-release, SL=sublingual, TD=transdermal

V. Drug Interactions

Significant drug interactions with the opiate agonists are listed in Table 8.

Table 8. Significant Drug Interactions with the Opiate Agonists[4]

Generic Name(s)	Significance Level	Interaction	Mechanism
Opiate agonists (fentanyl, methadone, oxycodone)	1	Azole antifungal agents	Pharmacologic effects and adverse reactions of opiates may be increased due to inhibition of CYP3A4 metabolism by azole antifungals.
Opiate agonists (fentanyl, oxycodone)	1	Human immuno-deficiency virus protease inhibitors	Human immunodeficiency virus protease inhibitors may increase plasma concentrations and pharmacologic effects of opiate agonists. Severe respiratory depression may occur. Inhibition of

Generic Name(s)	Significance Level	Interaction	Mechanism
			cytochrome P450 3A4 isoenzymes by Human immunodeficiency virus protease inhibitors may decrease the metabolic elimination of opiate agonists.
Opiate agonists (codeine, fentanyl, methadone, oxycodone)	1	Macrolide and related antibiotics	Inhibition of opiate agonist metabolism (CYP 3A4) by macrolide and related antibiotics may increase opiate plasma concentrations, increasing the pharmacologic effects and toxicity.
Acetaminophen	1	Isoniazid	Isoniazid may increase the toxic effects of acetaminophen. The mechanism of this interaction is unknown.
Aspirin	1	Anticoagulants	The use of anticoagulants with aspirin may increase the risk of bleeding, especially gastrointestinal bleeding. However, when low-dose aspirin is used with anticoagulants, the therapeutic benefit may outweigh the risk of minor bleeding.
Aspirin	1	Heparin and factor Xa inhibitors	The risk of bleeding in heparin and factor Xa inhibitors treated patients may be increased by aspirin due to additive anticoagulant effects.
Aspirin	1	Methotrexate	Therapeutic and toxic effects (bone marrow depression, hepatotoxicity) of methotrexate may be increased by concurrent use of aspirin. Aspirin may inhibit renal excretion of methotrexate and displace it from plasma protein binding sites.
Aspirin	1	Nonsteroidal anti-inflammatory drugs	Regular use of nonsteroidal anti-inflammatory drugs may decrease the antiplatelet effects of aspirin. Reduced antiplatelet efficacy in patients with underlying cardiovascular risk may occur. Additionally, the potential for gastrointestinal side effects, including bleeding, may be increased with regular use of full-dose aspirin.
Butalbital	1	Anticoagulants	Butalbital may decrease the hypoprothrombinemic effects of anticoagulants. Induction of hepatic microsomal enzymes by butalbital may increase the metabolism of anticoagulants. Butalbital may decrease the gastrointestinal absorption of dicumarol.
Butalbital	1	Estrogens	Butalbital may decrease the pharmacologic effects of estrogens with potential subsequent reductions of contraceptive or non-contraceptive estrogen efficacy. Butalbital may increase hepatic metabolism of estrogens.
Fentanyl	1	Amiodarone	Profound bradycardia, sinus arrest, and hypotension have occurred.
Fentanyl	1	Diltiazem	Diltiazem may increase plasma concentrations of fentanyl, increasing the potential for enhanced pharmacologic effects and toxicity. Inhibition of

Generic Name(s)	Significance Level	Interaction	Mechanism
			cytochrome P450 3A4 isoenzyme by diltiazem may decrease the metabolic elimination of fentanyl.
Fentanyl	1	Verapamil	Verapamil may increase plasma concentrations of fentanyl, increasing the potential for enhanced pharmacologic effects and toxicity. Inhibition of cytochrome P450 3A4 isoenzyme by verapamil may decrease the metabolic elimination of fentanyl.
Ibuprofen	1	Anticoagulants	The use of anticoagulants with ibuprofen may increase the risk of bleeding. Ibuprofen may impair platelet function and irritate the gastrointestinal mucosa leading to an increased risk of hemorrhage.
Ibuprofen	1	Heparin and factor Xa inhibitors	The risk of bleeding in heparin and factor Xa inhibitors treated patients may be increased by ibuprofen due to additive anticoagulant effects.
Ibuprofen	1	Methotrexate	Plasma concentrations and toxic effects of methotrexate may be increased by ibuprofen. Severe toxicity characterized by bone marrow suppression, nephrotoxicity and mucositis has occurred in patients receiving ibuprofen high-dose methotrexate chemotherapy.
Ibuprofen	1	Salicylates	Regular use of ibuprofen may decrease the antiplatelet effects of salicylates. Reduced antiplatelet efficacy in patients with underlying cardiovascular risk may occur. Additionally, the potential for gastrointestinal side effects, including bleeding, may be increased with regular use of full-dose aspirin.
Meperidine	1	Monoamine oxidase inhibitors	A severe and potentially fatal reaction may occur shortly after administering meperidine to patients receiving monoamine oxidase inhibitors.
Methadone	1	Benzodiazepines	The synergistic effects of opioids and benzodiazepines may increase the risk of sedation and life-threatening respiratory depression, especially with overdosage.
Methadone	1	Class IA and IC antiarrhythmics	Co-administration of methadone and class IA and IC antiarrhythmics may cause significant prolongation of the cardiac QT interval, and possibly lead to torsades de pointes arrhythmias, especially in high doses, female sex, hypokalemia, or patients with a history of cardiac conduction disease. Methadone inhibits cardiac potassium channels and prolongs the QT interval. This may become significant with larger doses and in combination with other drugs that may also prolong the QT interval, such as class IA and IC antiarrhythmics.

Generic Name(s)	Significance Level	Interaction	Mechanism
Methadone	1	Class III antiarrhythmics	Prolongation of the QT interval with possible development of cardiac arrhythmias, including torsades de pointes, should be considered when class III antiarrhythmics are co-administered with methadone. Pharmacologic effects of class III antiarrhythmics and methadone on electrical conduction of the heart may be additive.
Methadone	1	Dofetilide	Co-administration of methadone and dofetilide may cause significant prolongation of the cardiac QT interval, and possibly lead to torsades de pointes arrhythmias, especially in high doses, female sex, hypokalemia, or patients with a history of cardiac conduction disease. Methadone inhibits cardiac potassium channels and prolongs the QT interval. This may become significant with larger doses and in combination with other drugs that may also prolong the QT interval, such as dofetilide.
Methadone	1	Dronedarone	Prolongation of the QT interval with possible development of cardiac arrhythmias, including torsades de pointes, should be considered when dronedarone is co-administered with methadone. Pharmacologic effects of dronedarone and methadone on electrical conduction of the heart may be additive.
Methadone	1	H-1 antagonists	Co-administration of methadone and H-1 antagonists may cause significant prolongation of the cardiac QT interval, and possibly lead to torsades de pointes arrhythmias, especially in high doses, female sex, hypokalemia, or patients with a history of cardiac conduction disease. Methadone inhibits cardiac potassium channels and prolongs the QT interval. This may become significant with larger doses and in combination with other drugs that may also prolong the QT interval, such as H-1 antagonists.
Methadone	1	Nilotinib	Additive QT prolongation may occur during coadministration of nilotinib and methadone. QT interval effects of each agent may be additive.
Methadone	1	Quinolones	Co-administration of methadone and quinolones may cause significant prolongation of the cardiac QT interval, and possibly lead to torsades de pointes arrhythmias, especially in high doses, female sex, hypokalemia, or patients with a history of cardiac conduction disease. Additionally, ciprofloxacin may increase pharmacologic effects of methadone.

Generic Name(s)	Significance Level	Interaction	Mechanism
			Methadone inhibits cardiac potassium channels and prolongs the QT interval. This may become significant with larger doses and in combination with other drugs that may also prolong the QT interval, such as quinolones.
Tapentadol	1	Monoamine oxidase inhibitors	Toxic effects may be increased with concurrent administration of tapentadol and monoamine oxidase inhibitors. Serious and sometimes fatal reactions have occurred. Pharmacologic effects of tapentadol and monoamine oxidase inhibitors may be additive.
Tramadol	1	Monoamine oxidase inhibitors	A severe reaction potentially involving the respiratory, cardiac and central nervous systems may occur shortly after administering tramadol to patients receiving monoamine oxidase inhibitors. The seizure threshold may also be reduced.
Tramadol	1	Serotonin–norepinephrine reuptake inhibitors and serotonin reuptake blockers	Co-administration of Serotonin–norepinephrine reuptake inhibitors and serotonin reuptake blockers with tramadol may result in the development of serotonin syndrome (e.g., agitation, altered consciousness, ataxia, myoclonus, overactive reflexes, shivering).
Opiate agonists (codeine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine, methadone, morphine, opium and belladonna, oxycodone, oxymorphone, tapentadol)	2	Naltrexone	Naltrexone may decrease or attenuate the pharmacologic effects of opiate agonists. Coadministration of naltrexone and opiate agonists may precipitate withdrawal symptoms in individuals who are physically dependent on opioid drugs.
Opiate agonists (codeine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine, methadone, morphine, opium and belladonna, oxycodone, oxymorphone)	2	Barbiturate anesthetics	The combination of barbiturate anesthetics and opiate agonists may result in increased respiratory and central nervous system depressive effects. Additive pharmacologic effects may produce increased clinical effects.
Opiate agonists (codeine, dihydrocodeine,	2	Rifamycins	Rifamycins may decrease pharmacologic effects and plasma concentrations of opiate agonists. Pain control may be decreased.

Generic Name(s)	Significance Level	Interaction	Mechanism
fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine, methadone, morphine, opium and belladonna, oxycodone, oxymorphone)			
Opiate agonists (fentanyl, meperidine, oxycodone)	2	Serotonin reuptake inhibitors	Toxic effects of serotonin reuptake inhibitors may be increased, resulting in development of serotonin syndrome.
Opiate agonists (codeine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine, methadone, morphine, opium and belladonna, oxycodone, oxymorphone)	2	Sodium oxybate	Concurrent use of sodium oxybate and opiate agonists may result in an increase in sleep duration and central nervous system depression. Pharmacologic effects of sodium oxybate and opiate agonists may be additive.
Opiate agonists (fentanyl, meperidine)	2	Sibutramine	Use of sibutramine with opiate agonists has been reported by the manufacturer of sibutramine to increase the potential risk for serotonin syndrome. The mechanism is unknown.
Opium and belladonna	2	Phenothiazines	The antipsychotic effectiveness of phenothiazines may be decreased by opium/belladonna. Additive central and peripheral anticholinergic effects and decreased Phenothiazines bioavailability have been proposed.
Acetaminophen	2	Anticoagulants	The hypoprothrombinemic effects of anticoagulants may be increased by acetaminophen in a dose-dependent manner. Bleeding may occur, especially when acetaminophen use exceeds 2,000 mg daily or is prolonged for several days.
Aspirin	2	Carbonic anhydrase inhibitors	Aspirin may increase the toxic effects of carbonic anhydrase inhibitors; Carbonic anhydrase inhibitors may decrease the pharmacologic effects of aspirin.
Aspirin	2	Celecoxib	Aspirin and celecoxib may cause additive adverse effects when co-administered. An increased rate of gastrointestinal ulceration or other complications may occur. Additive toxicity may occur.
Aspirin	2	Clopidogrel	The risk of life-threatening bleeding such as intracranial or gastrointestinal hemorrhage may be increased in high-risk patients with

Generic Name(s)	Significance Level	Interaction	Mechanism
			transient ischemic attack or ischemic stroke when given the combination of clopidogrel with aspirin.
Aspirin	2	Direct thrombin inhibitors	Use of direct thrombin inhibitors with aspirin may increase the risk of bleeding. Inhibition of the clotting cascade by multiple mechanisms may increase the risk of bleeding.
Aspirin	2	Meglitinides	Hypoglycemic effects of meglitinides may be increased by aspirin. The mechanism of action in unknown.
Aspirin	2	Probenecid	The uricosuric action of probenecid is decreased. Hyperuricemia with possible exacerbation of gout may occur. The effects of this interaction depend on the dose of aspirin.
Aspirin	2	Serotonin reuptake blockers	The risk of upper gastrointestinal bleeding may be increased with concurrent administration of aspirin and serotonin reuptake blockers. The mechanism of action is unknown.
Aspirin	2	Sulfinpyrazone	The uricosuric effect of sulfinpyrazone may be decreased. Hyperuricemia with possible exacerbation of gout may occur. The effects of this interaction depend on the dose of aspirin.
Butalbital	2	Clozapine	Butalbital may decrease pharmacologic effects and plasma concentrations of clozapine. The mechanism of this interaction is unknown.
Butalbital	2	Corticosteroids	Pharmacologic effects of corticosteroids may be decreased with possible exacerbation of the disease being treated. Induction of hepatic microsomal enzymes by butalbital may increase the metabolic elimination of corticosteroids.
Butalbital	2	Doxycycline	The antimicrobial effectiveness of doxycycline may be decreased. Induction of hepatic microsomal enzymes by butalbital may increase the metabolic elimination of doxycycline.
Butalbital	2	Metronidazole	The antimicrobial effectiveness of metronidazole may be decreased. Induction of hepatic microsomal enzymes by butalbital may increase the metabolic elimination of metronidazole.
Butalbital	2	Tacrolimus	Plasma concentrations and pharmacologic effects of tacrolimus may be decreased. Increased hepatic metabolism via CYP3A4 of tacrolimus by butalbital may occur.
Butalbital	2	Teniposide	The therapeutic and toxic effects of teniposide may be decreased by butalbital. The mechanism of this interaction in unknown.
Butalbital	2	Theophyllines	Pharmacologic effects of theophyllines may be decreased by butalbital. Decreased

Generic Name(s)	Significance Level	Interaction	Mechanism
			theophylline plasma concentrations, possibly with a suboptimal therapeutic response, may occur. Hepatic metabolism of theophyllines may be increased by butalbital.
Codeine	2	Quinidine	Quinidine may decrease pharmacologic effects of codeine. Loss of analgesic effect may occur.
Fentanyl	2	Monoamine oxidase inhibitors	A severe reaction potentially involving the respiratory, cardiac and central nervous systems may occur shortly after administering fentanyl to patients receiving monoamine oxidase inhibitors. The mechanism is unknown.
Fentanyl	2	Nefazodone	Plasma concentrations and pharmacologic effects of fentanyl may be increased by nefazodone. Inhibition of cytochrome P450 3A4 metabolism by nefazodone may decrease the metabolic elimination of fentanyl.
Ibuprofen	2	Angiotensin-converting-enzyme inhibitor inhibitors	The antihypertensive effects of Angiotensin-converting-enzyme inhibitor inhibitors may be decreased by ibuprofen. Also, the risk Angiotensin-converting-enzyme inhibitor inhibitors or ibuprofen-related nephrotoxicity, including hyperkalemia, may be increased by this drug combination.
Ibuprofen	2	Bisphosphonates	Gastrointestinal adverse effects may be increased with concurrent administration of bisphosphonates and ibuprofen. The mechanism is unknown.
Ibuprofen	2	Cyclosporine	Combination therapy with cyclosporine and ibuprofen may increase the probability and severity of renal impairment. Plasma concentrations of cyclosporine and ibuprofen may be increased.
Ibuprofen	2	Lithium	Pharmacologic effects of lithium may be increased. Elevated lithium serum concentrations and toxicity characterized by gastrointestinal symptoms, polyuria, muscular weakness, lethargy, and tremor may occur.
Ibuprofen	2	Loop diuretics	Diuretic effects of loop diuretics may be decreased by ibuprofen. Sodium retention and hypervolemia may occur. Ibuprofen may decrease natriuresis and diuresis of loop diuretics by inhibiting the synthesis of renal prostaglandins.
Ibuprofen	2	Probenecid	Pharmacologic and toxic effects of ibuprofen may be increased by probenecid.
Ibuprofen	2	Thienopyridines	Use of ibuprofen with thienopyridines may increase the risk of bleeding. Ibuprofen-induced alteration in gastric mucosal function coupled with inhibition of platelet aggregation by thienopyridines may further

Generic Name(s)	Significance Level	Interaction	Mechanism
			increase the risk of gastrointestinal bleeding compared to ibuprofen alone.
Meperidine	2	Human immuno-deficiency virus protease inhibitors	Cardiac, hematologic, neurologic (seizures), or other potentially serious toxicities are listed in the manufacturer's package labeling when meperidine and human immunodeficiency virus protease inhibitors are coadministered. The mechanism is unknown.
Meperidine	2	Phenothiazines	Excessive or prolonged central nervous system depression, respiratory depression and hypotension may occur, when phenothiazines and meperidine are used concomitantly.
Meperidine	2	Serotonin reuptake inhibitors	Risk of serotonin syndrome may be increased due to an unknown mechanism. Monitor closely for adverse reactions.
Methadone	2	Efavirenz	Efavirenz may decrease pharmacologic effects and plasma concentrations of methadone. Induction of hepatic cytochrome P450 3A4 isoenzymes by efavirenz may increase the metabolic elimination of methadone.
Methadone	2	Human immuno-deficiency virus protease inhibitors	Human immunodeficiency virus protease inhibitors may decrease the pharmacologic effects and plasma concentrations of methadone. Induction of CYP2B6 by human immunodeficiency virus protease inhibitors may increase the metabolic elimination of methadone.
Methadone	2	Hydantoins	Serum concentrations and pharmacologic effects of methadone may be decreased by hydantoins. Methadone withdrawal signs (abdominal cramping, rhinorrhea, lacrimation, chills, and tremulousness) may occur. Hydantoins may induce the hepatic metabolism of methadone.
Methadone	2	Monoamine oxidase inhibitors-type B agents	A severe reaction potentially involving the respiratory, cardiac and central nervous systems may occur shortly after administering methadone to patients receiving monoamine oxidase inhibitors - type B specific agents. The mechanism of this interaction is unknown.
Methadone	2	Nevirapine	Nevirapine may decrease the plasma concentrations of methadone. Induction of cytochrome P450 3A4 isoenzymes by nevirapine may increase the metabolic elimination of methadone.
Methadone	2	Nucleoside reverse transcriptase inhibitors	Plasma concentrations and pharmacologic effects of nucleoside reverse transcriptase inhibitors may be decreased by methadone. The mechanism of this interaction is unknown.
Tramadol	2	Anticoagulants	Tramadol may increase hypoprothrombinemic effects of

Generic Name(s)	Significance Level	Interaction	Mechanism
			anticoagulants. The mechanism of this interaction is unknown.
Tramadol	2	Atypical antipsychotics	Increased risk of seizures is listed in the manufacturer's package labeling as a possibility when tramadol and atypical antipsychotics are coadministered. The mechanism of this interaction is unknown.
Tramadol	2	Carbamazepine	Carbamazepine may decrease the plasma concentrations and pharmacologic effects of tramadol. The mechanism of this interaction is unknown.
Tramadol	2	Cyclobenzaprine	Increased risk of seizures is listed in the manufacturer's package labeling as a possibility when tramadol and cyclobenzaprine are coadministered. The mechanism of this interaction is unknown.
Tramadol	2	Loxapine	Use of tramadol with loxapine may increase the risk of seizures. The mechanism of this interaction is unknown.
Tramadol	2	Molindone	Use of tramadol with molindone may increase the risk of seizures. The mechanism of this interaction is unknown.
Tramadol	2	Phenothiazines	Use of tramadol with phenothiazines may increase the risk of seizures. The mechanism of this interaction is unknown.
Tramadol	2	Thioxanthenes	Use of tramadol with thioxanthenes may increase the risk of seizures. The mechanism of this interaction is unknown.
Tramadol	2	Tiagabine	Use of tramadol with tiagabine may increase the risk of seizures. The mechanism of this interaction is unknown.
Tramadol	2	Tricyclic antidepressants	Use of tramadol with tricyclic antidepressants may increase the risk of seizures. The mechanism of this interaction is unknown.

Significance level 1=major severity, significance level 2=moderate severity.

VI. Adverse Drug Events

The most common adverse drug events reported with the opiate agonists are listed in Tables 9 to 11. Adverse events of the combination products not listed in the tables below would be in line with the properties of their individuals components listed in the tables below. The boxed warnings for the opiate agonists are listed in Tables 12 to 24.

Table 9. Adverse Drug Events (%) Reported with the Opiate Agonists (Drugs A-M)[4-6]

Adverse Events	Codeine	Dihydro-codeine	Fentanyl	Hydrocodone	Hydro-morphone	Levorphanol	Meperidine	Methadone
Cardiovascular								
Abnormal ECG	-	-	-	-	-	-	-	✔
Angina	-	-	<1	-	-	-	-	-
Arrhythmia	-	-	-	-	-	✔	-	✔
Atrial fibrillation	-	-	-	-	-	-	-	-
Bigeminal rhythms	-	-	-	-	-	-	-	✔
Bradycardia	✔	-	✔	✔	✔	✔	✔	✔
Cardiac arrest	✔	-	✔	✔	✔	✔	✔	✔
Cardiomyopathy	-	-	-	-	-	-	-	✔
Chest pain	-	-	✔	-	-	-	-	-
Circulatory collapse	✔	-	✔	✔	✔	-	✔	✔
Deep thrombophlebitis	-	-	✔	-	✔	-	-	-
Extrasystoles	-	-	-	-	-	✔	-	✔
Faintness	✔	-	-	-	✔	-	-	✔
Flushing	✔	-	✔	-	✔	✔	✔	✔
Heart failure	-	-	-	-	✔	-	-	✔
Hypertension	-	-	✔	-	✔	-	-	✔
Hypotension	✔	-	✔	✔	✔	✔	✔	✔
Myocardial ischemia	-	-	-	-	-	-	-	✔
Orthostatic hypotension	-	-	-	-	-	-	-	✔
Palpitation	-	-	✔	-	✔	✔	✔	✔
Peripheral vascular disorder	-	-	✔	-	-	-	-	-
Phlebitis	-	-	-	-	-	-	✔	✔
Prolonged QT interval	-	-	-	-	-	-	-	✔
Shock	-	-	-	-	-	-	-	✔
Syncope	✔	-	✔	-	✔	✔	✔	✔
Tachycardia	✔	-	✔	-	✔	✔	✔	✔
Torsade de pointes	-	-	-	-	-	-	-	✔
Vascular disorder	-	-	✔	-	-	-	-	-
Vasodilation	-	-	≤4	-	-	-	-	✔

Adverse Events	Codeine	Dihydro-codeine	Fentanyl	Hydrocodone	Hydro-morphone	Levorphanol	Meperidine	Methadone
Ventricular fibrillation	-	-	-	-	-	-	-	✔
Ventricular tachycardia	-	-	-	-	-	-	-	✔
Central Nervous System								
Abnormal coordination	-	-	≥1	-	-	-	-	-
Abnormal dreams	-	✔	✔	-	-	-	-	-
Abnormal gait	-	-	1 to 5	-	-	-	-	-
Abnormal thinking	-	-	1 to 2	-	-	-	-	-
Acute brain syndrome	-	-	✔	-	-	-	-	-
Addiction	-	✔	-	✔	-	✔	-	-
Agitation	✔	-	✔	-	-	-	✔	✔
Amnesia	-	-	✔	-	-	-	-	-
Anxiety	✔	-	3 to 15	-	✔	-	-	-
Aphasia	-	-	✔	-	-	-	-	-
Asthenia	-	-	0 to 38	-	-	-	-	-
Cerebral ischemia	-	-	✔	-	-	-	-	-
Central nervous system stimulation	-	-	-	-	-	✔	-	-
Coma	-	✔	-	✔	-	✔	-	-
Confusion	-	✔	10 to 13	✔	-	✔	-	✔
Convulsion	✔	-	0 to 2	-	-	✔	✔	✔
Depersonalization	-	-	✔	-	-	-	-	-
Depression	-	-	2 to 10	-	-	✔	-	-
Disorientation	✔	-	-	-	✔	✔	✔	✔
Dizziness	✔	✔	3 to 17	✔	✔	-	-	✔
Drowsiness	>10	✔	-	✔	✔	✔	-	✔
Dysphoria	✔	-	-	✔	✔	-	✔	✔
Emotional lability	-	-	✔	-	-	-	-	-
Euphoria	✔	-	3 to 10	✔	✔	-	✔	✔
Fear	✔	-	-	✔	✔	-	-	-
Hallucinations	✔	✔	3 to 10	-	✔	-	✔	✔
Headache	✔	✔	3 to 20	-	✔	-	✔	✔
Hemiplegia	-	-	✔	-	-	-	-	-
Hostility	-	-	✔	-	-	-	-	-
Hyperkinesia	-	-	-	-	-	✔	-	-
Hypertonia	-	-	✔	-	-	-	-	-
Hypesthesia	-	-	✔	-	-	-	-	-
Hypokinesia	-	-	✔	-	-	✔	-	-

Adverse Events	Codeine	Dihydro-codeine	Fentanyl	Hydrocodone	Hydro-morphone	Levorphanol	Meperidine	Methadone
Hypotonia	-	-	✔	-	-	-	-	-
Impairment of performance	✔	✔	-	✔	✔	-	-	-
Incoordination	-	-	✔	-	✔	-	✔	-
Increased intracranial pressure	-	-	-	-	✔	-	-	-
Insomnia	✔	-	1 to 10	-	✔	✔	-	✔
Lethargy	✔	-	-	✔	✔	✔	✔	-
Lightheadedness	✔	-	-	✔	✔	-	-	✔
Mental clouding	✔	-	-	✔	✔	-	-	-
Migraine	-	-	✔	-	-	-	-	-
Mood changes	✔	-	-	✔	✔	-	-	-
Myoclonic movements	-	-	1 to 4	-	-	-	✔	-
Nervousness	-	-	1 to 10	-	-	✔	-	-
Paranoid reaction	-	-	✔	-	-	-	-	-
Paresthesia	-	-	✔	-	✔	-	-	-
Personality disorder	-	-	-	-	-	✔	-	-
Shivering	-	-	✔	-	-	-	-	-
Sedation	✔	-	3 to 20	✔	✔	-	✔	✔
Speech disorder	-	-	✔	-	-	-	-	-
Stupor	-	-	1 to 4	✔	-	-	-	-
Subdural hematoma	-	-	✔	-	-	-	-	-
Suicide attempt	-	-	-	-	-	✔	-	-
Tremor	-	-	1 to 2	-	✔	-	✔	-
Twitching	-	-	-	-	-	-	✔	-
Vertigo	-	-	✔	-	-	-	-	-
Weakness	✔	-	-	-	✔	-	✔	✔
Withdrawal syndrome	-	✔	-	-	-	✔	-	-
Dermatological								
Alopecia	-	-	✔	-	-	-	-	-
Application-site reactions	-	-	1 to 10	-	-	-	-	-
Exfoliative dermatitis	-	-	✔	-	-	-	-	-
Herpes zoster	-	-	✔	-	-	-	-	-
Injection site pain/reaction	-	-	-	-	✔	✔	-	-
Itching	✔	-	1 to 10	-	✔	✔	-	✔
Localized skin reaction	-	-	✔	-	-	-	-	-
Pruritus	-	✔	-	✔	-	-	-	✔
Pustules	-	-	✔	-	-	-	-	✔
Rash	-	-	1 to 8	✔	✔	✔	-	✔

Adverse Events	Codeine	Dihydro-codeine	Fentanyl	Hydrocodone	Hydro-morphone	Levorphanol	Meperidine	Methadone
Skin discoloration	-	-	✔	-	-	-	-	-
Skin ulcer	-	-	✔	-	-	-	-	-
Sweating	✔	-	-	-	✔	✔	✔	✔
Urticaria	-	-	✔	-	✔	✔	-	✔
Vesiculobullous rash	-	-	✔	-	-	-	-	-
Wheal/flare	-	-	-	-	✔	-	-	✔
Endocrine and Metabolic								
Acidosis	-	-	✔	-	-	-	-	-
Antidiuretic effect	-	-	-	-	-	-	-	✔
Amenorrhea	-	-	-	-	-	-	-	✔
Cyanosis	-	-	-	-	-	-	✔	-
Hypercalcemia	-	-	✔	-	-	-	-	-
Hyperglycemia	-	-	✔	-	-	-	-	-
Hypocalcemia	-	-	✔	-	-	<1	-	-
Hypoglycemia	-	-	✔	✔	-	-	-	-
Hypokalemia	-	-	✔	-	-	-	✔	✔
Hypomagnesemia	-	-	✔	-	-	-	✔	✔
Hyponatremia	-	-	✔	-	-	-	-	-
Hypoproteinemia	-	-	✔	-	-	-	-	-
Gastrointestinal								
Abdominal distention	-	-	✔	-	-	-	-	-
Abdominal pain	-	✔	1 to 10	✔	-	✔	-	✔
Anorexia	✔	-	-	-	-	-	-	✔
Biliary spasm	✔	-	-	-	-	✔	✔	✔
Cheilitis	-	-	✔	-	-	-	-	-
Colon hemorrhage	-	-	✔	-	-	-	-	-
Constipation	>10	✔	3 to 20	✔	✔	-	✔	✔
Cramps	-	-	-	-	✔	-	-	✔
Dry mouth	✔	✔	1 to 10	✔	✔	✔	✔	✔
Diarrhea	-	✔	3 to 10	-	✔	-	-	-
Dyspepsia	-	-	3 to 10	-	-	✔	-	-
Dysphagia	-	-	✔	-	-	-	-	-
Eructation	-	-	✔	-	-	-	-	-
Esophageal stenosis	-	-	✔	-	-	-	-	-
Esophagitis	-	-	✔	-	-	-	-	-
Fecal impaction	-	-	✔	-	-	-	-	-
Fecal incontinence	-	-	✔	-	-	-	-	-

Adverse Events	Codeine	Dihydro-codeine	Fentanyl	Hydrocodone	Hydro-morphone	Levorphanol	Meperidine	Methadone
Flatulence	-	-	✔	-	-	-	-	-
Gastritis	-	-	✔	-	-	-	-	-
Gastroenteritis	-	-	✔	-	-	-	-	-
Gastrointestinal disorder	-	-	✔	-	-	-	-	-
Gastrointestinal hemorrhage	-	-	✔	-	-	-	-	-
Gingivitis	-	-	✔	-	-	-	-	-
Glossitis	-	-	✔	-	-	-	-	✔
Gum hemorrhage	-	-	✔	-	-	-	-	-
Heartburn	-	-	-	✔	-	-	-	-
Hepatorenal syndrome	-	-	✔	-	-	-	-	-
Ileus	-	-	-	-	✔	-	-	-
Increased biliary tract pressure	✔	-	1 to 4	-	-	-	-	-
Jaundice	-	-	✔	-	-	-	-	-
Liver tenderness	-	-	✔	-	-	-	-	-
Mouth ulceration	-	-	✔	-	-	-	-	-
Nausea	✔	✔	10 to 45	✔	✔	✔	✔	✔
Oral moniliasis	-	-	✔	-	-	-	-	-
Periodontal abscess	-	-	✔	-	-	-	-	-
Rectal disorder	-	-	✔	-	-	-	-	-
Rectal hemorrhage	-	-	✔	-	-	-	-	-
Stomatitis	-	-	✔	-	-	-	-	-
Tooth caries	-	-	✔	-	-	-	-	-
Tooth disorder	-		✔	-	-	-	-	-
Vomiting	✔	✔	6 to 31	✔	-	✔	✔	✔
Weight loss	-	-	✔	-	-	-	-	-
Genitourinary								
Amenorrhea	-	-	-	-	-	-	-	✔
Antidiuretic effect	✔	-	-	-	✔	-	✔	✔
Bladder pain	-	-	✔	-	-	-	-	-
Bladder spasm	-	-	-	✔	-	-	-	-
Breast neoplasm	-	-	✔	-	-	-	-	-
Breast pain	-	-	✔	-	-	-	-	-
Decreased libido/potency	✔	-	✔	-	-	-	-	✔
Dysuria	-	-	✔	-	-	-	-	-
Hematuria	-	-	✔	-	-	-	-	-
Hydronephrosis	-	-	✔	-	-	-	-	-
Impotence	-	-	✔	-	-	-	-	-

Adverse Events	Codeine	Dihydro-codeine	Fentanyl	Hydrocodone	Hydro-morphone	Levorphanol	Meperidine	Methadone
Kidney failure	-	✔	✔	-	-	✔	-	-
Kidney pain	-	-	✔	-	-	-	-	-
Nephritis	-	✔	-	-	-	-	-	-
Nocturia	-	-	✔	-	-	-	-	-
Oliguria	-	-	✔	-	-	-	-	-
Polyuria	-	-	✔	-	-	-	-	-
Scrotal edema	-	-	✔	-	-	-	-	-
Spasm of vesical sphincters	✔	-	-	-	✔	-	-	-
Ureteral spasm	✔	-	-	✔	-	-	-	-
Urinary frequency	-	-	-	-	✔	-	-	-
Urinary hesitancy	✔	-	-	-	✔	-	-	✔
Urinary incontinence	-	-	✔	-	✔	-	-	-
Urinary retention	✔	-	1 to 10	✔	✔	-	✔	✔
Urinary tract infection	-	-	✔	-	-	-	-	-
Urinary urgency	-	-	✔	-	-	-	-	-
Urination impaired	-	-	✔	-	-	-	-	-
Vaginal hemorrhage	-	-	✔	-	-	-	-	-
Vaginitis	-	-	✔	-	-	-	-	-
Hematologic								
Agranulocytosis	-	-	-	✔	-	-	-	-
Anemia	-	-	✔	✔	-	-	-	-
Bleeding time increased	-	-	✔	-	-	-	-	-
Ecchymosis	-	-	✔	-	-	-	-	-
Hemoglobin disease	-	-	✔	-	-	-	-	-
Leukopenia	-	-	✔	-	-	-	-	-
Leukocytosis	-	-	✔	-	-	-	-	-
Lymphadenopathy	-	-	✔	-	-	-	-	-
Lymphedema	-	-	✔	-	-	-	-	-
Lymphoma-like reaction	-	-	✔	-	-	-	-	-
Pancytopenia	-	-	✔	-	-	-	-	-
Thrombocytopenia	-	-	✔	✔	-	-	-	✔
Laboratory Test Abnormalities								
Alanine transaminase increased	✔	-	-	-	-	-	-	-
Aspartate aminotransferase increased	✔	-	-	-	-	-	-	-
Musculoskeletal								
Arthralgia	-	-	✔	-	-	-	-	-

Adverse Events	Codeine	Dihydro-codeine	Fentanyl	Hydrocodone	Hydro-morphone	Levorphanol	Meperidine	Methadone
Arthritis	-	-	✔	-	-	-	-	-
Back pain	-	-	✔	-	-	-	-	-
Bone disorder	-	-	✔	-	-	-	-	-
Chest wall rigidity	-	-	-	-	-	-	-	-
Joint disorder	-	-	✔	-	-	-	-	-
Leg cramps	-	-	✔	-	-	-	-	-
Muscle tremor	-	-	✔	-	-	-	-	-
Myalgia	-	-	✔	-	-	-	-	-
Myasthenia	-	-	✔	-	-	-	-	-
Myopathy	-	-	✔	-	-	-	-	-
Neck pain	-	-	✔	-	-	-	-	-
Neck rigidity	-	-	-	-	-	-	-	-
Pathological fracture	-	-	✔	-	-	-	-	-
Skeletal muscle movement	-	-	-	-	-	-	-	-
Synovitis	-	-	✔	-	-	-	-	-
Tendon disorder	-	-	✔	-	-	-	-	-
Weakness	-	-	-	-	-	-	-	✔
Respiratory								
Asthma	-	-	✔	-	-	-	-	-
Bronchitis	-	-	✔	-	-	-	-	-
Cough	-	-	✔	-	-	-	-	-
Dyspnea	-	-	2 to 22	✔	-	-	-	-
Epistaxis	-	-	✔	-	-	-	-	-
Hemoptysis	-	-	✔	-	-	-	-	-
Hiccoughs	-	-	✔	-	-	-	-	-
Hyperventilation	-	-	✔	-	-	-	-	-
Laryngospasm	-	-	✔	-	✔	-	-	-
Lung disorder	-	-	✔	-	-	-	-	-
Pharyngitis	-	-	3 to 10	-	-	-	-	-
Pleural effusion	-	-	✔	-	-	-	-	-
Pneumonia	-	-	✔	-	-	-	-	-
Pneumothorax	-	-	✔	-	-	-	-	-
Pulmonary edema	-	-	-	-	-	-	-	✔
Pulmonary embolus	-	-	✔	-	-	-	-	-
Respiratory arrest	✔	-	✔	-	✔	-	✔	✔
Respiratory depression	✔	✔	✔	✔	✔	-	✔	✔
Respiratory disorder	-	-	✔	-	-	-	-	-

Adverse Events	Codeine	Dihydro-codeine	Fentanyl	Hydrocodone	Hydro-morphone	Levorphanol	Meperidine	Methadone
Respiratory insufficiency	-	-	✔	-	-	-	-	-
Rhinitis	-	-	✔	-	-	-	-	-
Sinusitis	-	-	✔	-	-	-	-	-
Sputum increased	-	-	✔	-	-	-	-	-
Stertorous breathing	-	-	✔	-	-	-	-	-
Suppressed cough reflex	✔	-	-	-	-	-	-	-
Other								
Abnormal vision	-	-	0 to 3	-	-	✔	-	-
Abscess	-	-	✔	-	-	-	-	-
Accidental injury	-	-	0 to 9	-	-	-	-	-
Allergic reaction	✔	✔	✔	✔	✔	-	-	-
Amblyopia	-	-	✔	-	-	-	-	-
Anaphylaxis	-	-	✔	-	-	-	✔	✔
Ascites	-	-	✔	-	-	-	-	-
Blurred vision	-	-	✔	-	-	-	-	-
Bone pain	-	-	✔	-	-	-	-	-
Cataracts	-	-	✔	-	-	-	-	-
Cellulitis	-	-	✔	-	-	-	-	-
Chills	-	-	✔	-	✔	-	-	-
Conjunctivitis	-	-	✔	-	-	-	-	-
Death	-	-	-	-	-	-	-	✔
Dehydration	-	-	✔	-	-	-	-	-
Diaphoresis	-	-	-	-	-	-	-	✔
Diplopia	-	-	✔	-	-	✔	-	-
Dry eyes	-	-	✔	-	-	-	-	-
Dysgeusia	-	-	✔	-	-	-	-	-
Ear disorder	-	-	✔	-	-	-	-	-
Ear pain	-	-	✔	-	-	-	-	-
Edema	-	-	✔	-	-	-	-	✔
Eye hemorrhage	-	-	✔	-	-	-	-	-
Fever	-	-	✔	-	-	-	-	-
Flu syndrome	-	-	✔	-	-	-	-	-
Fungal infection	-	-	✔	-	-	-	-	-
Hyperacusis	-	-	✔	-	-	-	-	-
Infection	-	-	✔	-	-	-	-	-
Lacrimation disorder	-	-	✔	-	-	-	-	-
Malaise	-	-	✔	-	-	-	-	-

Adverse Events	Codeine	Dihydro-codeine	Fentanyl	Hydrocodone	Hydro-morphone	Levorphanol	Meperidine	Methadone
Miosis	✔	-	✔	-	✔	-	-	✔
Nystagmus	-	-	✔	-	✔	-	-	-
Pain	-	-	✔	-	-	-	-	-
Pelvic pain	-	-	✔	-	-	-	-	-
Sepsis	-	-	✔	-	-	-	-	-
Shock	✔	-	-	-	✔	✔	✔	✔
Taste perversion	-	-	✔	-	✔	-	-	-
Tinnitus	-	-	✔	-	-	-	✔	-
Transitory deafness	-	-	✔	-	-	-	-	-
Viral infection	-	-	✔	-	-	-	-	-
Visual disturbances	✔	-	✔	-	✔	✔	✔	✔

✔ Percent not specified.
- Event not reported.

Table 10. Adverse Drug Events (%) Reported with the Opiate Agonists (Drugs M-Z)[4-6]

Adverse Events	Morphine	Oxycodone	Oxymorphone	Tapentadol	Tramadol
Cardiovascular					
Abnormal ECG	-	-	-	-	<1
Arrhythmia	-	-	-	-	-
Atrial fibrillation	✔	-	-	-	-
Bradycardia	✔	-	✔	<1	<1
Cardiac arrest	✔	✔	-	-	-
Chest pain	✔	-	-	-	-
Circulatory depression/collapse	✔	✔	-	-	-
Congestive heart failure	-	<3	-	-	-
Extrasystoles	✔	-	-	-	-
Faintness	✔	-	-	-	-
Heart failure	-	-	-	-	-
Hypertension	-	-	-	<1	<1
Hypotension	✔	1 to 5	✔	<1	<1
Myocardial infarction	-	-	-	-	<1
Myocardial ischemia	-	-	-	-	<1
Orthostatic hypotension	-	-	-	-	<1
Palpitation	✔	<3	-	-	<1
Pallor	✔	-	-	-	-
Peripheral edema	-	-	-	-	<1
Presyncope	-	-	-	<1	-

Adverse Events	Morphine	Oxycodone	Oxymorphone	Tapentadol	Tramadol
ST suppression	-	<1	-	-	-
Suicidal tendency	-	-	-	-	<1
Syncope	✔	-	-	<1	<1
Tachycardia	✔	<3	✔	<1	<1
Vasodilation	✔	<3	-	-	1 to 5
Central Nervous System					
Abnormal dreams	✔	-	-	1	<1
Abnormal gait	✔	-	-	-	<1
Abnormal thinking	✔	-	-	-	<1
Agitation	✔	<1	-	<1	<1
Amnesia	✔	-	-	-	<1
Anxiety	✔	-	-	1	1 to 5
Asthenia	✔	6	-	-	6 to 12
Ataxia	✔	-	-	<1	-
Attention disturbances	-	-	-	<1	-
Central nervous system stimulation	-	-	✔	-	7 to 14
Cognitive dysfunction	-	-	-	-	<1
Coma	✔	-	-	-	-
Concentration difficulty	-	-	-	-	<1
Confusion	✔	1 to 5	✔	1	1 to 5
Consciousness decreased	-	-	-	<1	-
Convulsion	✔	<1	-	-	<1
Coordination abnormal	-	-	-	<1	-
Delirium	✔	-	-	-	-
Depression	✔	<1	✔	-	<1
Disorientation	✔	<1	-	<1	<1
Dizziness	✔	13	-	24	26 to 33
Drowsiness	✔	-	✔	-	-
Dysphoria	-	✔	-	-	-
Emotional lability	-	<1	-	-	-
Euphoria	✔	1 to 5	✔	<1	1 to 5
Hallucinations	-	<1	✔	<1	<1
Headache	✔	7	✔	<1	18 to 32
Insomnia	✔	1 to 5	-	2	-
Irritability	-	-	-	<1	<1
Lethargy	-	-	-	1	-
Lightheadedness	✔	-	-	-	-

Adverse Events	Morphine	Oxycodone	Oxymorphone	Tapentadol	Tramadol
Memory impairment	-	-	-	<1	-
Migraine	-	<3	-	-	<1
Nervousness	-	1 to 5	-	<1	1 to 5
Paresthesia	✔	-	-	<1	<1
Personality disorder	-	<3	-	-	-
Restlessness	-	-	✔	<1	-
Serotonin syndrome	-	-	-	-	<1
Sedation	✔	23	✔	<1	16 to 25
Seizure	-	-	-	<1	<1
Sleep disorder	-	-	-	-	<1
Somnolence	-	-	-	15	-
Speech disorder	-	<1	-	-	<1
Stupor	-	<1	-	-	-
Suicide	-	-	-	-	<1
Tremor	✔	<3	-	1	<1
Twitching	-	1 to 5	-	-	26 to 33
Vertigo	✔	<1	-	-	-
Weakness	✔	-	✔	-	-
Withdrawal syndrome	✔	<1	-	<1	-
Dermatological					
Cellulitis	-	-	-	-	<1
Dry skin	✔	-	<1	-	-
Exfoliative dermatitis	-	-	<1	-	-
Flushing	-	-	✔	1	-
Hyperhidrosis	-	-	-	3	-
Itching/pruritus	✔	✔	13	-	8 to 11
Pruritus	-	-	-	3 to 5	-
Rash	✔	-	1 to 5	1	1 to 5
Stevens-Johnson Syndrome	-	-	-	-	<1
Sweating	✔	✔	5	-	6 to 9
Toxic epidermal necrolysis	-	-	-	-	<1
Urticaria	✔	-	<3	<1	<1
Vesicles	-	-	-	-	<1
Wheal/flare	✔	-	-	-	1 to 5
Endocrine and Metabolic					
Gout	-	-	<3	-	-
Hyperglycemia	-	-	<3	-	-

Adverse Events	Morphine	Oxycodone	Oxymorphone	Tapentadol	Tramadol
Menstrual disorder	-	-	-	-	<1
Metabolic acidosis	-	-	-	-	-
Gastrointestinal					
Abdominal distention	-	-	1 to 5	-	-
Abdominal pain	-	✔	-	<1	1 to 5
Abnormal liver function tests	✔	-	-	-	✔
Anorexia	✔	✔	1 to 5	-	1 to 5
Appetite increased	-	-	<1	-	-
Biliary spasm	✔	✔	✔	-	-
Cholecystitis	-	-	-	-	<1
Cholelithiasis	-	-	-	-	<1
Colonic motility increased	✔	-	-	-	-
Constipation	✔	✔	23	8	24 to 46
Cramps	✔	-	✔	-	-
Diverticulitis	-	-	-	-	<1
Dry mouth	✔	✔	6	4	5 to 10
Diarrhea	✔	-	1 to 5	<1	5 to 10
Dyspepsia	✔	-	1 to 5	2	5 to 13
Dysphagia	✔	-	<1	-	<1
Eructation	-	-	<1	-	-
Flatulence	-	-	<1	-	1 to 5
Gastric emptying decreased	-	-	-	<1	-
Gastritis	-	-	1 to 5	-	-
Gastroenteritis	✔	-	-	-	-
Gastrointestinal disorder	-	-	<1	-	-
Gastrointestinal hemorrhage	-	-	-	-	✔
Hepatic failure	-	-	-	-	✔
Hepatitis	-	-	-	-	✔
Ileus	✔	✔	<1	-	-
Intestinal obstruction	✔	-	-	-	-
Nausea	✔	✔	23	30	24 to 40
Rectal disorder	✔	-	-	-	-
Stomatitis	-	-	<1	-	<1
Taste perversion	-	-	-	-	<1
Toxic megacolon	-	✔	-	-	-
Vomiting	✔	✔	12	18	9 to 17
Weight loss	✔	-	-	-	<1

Adverse Events	Morphine	Oxycodone	Oxymorphone	Tapentadol	Tramadol
Genitourinary					
Abnormal ejaculation	✔	-	-	-	-
Amenorrhea	✔	-	<1	-	-
Antidiuretic effect	-	✔	<1	-	-
Dysmenorrhea	-	-	-	-	<1
Dysuria	✔	-	<1	-	<1
Fecal impaction	-	-	-	-	<1
Gastroenteritis	-	-	-	-	<1
Gastrointestinal bleeding	-	-	-	-	<1
Hematuria	-	-	<1	-	<1
Impotence	✔	-	-	-	-
Libido decreased	-	-	<1	<1	<1
Menopausal symptoms	-	-	-	-	1 to 5
Menstrual disorder	-	-	-	-	<1
Pollakiuria	✔	-	-	-	-
Polyuria	-	-	<1	-	-
Proteinuria	-	-	-	-	<1
Spasm of vesical sphincters	✔	-	-	-	-
Ureteral spasm	✔	✔	-	-	-
Urinary frequency	-	-	-	-	1 to 5
Urinary hesitancy	✔	✔	-	<1	-
Urinary retention	✔	✔	-	-	1 to 5
Urinary tract infection	✔	-	-	1	-
Urination impaired	-	-	-	-	-
Hematologic					
Anemia	✔	-	-	-	<1
Hemoglobin decreased	-	-	-	-	<1
Lymphadenopathy	-	-	<1	-	-
Thrombocytopenia	✔	-	-	-	<1
Hepatic					
Hepatic steatosis	-	-	-	-	-
Hepatitis	-	-	-	-	<1
Hepatocellular injury	-	-	-	-	-
Hepatomegaly	-	-	-	-	-
Jaundice	-	-	-	-	-
Liver dysfunction	-	-	-	-	-
Liver failure	-	-	-	-	<1

Adverse Events	Morphine	Oxycodone	Oxymorphone	Tapentadol	Tramadol
Laboratory Test Abnormalities					
Alanine transaminase increased	-	-	-	<1	<1
Aspartate aminotransferase increased	-	-	-	<1	<1
Creatinine increased	-	-	-	-	<1
Hyperglycemia	-	-	-	-	<1
Musculoskeletal					
Arthralgia	-	-	<3	1	-
Arthritis	-	-	<3	-	-
Dysarthria	-	-	-	<1	-
Hypertonia	-	-	-	-	1 to 5
Hypotonia	-	<1	-	-	-
Involuntary muscle contractions	-	-	-	<1	-
Muscle cramps	-	-	-	-	<1
Muscle spasms	-	-	-	-	<1
Muscle twitching	-	-	-	-	<1
Myalgia	-	-	<3	-	<1
Weakness	-	-	-	<1	-
Respiratory					
Bronchitis	-	-	<3	-	-
Bronchospasm	-	-	-	-	<1
Cough	-	-	<3	<1	-
Dyspnea	-	-	1 to 5	<1	<1
Epistaxis	-	-	<3	-	-
Hiccoughs	-	-	1 to 5	-	-
Hypoxia	-	-	<3	-	-
Laryngospasm	✔	-	<3	-	-
Lung disorder	-	-	<3	-	-
Pharyngitis	-	-	-	1	-
Pneumonia	-	-	-	-	<1
Pulmonary edema	-	-	-	-	<1
Pulmonary embolus	-	-	-	-	<1
Respiratory arrest	✔	-	-	-	-
Respiratory depression	✔	✔	-	<1	-
Rhinitis	-	-	<3	-	-
Sinusitis	-	-	<3	-	-
Other					
Abnormal vision	-	-	<1	-	-

Adverse Events	Morphine	Oxycodone	Oxymorphone	Tapentadol	Tramadol
Abscess	✔	-	-	-	<1
Accidental injury	-	-	<3	-	<1
Allergic laryngeal edema	-	✔	-	-	-
Allergic laryngospasm	-	✔	-	-	-
Allergic reaction	-	✔	<3	<1	<1
Amblyopia	-	<3	-	-	-
Anaphylaxis	✔	-	<1	-	<1
Angioedema	-	-	-	-	<1
Appendicitis	-	-	-	-	<1
Back pain	-	-	<3	-	-
Blurred vision	-	✔	-	-	-
Bone pain	-	-	<3	-	-
Cataracts	-	-	-	-	<1
Chills	✔	-	<3	-	-
Deafness	-	-	-	-	<1
Deep thrombophlebitis	-	<3	-	-	-
Dehydration	✔	-	<3	-	-
Diplopia	✔	✔	-	-	-
Dry eyes	-	-	-	-	<1
Ear infection	-	-	-	-	<1
Ear pain	-	-	-	<1	-
Edema	✔	-	-	<1	<1
Eye edema	-	-	-	-	-
Eye hemorrhage	✔	-	-	-	-
Flank pain	-	-	<3	-	-
Flu syndrome	✔	-	-	-	-
Fracture	-	-	<3	-	-
Fungal infection	-	-	<3	-	-
Hemorrhage	-	<3	-	-	-
Herpes simplex	-	-	<3	-	-
Hypersensitivity	-	-	-	<1	<1
Hypoesthesia	-	-	-	<1	-
Infection	✔	-	-	1	-
Joint stiffness	-	-	-	-	<1
Malaise	✔	-	-	-	1 to 5
Miosis	✔	✔	-	-	-
Night sweats	-	-	-	-	<1

Adverse Events	Morphine	Oxycodone	Oxymorphone	Tapentadol	Tramadol
Nystagmus	✔	-	-	-	-
Pain	-	-	<3	-	-
Pancreatitis	-	-	-	-	<1
Pharyngolaryngeal pain	-	-	-	<1	-
Phlebitis	✔	-	-	-	-
Sepsis	✔	-	<3	-	-
Serotonin syndrome	-	-	-	-	<1
Shock	✔	-	✔	-	-
Taste perversion	✔	-	<1	-	-
Tinnitus	-	-	<1	-	<1
Visual disturbances	✔	-	-	<1	<1

✔ Percent not specified.
- Event not reported.

Table 11. Adverse Drug Events (%) Reported with the Combination Opiate Agonists[4-6]

Adverse Events	Opium and Belladonna
Cardiovascular	
Palpitation	✔
Central Nervous System	
Asthenia	✔
Dizziness	✔
Drowsiness	✔
Seizure	✔
Somnolence	✔
Dermatological	
Pruritus	✔
Urticaria	✔
Gastrointestinal	
Constipation	✔
Dry mouth	✔
Dyspepsia	✔
Nausea	✔
Vomiting	✔
Genitourinary	
Urinary retention	✔
Respiratory	
Respiratory depression	✔
Other	
Blurred vision	✔

✔ Percent not specified.

Table 12. Boxed Warning for Acetaminophen-Containing Products[6]

WARNING
Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed 4,000 milligrams per day, and often involve more than one acetaminophen-containing product.

Table 13. Boxed Warning for Codeine- and Dihydrocodeine-Containing Products[6]

WARNING
Respiratory depression and death have occurred in children who received codeine following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine due to a CYP2D6 polymorphism.

Table 14. Boxed Warning for Transmucosal Fentanyl[7]

WARNING
Respiratory Depression: Fatal respiratory depression has occurred in patients treated with transmucosal immediate-release fentanyl, including following use in opioid non-tolerant patients and improper dosing. The substitution of one transmucosal fentanyl product for any other fentanyl product may result in fatal overdose. Due to the risk of respiratory depression, transmucosal immediate-release fentanyl is contraindicated in the management of acute or postoperative pain including headache/migraine and in opioid non-tolerant patients. Transmucosal immediate-release fentanyl must be kept out of reach of children. Death has been reported in some children who have ingested transmucosal immediate-release fentanyl formulations. The concomitant use of transmucosal immediate-release fentanyl with CYP3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression.

WARNING
Medication Errors: Substantial differences exist in the pharmacokinetic profile of each transmucosal immediate-release fentanyl product compared to other fentanyl products that result in clinically important differences in the extent of absorption of fentanyl that could result in fatal overdose. When prescribing, do not convert patients on a µg per µg basis from any other fentanyl products to a transmucosal immediate-release fentanyl product. When dispensing, do not substitute a transmucosal immediate-release fentanyl prescription for any other fentanyl products. **Abuse Potential:** Transmucosal immediate-release fentanyl products are opioid agonists and Schedule II controlled substances, with an abuse liability similar to other opioid analgesics. Transmucosal immediate-release fentanyl can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing transmucosal immediate-release fentanyl in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Because of the risk for misuse, abuse, addiction, and overdose, transmucosal immediate-release fentanyl products are available only through a restricted program, required by the Food and Drug Administration, called a Risk Evaluation and Mitigation Strategy (REMS). Under the Transmucosal Immediate Release Fentanyl REMS Access program, outpatients, healthcare professionals who prescribe to outpatients, pharmacies, and distributors must enroll in the program. Further information is available at www.TIRFREMSAccess.com or by calling 1-866-822-1483.

Table 15. Boxed Warning for Transdermal Fentanyl[6]

WARNING
Addiction, abuse, and misuse: Fentanyl exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing fentanyl, and monitor all patients regularly for the development of these behaviors or conditions. **Life-threatening respiratory depression**: Serious, life-threatening, or fatal respiratory depression may occur with use of fentanyl, even when used as recommended. Monitor for respiratory depression, especially during initiation of fentanyl or following a dose increase. Because of the risk of respiratory depression, fentanyl is contraindicated for use as an as-needed analgesic, in nonopioid tolerant patients, in acute pain, and in postoperative pain. **Accidental exposure**: Deaths due to a fatal overdose of fentanyl have occurred when children and adults were accidentally exposed to fentanyl, including an intact Ionsys device or the hydrogel component in Ionsys, through contact with skin or contact with mucous membranes. Strict adherence to the recommended handling and disposal instructions is of the utmost importance to prevent accidental exposure. **Neonatal opioid withdrawal syndrome**: Prolonged use of fentanyl during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. **Cytochrome P450 3A4 interaction**: The concomitant use of fentanyl with all cytochrome P450 (CYP-450) 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in fentanyl plasma concentration. Monitor patients receiving fentanyl and any CYP3A4 inhibitor or inducer. **Exposure to heat (Duragesic only)**: Exposure of the fentanyl application site and surrounding area to direct external heat sources, such as heating pads or electric blankets, heat or tanning lamps, sunbathing, hot baths, saunas, hot tubs, and heated water beds may increase fentanyl absorption and has resulted in fatal overdose of

WARNING
fentanyl and death. Patients wearing fentanyl systems who develop fever or increased core body temperature due to strenuous exertion are also at risk for increased fentanyl exposure and may require an adjustment in the dose of fentanyl to avoid overdose and death.

Table 16. Boxed Warning for Hydromorphone Oral[6]

WARNING
Hydromorphone immediate release: Hydromorphone is a potent Schedule II controlled opioid agonist. Schedule II opioid agonists have the highest potential for abuse and risk of producing respiratory depression. Alcohol, other opioids, and CNS depressants (sedative-hypnotics) potentiate the respiratory depressant effects of hydromorphone, increasing the risk of respiratory depression that might result in death. **Hydromorphone extended release**: **Addiction, abuse, and misuse**: Hydromorphone extended release (ER) exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing hydromorphone ER, and monitor all patients regularly for the development of these behaviors or conditions. **Life-threatening respiratory depression**: Serious, life-threatening, or fatal respiratory depression may occur with use of hydromorphone ER. Monitor for respiratory depression, especially during initiation of hydromorphone ER or following a dose increase. Instruct patients to swallow hydromorphone ER tablets whole; crushing, chewing, or dissolving tablets can cause rapid release and absorption of a potentially fatal dose of hydromorphone. **Accidental ingestion**: Accidental ingestion of even 1 dose, especially in children, can result in a fatal overdose of hydromorphone. **Neonatal opioid withdrawal syndrome**: Prolonged use during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Table 17. Boxed Warning for Hydromorphone Injection[6]

WARNING
Hydromorphone high potency injection is for use in opioid-tolerant patients only. Patients considered opioid tolerant are those who are taking at least 60 mg oral morphine/day, 25 µg transdermal fentanyl/hour, 30 mg oral oxycodone/day, 8 mg oral hydromorphone/day, 25 mg oral oxymorphone/day, or an equianalgesic dose of another opioid for one week or longer. Hydromorphone high potency injection is a more concentrated solution of hydromorphone than hydromorphone injection, and is for use in opioid-tolerant patients only. Do not confuse hydromorphone high potency injection with standard parenteral formulations of hydromorphone injection or other opioids, as overdose and death could result. Hydromorphone injection and hydromorphone high potency injection are opioid agonists and Schedule II controlled substances with an abuse liability similar to other opioid analgesics. Hydromorphone injection and hydromorphone high potency injection can be abused in a manner similar to other opioid agonists, legal or illicit. These risks should be considered when administering, prescribing, or dispensing hydromorphone injection and hydromorphone high potency injection in situations where the healthcare professional is concerned about increased risk of misuse, abuse, or diversion. Schedule II opioid agonists, including morphine, oxymorphone, hydromorphone, oxycodone, fentanyl, and methadone, have the highest potential for abuse and risk of producing fatal overdose due to respiratory

depression. Ethanol, other opioids, and other central nervous system depressants (e.g., sedative-hypnotics, skeletal muscle relaxants) can potentiate the respiratory-depressant effects of hydromorphone and increase the risk of adverse outcomes, including death.

Table 18. Boxed Warning for Methadone Injection[6]

WARNING
To treat narcotic addiction in detoxification or maintenance programs, methadone should be dispensed only by hospitals, community pharmacies, and maintenance programs approved by the Food and Drug Administration (FDA) and designated state authorities. Approved maintenance programs shall dispense and use methadone in oral form only and according to treatment requirements stipulated in *Federal Methadone Regulations*. Failure to abide by the requirements in these regulations may result in criminal prosecution, seizure of drug supply, revocation of program approval, and injunction precluding program operation. Methadone, used as an analgesic, may be dispensed in any licensed pharmacy. **Cardiac conduction effects:** Laboratory studies, in vivo and in vitro, have demonstrated that methadone inhibits cardiac potassium channels and prolongs the QT interval. Cases of QT interval prolongation and serious arrhythmia (torsades de pointes) have been observed during treatment with methadone. These cases appear to be more commonly associated with, but not limited to, higher dose treatment (greater than 200 mg/day). Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction.

Table 19. Boxed Warning for Oral Methadone[6]

WARNING
Addiction, abuse, and misuse: Methadone exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing methadone, and monitor all patients regularly for the development of these behaviors or conditions. **Life-threatening Respiratory Depression**: Life-threatening, or fatal respiratory depression may occur with use of methadone. Monitor for respiratory depression, especially during initiation of methadone or following a dose increase. **Life-threatening QT Prolongation**: QT interval prolongation and serious arrhythmia (torsades de pointes) have occurred during treatment with methadone. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction. Closely monitor patients for changes in cardiac rhythm during initiation and titration of methadone. **Neonatal opioid withdrawal syndrome**: Prolonged use of methadone during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. **Accidental ingestion**: Accidental ingestion of methadone, especially in children, can result in a fatal overdose of methadone. **Conditions For Distribution And Use Of Methadone Products For The Treatment Of Opioid Addiction**: For detoxification and maintenance of opioid dependence, methadone should be administered in accordance with the treatment standards cited in 42 CFR Section 8, including limitations on unsupervised administration.

Table 20. Boxed Warning for Morphine Injection[6]

WARNING
Risk of overdose (Infumorph): Infumorph is not recommended for single-dose intravenous (IV),

intramuscular (IM), or subcutaneous administration because of the very large amount of morphine in the ampul and the associated risk of overdosage.

Product interchange (Infumorph): Improper or erroneous substitution of **Infumorph** 200 or 500 (10 or 25 mg/mL, respectively) for regular **Duramorph** (0.5 or 1 mg/mL) is likely to result in serious overdosage, leading to seizures, respiratory depression and, possibly, fatal outcome.

Intrathecal use (Duramorph): Intrathecal dosage is usually 1/10 that of epidural dosage.

Appropriate administration (Infumorph, Duramorph):
Because of the risk of severe adverse effects when the epidural or intrathecal route of administration is employed, patients must be observed in a fully equipped and staffed environment for at least 24 hours after the initial dose. For patients receiving **Infumorph**, monitor, as appropriate, for the first several days after catheter implantation.

Infumorph: Naloxone injection and resuscitative equipment should be immediately available for use in case of case of life-threatening or intolerable side effects and whenever **Infumorph** therapy is being initiated, the reservoir is being refilled or any manipulation of the reservoir system is taking place.

Duramorph: Naloxone injection and resuscitative equipment should be immediately available for administration in case of life-threatening or intolerable side effects and whenever **Duramorph** therapy is being initiated.

Safety and handling (Infumorph, Duramorph):
Infumorph and **Duramorph** are supplied in sealed ampuls. Accidental dermal exposure should be treated by the removal of any contaminated clothing and rinsing the affected area with water.

Each ampul of **Infumorph** and **Duramorph** contains a large amount of a potent narcotic which has been associated with abuse and dependence among health care providers. Due to the limited indications for this product, the risk of overdosage and the risk of its diversion and abuse, it is recommended that special measures be taken to control this product within the hospital or clinic. **Infumorph** and **Duramorph** should be subject to rigid accounting, rigorous control of wastage, and restricted access.

Parenteral drug products should be inspected for particulate matter before opening the amber ampul and again for color after removing contents from the ampul. Do not use if the solution in the unopened ampul contains a precipitate which does not disappear upon shaking. After removal, do not use unless the solution is colorless or pale yellow.

Table 21. Boxed Warning for Morphine Oral[6]

WARNING
Avinza and Kadian: **Interaction with alcohol**: Instruct patients not to consume alcoholic beverages or use prescription or nonprescription products that contain alcohol while taking morphine extended-release (ER) capsules. The co-ingestion of alcohol with morphine may result in increased plasma levels and a potentially fatal overdose of morphine. **Avinza, Kadian, and MS Contin**: **Addiction, abuse, and misuse**: Morphine ER exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing morphine ER and monitor all patients regularly for the development of these behaviors or conditions. **Life-threatening respiratory depression**: Serious, life-threatening, or fatal respiratory depression may occur with use of morphine ER. Monitor for respiratory depression, especially during initiation of morphine or following a dose increase. Instruct patients to swallow morphine ER formulations whole; Avinza capsule contents may be sprinkled on applesauce and swallowed without chewing. Crushing, chewing, or dissolving the tablets or contents within the capsule can cause rapid release and absorption of a potentially fatal dose of

WARNING

morphine.

Neonatal opioid withdrawal syndrome: Prolonged use of morphine during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Accidental ingestion: Accidental ingestion of even 1 dose of morphine, especially by children, can result in a fatal overdose of morphine.

Oral solution:
Morphine oral solution is available in 10 mg per 5 mL, 20 mg per 5 mL, and 100 mg per 5 mL (20 mg/mL) concentrations.

The 100 mg per 5 mL (20 mg/mL) concentration is indicated for use in opioid-tolerant patients only.

Take care when prescribing and administering morphine oral solution to avoid dosing errors due to confusion between different concentrations and between milligrams and milliliters, which could result in accidental overdose and death. Take care to ensure the proper dose is communicated and dispensed.

Keep morphine oral solution out of the reach of children. In case of accidental ingestion, seek emergency medical help immediately.

Table 22. Boxed Warning for Oxycodone[6]

WARNING

Extended release:
Addiction, abuse, and misuse: Oxycodone extended release (ER) exposes patients and other users to the risks of opioid addiction, abuse and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing oxycodone and monitor all patients regularly for the development of these behaviors or conditions.

Life-threatening respiratory depression: Serious, life-threatening, or fatal respiratory depression may occur with use of oxycodone ER. Monitor for respiratory depression, especially during initiation of oxycodone ER or following a dose increase. Instruct patients to swallow oxycodone ER tablets whole; crushing, dissolving, or chewing the tablet can cause rapid release and absorption of a potentially fatal dose of oxycodone.

Accidental ingestion: Accidental ingestion of even one dose of oxycodone ER, especially by children, can result in a fatal overdose of oxycodone.

Neonatal opioid withdrawal syndrome: Prolonged use of oxycodone ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Cytochrome P450 3A4 interaction: The concomitant use of oxycodone ER with all cytochrome P450 (CYP-450) 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used CYP3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving oxycodone ER and any CYP3A4 inhibitor or inducer.

Concentrated (20 mg/mL) oral solution:
Oxycodone concentrated oral solution is available as a 20 mg/mL concentration and is indicated for use in

opioid-tolerant patients only.

Take care when prescribing and administering oxycodone concentrated oral solution to avoid dosing errors due to confusion between milligram and milliliter, and other oxycodone solutions with different concentrations, which could result in accidental overdose and death. Take care to ensure the proper dose is communicated and dispensed. Keep oxycodone out of the reach of children. In case of accidental ingestion, seek emergency medical help immediately.

Oral solution (5 mg/5 mL): Take care when prescribing and administering oxycodone oral solution to avoid dosing errors due to confusion between milligram and milliliter, and other oxycodone solutions with different concentrations, which could result in accidental overdose and death. Take care to ensure the proper dose is communicated and dispensed. Keep oxycodone out of the reach of children. In case of accidental ingestion, seek emergency medical help immediately.

Table 23. Boxed Warning for Oxymorphone[6]

WARNING
Extended-release tablets: **Addiction, abuse, and misuse**: Oxymorphone extended release (ER) exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing oxymorphone ER, and monitor all patients regularly for the development of these behaviors and conditions. **Life-threatening respiratory depression**: Serious, life-threatening, or fatal respiratory depression may occur with use of oxymorphone ER. Monitor for respiratory depression, especially during initiation of oxymorphone ER or following a dose increase. Instruct patients to swallow oxymorphone ER tablets whole; crushing, chewing, or dissolving oxymorphone ER tablets can cause rapid release and absorption of a potentially fatal dose of oxymorphone. **Accidental ingestion**: Accidental ingestion of even 1 dose of oxymorphone ER, especially by children, can result in a fatal overdose of oxymorphone. **Neonatal opioid withdrawal syndrome**: Prolonged use of oxymorphone ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. **Interaction with alcohol**: Instruct patients not to consume alcoholic beverages or use prescription or nonprescription products that contain alcohol while taking oxymorphone ER. The co-ingestion of alcohol with oxymorphone ER may result in increased plasma levels and a potentially fatal overdose of oxymorphone.

Table 24. Boxed Warning for Tapentadol Extended-Release[6]

WARNING
Abuse Potential: Tapentadol extended-release is an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal or illicit. Assess each patient's risk for opioid abuse or addiction prior to prescribing tapentadol extended-release. The risk for opioid abuse is increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depressive disorder). Routinely monitor all patients receiving tapentadol extended-release for signs of misuse, abuse, and addiction during treatment. **Life-threatening Respiratory Depression**: Respiratory depression, including fatal cases, may occur with use of tapentadol extended-release, even when the drug has been used as recommended and not misused or abused. Proper dosing and titration are essential and tapentadol extended-release should only be prescribed by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic

pain. Monitor for respiratory depression, especially during initiation of tapentadol extended-release or following a dose increase. Instruct patients to swallow tapentadol extended-release tablets whole. Crushing, dissolving, or chewing tapentadol extended-release can cause rapid release and absorption of a potentially fatal dose of tapentadol.

Accidental Exposure: Accidental ingestion of tapentadol extended-release, especially in children, can result in a fatal overdose of tapentadol.

Interaction with Alcohol: The co-ingestion of alcohol with tapentadol extended-release may result in an increase of plasma levels and potentially fatal overdose of tapentadol. Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products that contain alcohol while on tapentadol extended-release.

VII. Dosing and Administration

The usual dosing regimens for the opiate agonists are listed in Table 25.

Table 25. Usual Dosing Regimens for the Opiate Agonists[4-6]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Codeine	Analgesia: Solution, tablet: 15 to 60 mg every four to six hours	Safety and efficacy in children have not been established.	Solution: 30 mg/5 mL Tablet: 15 mg 30 mg 60 mg
Fentanyl	Analgesia: Buccal lozenge: initial, 200 µg; titrate as necessary; maximum, two doses per breakthrough pain episode; wait at least four hours before treating another episode of breakthrough pain Buccal tablet: initial, 100 µg; maximum, two doses per breakthrough pain episode; may repeat dosing after 30 minutes for a single episode of breakthrough pain; wait at least four hours before treating another episode of breakthrough pain; titrate as necessary Injection: 50 to 100 µg IM or slow IV Nasal spray: initial, 100 µg; if after 30 minutes pain is unrelieved, an alternative rescue medication may be used as directed by the health care provider. Must wait at least two hours before treating another	Analgesia: Buccal lozenge: ≥16 years of age, initial, 200 µg; titrate as necessary; maximum, two doses per breakthrough pain episode; wait at least four hours before treating another episode of breakthrough pain Injection: ≥12 years of age:, 50 to 100 µg IM or slow IV; two to 12 years of age, 2 to 3 µg/kg Transdermal patch: ≥2 years of age, dose should be based on individual need; one patch is to be applied every 72 hours; however, some may require application of every 48 hours rather than every 72 hours	Buccal lozenge: 200 µg 400 µg 600 µg 800 µg 1,200 µg 1,600 µg Buccal tablet: 100 µg 200 µg 400 µg 600 µg 800 µg Injection: 50 µg/mL Nasal spray: 100 µg 400 µg Sublingual spray: 100 µg 200 µg 400 µg 600 µg 800 µg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	episode with fentanyl intranasal. However, for the next pain episode, increase to a higher dose Sublingual spray: initial, 100 µg; titrate to tolerable dose that provides adequate analgesia using a single dose; maximum, two doses per breakthrough pain episode; wait at least four hours before treating another episode Sublingual tablet: initial, 100 µg; titrate to tolerable dose that provides adequate analgesia; maximum, two doses per breakthrough pain episode; wait at least two hours before treating another episode Transdermal patch: dose should be based on individual need; one patch is to be applied every 72 hours; however, some may require application of every 48 hours rather than every 72 hours		1,200 µg 1,600 µg Sublingual tablet: 100 µg 200 µg 300 µg 400 µg 600 µg 800 µg Transdermal patch: 12 µg/hr 25 µg/hr 37.5 µg/hr 50 µg/hr 62.5 µg/hr 75 µg/hr 87.5 µg/hr 100 µg/hr
Hydromorphone	Analgesia: Injection: 1 to 2 mg SC or IM every two to three hours, if given IV, inject slowly over at least two to three minutes. Liquid: 2.5 to 10 mg every three to six hours as directed Rectal suppository: one suppository (3 mg) inserted every six to eight hours Tablet: 2 to 4 mg every four to six hours as necessary	Safety and efficacy in children have not been established.	Injection: 0.5 mg/0.5 mL 1 mg/mL 2 mg/mL 4 mg/mL 10 mg/mL 250 mg Liquid: 1 mg/mL Rectal suppository: 3 mg Tablet: 2 mg 4 mg 8 mg
Levorphanol	Analgesia: Tablet: one tablet every three to six hours	Safety and efficacy in children have not been established.	Tablet: 2 mg
Meperidine	Analgesia: Injection: 50 to 150 mg IM or SC every three to four hours as necessary Solution, tablet: 50 to 150 mg every three to four hours as necessary	Analgesia: Injection: 1.1 to 1.8 mg/kg (0.5 to 0.8 mg/lb) IM or SC up to the adult dose every three to four hours as necessary Solution, tablet: 1.1 to 1.8	Injection: 10 mg/mL 25 mg/0.5 mL 25 mg/mL 50 mg/mL 75 mg/mL 75 mg/1.5 mL 100 mg/mL

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
		mg/kg (0.5 to 0.8 mg/lb) up to the adult dose, every three to four hours as necessary	100 mg/2 mL Solution: 50 mg/5 mL Tablet: 50 mg 100 mg
Methadone	Analgesia: Oral concentrate, solution, tablet: 2.5 to 10 mg every eight to 12 hours as necessary Detoxification: Oral concentrate, solution, tablet: initial, 20 to 30 mg to suppress withdrawal symptoms; individualize and adjust dose as tolerated and required up to 120 mg/day	Safety and efficacy in children have not been established.	Injection: 10 mg/mL Oral concentrate: 10 mg/mL Solution: 5 mg/5 mL 10 mg/5 mL Tablet: 5 mg 10 mg 40 mg
Morphine	Analgesia: Injection: 5 to 20 mg SC or IM every four hours Solution, tablet: 5 to 30 mg every four hours Rectal suppository: 10 to 20 mg every four hours	Analgesia: Injection: >6 months, 0.1 to 0.2 mg/kg every four hours	Injection: 0.5 mg/mL 1 mg/mL 2 mg/mL 4 mg/mL 5 mg/mL 8 mg/mL 10 mg/mL 15 mg/mL 25 mg/mL 30 mg/30 mL 50 mg/mL 100 mg/4 mL 150 mg/30 mL 250 mg/10 mL Rectal suppository: 5 mg 10 mg 20 mg 30 mg Solution 10 mg/5 mL 20 mg/5 mL 100 mg/5 mL Tablet: 15 mg 30 mg
Oxycodone	Analgesia: Capsule, oral concentrate, solution, tablet: 5 to 15 mg every four to six hours	Safety and efficacy in children have not been established.	Capsule: 5 mg Oral concentrate:

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
			20 mg/mL Solution: 5 mg/5 mL Tablet: 5 mg 7.5 mg 10 mg 15 mg 20 mg 30 mg
Oxymorphone	Analgesia: Tablet: 10 to 20 mg every four to six hours Injection: initial, SC or IM, 1 to 1.5 mg every four to six hours; IV, 0.5 mg; titrate to adequate pain relief	Safety and efficacy in children have not been established.	Injection: 1 mg/mL Tablet: 5 mg 10 mg
Tapentadol	Analgesia: Tablet (IR): 50 to 100 mg every four to six hours Tablet (ER): individualize based on prior analgesic treatment; for opioid to naïve patients, initial, 50 mg twice daily	Safety and efficacy in children have not been established.	Tablet (IR): 50 mg 75 mg 100 mg Tablet (ER): 50 mg 100 mg 150 mg 200 mg 250 mg
Tramadol	Analgesia: Capsule (ER): initial, 100 mg once daily; titrate by 100 mg increments every five days Tablet (ER): 100 to 300 mg daily Tablet (IR): 50 to 100 mg every four to six hours	Analgesia: Tablet (IR): ≥16 years of age, 50 to 100 mg every four to six hours	Capsule (ER): 100 mg 200 mg 300 mg Tablet (ER): 100 mg 200 mg 300 mg Tablet (IR): 50 mg
Combination Products			
Codeine and acetaminophen	Analgesia: Elixir, suspension: 15 mL every four hours Tablet: 0.5 to two tablets every four hours	Analgesia: Elixir, suspension: ≥12 years of age, 15 mL every four hours; seven to 12 years of age, 10 mL three to four times daily; three to six years of age, 5 mL three to four times daily Tablet: two to 12 years of age, 0.5 to 1 mg	Elixir: 12-120 mg/5 mL Suspension: 12-120 mg/5 mL Tablet: 15-300 mg 30-300 mg 60-300 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
		codeine/kg/dose every four to six hours (10 to 15 mg acetaminophen/kg/dose every four hours)	
Codeine, butalbital, acetaminophen, and caffeine	Headache: Capsule: one or two capsules every four hours	Headache: Capsule: ≥12 years of age, one or two tablets or capsules every four hours	Capsule: 30-50-300-40 mg 30-50-325-40 mg
Codeine, butalbital, aspirin, and caffeine	Headache: Capsule: one or two capsules every four hours	Headache: Capsule: ≥12 years of age, one or two tablets or capsules every four hours	Capsule: 30-50-325-40 mg
Dihydrocodeine, acetaminophen, and caffeine	Analgesia: Capsule: two capsules every four hours	Safety and efficacy in children have not been established.	Capsule: 16-320.5-30 mg
Dihydrocodeine, aspirin, and caffeine	Analgesia: Capsule: one to two capsules every four to six hours	Safety and efficacy in children have not been established.	Capsule: 16-356.4-30 mg
Hydrocodone and acetaminophen	Analgesia: , tablet: one to two e very four to six hours; 7.5-300 and 10-300 mg tablets, one every four six hours Solution: 15 mL every four to six hours; 10-300 mg/15 mL solution, 11.25 mL every four to six hours	Analgesia: Capsule, tablet: ≥15 years of age, one to two every four to six hours Solution: ≥15 years of age, 15 mL every four to six hours; two to 14 years of age, 0.27 ml/kg every four to six hours; 10-300/15 mL solution, >14 years of age, 11.25 mL every four to six hours; two to 13 years of age, 0.20 mL/kg every four to six hours	Solution: 2.5-167 mg/5 mL 5-163 mg/7.5 mL 7.5-325 mg/15 mL 10-300 mg/15 mL 10-325 mg/15 mL Tablet: 2.5-325 mg 5-300 mg 5-325 mg 7.5-300 mg 7.5-325 mg 10-300 mg 10-325 mg
Hydrocodone and ibuprofen	Analgesia: Tablet: one tablet every four to six hours	Analgesia: Tablet: ≥16 years of age, one tablet every four to six hours	Tablet: 2.5-200 mg 5-200 mg 7.5-200 mg 10-200 mg
Opium and belladonna	Analgesia: Rectal suppository: one or two suppositories inserted per day	Safety and efficacy in children have not been established.	Rectal suppository: 30-16.2 mg 60-16.2 mg
Oxycodone and acetaminophen	Analgesia: Tablet: one to two capsules or tablets every six hours Solution: 5 to 10 mL every six hours	Safety and efficacy in children have not been established.	Tablet (ER): 7.5-325 mg Solution: 5-325 mg/5 mL Tablet: 2.5-325 mg 5-300 mg 5-325 mg 7.5-300 mg 7.5-325 mg 7.5-500 mg 10-300 mg 10-325 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
			10-650 mg
Oxycodone and aspirin	Analgesia: Tablet: one tablet every six hours	Safety and efficacy in children have not been established.	Tablet: 4.8355-325 mg
Oxycodone and ibuprofen	Analgesia: Tablet: one tablet every six hours	Analgesia: Tablet: ≥14 years of age, one tablet every six hours	Tablet: 5-400 mg
Tramadol and acetaminophen	Analgesia: Tablet: two tablets every four to six hours	Safety and efficacy in children have not been established.	Tablet: 37.5-325 mg

IM=intramuscular, IR=immediate-release, IV=intravenous, SC=subcutaneous, ODT=orally disintegrating tablet, SR=sustained-release

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the opiate agonists are summarized in Table 26.

Table 26. Comparative Clinical Trials with the Opiate Agonists

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Acute Pain				
Drendel et al.[28] (2009) Codeine-APAP suspension 1 mg/kg/dose (codeine component) vs ibuprofen suspension 10 mg/kg/dose	AC, DB, RCT Children 4 to 18 years of age with a closed fracture of the radius, ulna, or humerus	N=336 72 hours after ED discharge	Primary: Failure of study medication as defined by use of a rescue analgesic Secondary: Pain scores, adverse events, and satisfaction	Primary: The proportion of treatment failures for children receiving ibuprofen (20.3%) was lower than that for codeine-APAP (31.0%), although not statistically significant. Secondary: The total mean pain scores for day zero to day three were 1.6 for children receiving ibuprofen and 1.6 for children receiving codeine-APAP. At the end of the study, 27.5% of the children said they would not use codeine-APAP again compared to only 10.0% of the children who took ibuprofen (95% CI, 7.3 to 28.3). The primary reason associated with dissatisfaction in children receiving codeine-APAP was taste. There was no significant difference in analgesic failure and pain scores among children with an arm fracture receiving ibuprofen or codeine-APAP.
Rauck et al.[29] (2012) Fentanyl sublingual spray (100 to 1,600 µg) vs placebo Fentanyl sublingual spray was titrated up to	DB, MC, OL, PC, RCT Adult patients with cancer, experiencing persistent cancer or treatment-related pain of no more than moderate severity, receiving ≥60 mg oral morphine, 30 mg oxycodone or 8 mg	N=130 10 BTP episodes	Primary: $SPID_{30}$ Secondary: $TOTPAR_{30}$, global evaluation of study medication at 30 minutes	Primary: The mean (SE) $SPID_{30}$ score was 640.3 (47.8) for fentanyl sublingual spray and 399.6 (40.8) for placebo; corresponding to a mean treatment difference of 240.7 (37.8) (P<0.0001). A significant difference in SPID values for episodes treated with fentanyl compared to placebo was seen as early as five minutes and maintained for up to 60 minutes. After 30 minutes, 79.3% of patients showed greater improvement with fentanyl sublingual spray compared to placebo (P<0.0001). Secondary: TOTPAR scores from five to 60 minutes were significantly greater in episodes treated with fentanyl sublingual spray compared to episodes treated with placebo (P<0.0001 for all time points). The $TOTPAR_{30}$ score in episodes treated with fentanyl sublingual spray was 78.3 compared to

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1,600 µg until an effective dose was reached. After titration to an effective dose of fentanyl sublingual spray, patients received ten doses of study medication (seven contained fentanyl and three were placebo).	oral hydromorphone/ day or 25 µg transdermal fentanyl/hour or equivalent			61.0 in episodes treated with placebo (P<0.0001). After 30 minutes, the global evaluation of treatment effectiveness score was 2.8 for fentanyl sublingual spray compared to 2.0 for placebo (P<0.0001). This significant difference was maintained at 60 minutes as well.
Rauck et al.[30] (2010) Fentanyl buccal film 200 µg vs placebo Patients were provided with a titration kit consisting of five units each of 200, 400, 600, 800 and 1,200 µg doses of fentanyl buccal film. After titration to an effective dose of fentanyl buccal	DB, MC, PC, RCT, XO Patients ≥18 years of age with pain associated with cancer or cancer treatment, receiving stable opioid therapy equivalent to 60 to 1,000 mg/day of oral morphine or 50 to 300 µg/hour of transdermal fentanyl, that had one to four BTP episodes/day despite persistent opioid therapy and who achieved at least partial relief from opioid therapy	N=151 Up to 14 days or 9 BTP episodes	Primary: $SPID_{30}$ Secondary: SPID at five, 10, 15, 45, and 60 minutes post dose, pain intensity difference, pain relief, global satisfaction	Primary: Mean±SEM $SPID_{30}$ values for fentanyl buccal film treated BTP episodes were significantly greater than for placebo treated BTP episodes (47.9±3.9 vs 38.1±4.3; P=0.004). Secondary: SPID values for buccal film fentanyl treated BTP episodes were significantly greater than for placebo from 15 minutes through 60 minutes post dose (all P<0.05). The mean pain intensity differences and pain relief for fentanyl treated BTP episodes were significantly greater (improved) than for placebo treated BTP episodes beginning at 30 minutes post dose (P<0.05). There was a significantly greater percentage of BTP episodes with a 33 or 50% decrease in pain with buccal film fentanyl compared to placebo starting at 30 minutes post dose (P<0.01). The percentage of BTP episodes when rescue medication was required was significantly lower when treated with buccal film fentanyl (30.0%±3.5%) than when treated with placebo (44.6%±4.4%; P=0.002). More patients rated their overall satisfaction with buccal film fentanyl as ‘good’, ‘very good’ or ‘excellent’ compared to placebo and fewer patients

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
film, patients received nine doses of study medication (six contained fentanyl and three were placebo). If adequate pain relief was not experienced after 30 minutes, patients were instructed to use their usual BTP medication if needed.				rated their overall satisfaction with buccal film fentanyl as 'poor' or 'fair' compared to placebo. The overall satisfaction with the study drug was greater with fentanyl buccal film compared to placebo (mean score, 2.0 vs 1.5; P<0.001). The most commonly reported adverse events included nausea (9.9%), vomiting (9.9%), and headache (1.2%). Twenty-three patients (15.3%) experienced a serious adverse event. None of the serious adverse events (including four deaths) were considered study drug-related.
Portenoy et al.[31] (2006) Fentanyl buccal tablet vs placebo Enrolled patients began with an OL titration phase to identify an effective dose of fentanyl buccal tablet ranging from 100 to 800 µg. After titration to an	PC, RCT, XO Adults with chronic cancer pain receiving 60 to 1,000 mg/day of oral morphine or equivalent or 50 to 300 µg/hour of transdermal fentanyl for at least one week who experienced one to four episodes of BTP per day	N=123 Duration not reported	Primary: $SPID_{30}$ Secondary: Pain relief and pain intensity difference scores, TOTPAR, global medication performance assessment, need for supplemental medication, proportion of episodes in which there were ≥33 or ≥50% improvement in pain intensity scores	Primary: The mean (±SD) $SPID_{30}$ was 3.00 (±0.12) vs 1.80 (±0.14) for fentanyl buccal tablet compared to placebo (P<0.0001). Secondary: The mean pain relief and pain intensity difference scores were significantly higher in the fentanyl group compared to the placebo group at each time point (P<0.003 at 15 minutes for both; P<0.0001 for all other time points for both). TOTPAR scores were significantly higher in the fentanyl group compared to the placebo group at all time points (P<0.0001 for all). At 30 minutes after treatment, 48% of fentanyl treated patients had ≥33% improvement in pain intensity score compared to 29% of placebo patients (P<0.0001). At the same time point, 24% of fentanyl treated patients had ≥50% improvement in pain intensity score compared to 16% of placebo patients (P=0.0023). A significant difference in clinical improvement (≥33%) between the two groups was seen as early as 15 minutes (P=0.045).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
effective dose of fentanyl buccal tablet, patients received ten doses of study medication (seven contained fentanyl and three were placebo).				Global performance assessment ratings showed that fentanyl received a significantly higher satisfaction rating than placebo at both 30 and 60 minutes (P<0.0001 for both). Supplemental medication was needed in 23% of episodes treated with fentanyl compared to 50% of episodes treated with placebo (RR, 0.47; 95% CI, 0.37 to 0.60). Two percent of patients withdrew from the study because of application site ulcers of the oral mucosa deemed by the investigators to be related to the study drug.
Slatkin et al.[32] (2007) Fentanyl buccal tablet Patients were provided with a titration kit consisting of 100, 200, 400, 600, and 800 µg doses of fentanyl buccal tablet. The starting dose and subsequent titration doses were specified in the protocol based on the medications the patient was using to treat BTP immediately before study enrollment. If adequate pain	DB, PC, RCT, XO Patients 18 to 80 years of age with a histologically documented diagnosis of a malignant solid tumor or a hematologic malignancy causing cancer-related pain, a life expectancy ≥2 months; the use of a fixed-dose, around-the-clock opioid regimen for persistent pain (oral morphine ≥60 mg/day, transdermal fentanyl ≥25 µg/hour, or an equivalent dose of an alternative opioid for ≥7 days), an average pain intensity pain <7 (11 point numerical	N=125 Up to 4 weeks	Primary: $SPID_{60}$ Secondary: Pain intensity at 0, five, 10, 15, 30, 45, 60, 90 and 120 minutes post dose; the percentage of BTP episodes with an improvement in pain intensity scores from baseline ≥33 and ≥50% post dose; pain relief; TOTPAR at 60, 90 and 120 minutes post dose; and proportion of BTP episodes that required the use of supplemental medication	Primary: The $SPID_{60}$ values were significantly greater for BTP episodes treated with fentanyl buccal tablet compared to BTP episodes treated with placebo (mean±SE, 9.70±0.63 vs 4.90±0.50; P<0.0001). There were no clinically meaningful differences in $SPID_{60}$ in terms of the different underlying pain pathophysiologies (nociceptive, neuropathic, or mixed). Secondary: As assessed by pain intensity difference, there was a greater reduction in pain intensity following buccal tablet fentanyl than placebo at 10 minutes (0.9 vs 0.5; P<0.0001). The difference in pain intensity difference between the two treatments increased at subsequent time points up to 90 minutes post dose and then was maintained through two hours (P<0.0001 for each time point). A clinically significant improvement in pain intensity scores from baseline ≥33% occurred in a larger proportion of BTP episodes treated with fentanyl buccal tablet compared to BTP episodes treated with placebo at 10 minutes (16 vs 10%; P=0.007), 15 minutes (29 vs 14%; P<0.0001) and 30 minutes (51 vs 26%; P<0.0001). The differential increased through 60 minutes and was maintained over the two hour observation period (P<0.0001 for each subsequent time point). The difference in the proportion of BTP episodes with an improvement in pain intensity ≥50% following buccal tablet fentanyl or placebo was also significant at 10 minutes (7 vs 4%; P=0.033), 15 minutes (18 vs 8%; P<0.0001), and 30 minutes (38 vs 15%; P<0.0001), and continued to increase through two hours (P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
relief was not experienced after 30 minutes, patients were instructed to use their usual BTP medication if needed. After titration to an effective dose of fentanyl buccal tablet, patients were given ten randomly ordered treatment units (seven buccal tablet fentanyl units and three placebo units) in the form of identical tablets.	scale) for their persistent pain during the 24 hours before consent, a report of one to four BTP episodes/day while taking around-the-clock opioids and the use of an opioid to treat BTP that is at least partially effective			Pain relief was significantly better with fentanyl buccal tablet compared to placebo as early as 10 minutes (0.815 vs 0.606; P<0.0001); the differential increased over time up to 90 minutes and was maintained for two hours (P<0.0001 for each time point). Similarly, TOTPAR values were significantly better (P<0.0001) following fentanyl buccal tablet compared to placebo at 60, 90, and 120 minutes post dose. Supplemental medication was used for 53/493 (11%) BTP episodes treated with buccal tablet fentanyl compared to 67/223 (30%) episodes treated with placebo (P value not reported).
Zeppetella et al.[33] (2010) Fentanyl buccal tablet vs placebo Combined analysis of patients previously enrolled in Portenoy et al and Slatkin et al.	DB, PC, RCT Patients ≥18 years of age with a histologically documented diagnosis of a malignant solid tumor or hematological malignancy who were experiencing persistent cancer-related pain and BTP, and who were	N=150 Duration not reported	Primary: Pain intensity, pain relief, global medication performance, use of rescue medication Secondary: Safety and tolerability	Primary: A greater effect was seen on the proportion of the BTP episodes with ≥33 or ≥50% improvement in pain intensity from baseline in the patients administering fentanyl buccal tablet compared to patients administering placebo, starting at the 15 minute time point and continuing to evaluation at 60 minutes (P<0.0001 at each time point). At 30 minutes, 59% of the episodes treated with fentanyl buccal tablet and 36% treated with placebo had a ≥2 point improvement in pain intensity, with the relative proportions increasing at 45 minutes to 74 and 44%, respectively (P<0.0001 at each time point). The percentage of BTP episodes with at least moderate pain relief also showed a difference, favoring fentanyl buccal tablet over placebo from 15 minutes (P=0.0004). At 30 minutes, 47% of the patients who took fentanyl buccal tablet had a least moderate pain relief compared to 28% who took

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
After titration to an effective dose of fentanyl buccal tablet, patients were given ten randomly ordered treatment units (seven fentanyl buccal tablet units and three placebo units) in the form of identical tablets.	receiving maintenance opioid therapy for ≥1 week prior to screening			placebo (P<0.0001). Respective differences favoring fentanyl buccal tablet over placebo were maintained at 45 minutes (64 vs 34%; P<0.0001) and at 60 minutes (69 vs 39%; P<0.0001). At 60 minutes, the mean global medication performance score for fentanyl buccal tablet was 2.1 and 1.2 for placebo (P value not reported). Patients were three times more likely to resort to rescue medication for a placebo-treated BTP episode (40 vs 17%; OR, 3.22; 95% CI, 2.43 to 4.28; P value not reported). Secondary: The adverse events noted were generally typical of those experienced by patients with cancer who take potent opioids. Most were classified as either mild or moderate in intensity and were transitory. The most common adverse events were nausea and dizziness.
Lennernäs et al.[34] (2010) Sublingual fentanyl tablet 100 µg vs sublingual fentanyl tablet 200 µg vs sublingual fentanyl tablet 400 µg vs placebo	DB, MC, RCT, XO Adult patients with cancer pain that were regularly experiencing at least four episodes of BTP over a period of 14 days and were receiving a fixed-schedule opioid regimen equivalent to 30 to 1,000 mg/day oral morphine or 25 to 300 µg transdermal fentanyl	N=38 Duration unknown	Primary: Pain intensity difference Secondary: Global assessment of treatment (none, mild, moderate or excellent), need for rescue medication	Primary: A significant overall improvement in pain intensity difference was seen in the fentanyl 400 µg group compared to the placebo group (P<0.0001) with the effect first becoming significant after 15 minutes (P=0.005). However, a significant difference was not seen in the 100 or 200 µg groups compared to placebo. Secondary: Nine patients reported treatment with fentanyl 400 µg as excellent compared to three with placebo (P=0.0146). Five and three patients taking fentanyl 100 and 200 µg, respectively rated treatment as excellent. Significantly fewer patients taking fentanyl 400 µg required rescue medications compared to patients taking placebo (P=0.001). Eleven and ten patients required a rescue medication with the 100 and 200 µg doses, respectively (P values not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Patients received one dose of placebo and one of each of the three doses of fentanyl sublingual tablet in random order for four episodes. Treatment periods were separated by a washout period of at least one day.				
Rauck et al.[35] (2009) Fentanyl sublingual tablet 100 to 800 µg vs placebo Fentanyl sublingual tablet was titrated up to 800 µg until an effective dose was reached.	DB, MC, PC, RCT Patients ≥17 years of age with stable cancer related pain, experiencing one to four episodes of BTP per day and receiving 60 to 1,000 mg oral morphine per day, transdermal fentanyl 50 to 300 µg per hour or equivalent	N=131 10 BTP episodes 12 month safety phase	Primary: $SPID_{30}$ Secondary: Pain intensity difference and pain relief scores	Primary: The mean $SPID_{30}$ in episodes treated with sublingual fentanyl tablets was 49.5 compared to 36.6 in episodes treated with placebo (P=0.0004). The significant difference in SPID score was maintained at 60 minutes (P=0.0002). Secondary: Treatment of BTP episodes with sublingual fentanyl tablets showed greater improvements in pain intensity difference scores compared to placebo at ten minutes after treatment administration (P=0.0055) and was maintained up to 60 minutes. In addition, pain relief scores were significantly greater in episodes treated with sublingual fentanyl tablets compared to placebo at ten minutes (P=0.0490). This significant difference was maintained up to 60 minutes. Among patients treated with sublingual fentanyl tablets, 11.2% required rescue medication compared to 27.4% in the placebo group. (P values not reported). During the safety phase, the most common treatment-emergent adverse events were nausea, vomiting, headache and somnolence.
Portenoy et al.[36] (2010)	DB, MC, PC, RCT, XO	N=114 10 BTP	Primary: Patient-averaged, $SPID_{30}$	Primary: The mean (±SD) $SPID_{30}$ score was 6.57 (±4.99) for fentanyl nasal spray and 4.45 (±5.51) for placebo; corresponding to a mean treatment

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Fentanyl nasal spray 100 to 800 µg vs placebo Fentanyl nasal spray was titrated up to 800 µg until the patient received adequate pain relief for each BTP episode. After titration to an effective dose of fentanyl nasal spray, patients received ten doses of study medication (seven contained fentanyl and three were placebo).	Adult patients with cancer experiencing at least one to four BTP episodes daily, who were also receiving fixed-dose opioids for pain at a total daily dose equivalent to 60 mg of oral morphine	episodes	Secondary: Patient-averaged, summed pain intensity difference scores, patient-averaged, mean differences in pain relief, TOTPAR score, clinically meaningful reduction in pain intensity (≥2), need for additional rescue medication, patient acceptability scores	difference of 2.12 (±3.91) (95% CI, 1.21 to 3.03; P<0.0001). Secondary: The mean pain intensity score for patient-averaged fentanyl-treated episodes was significantly different from that for placebo-treated episodes at the five minute time point (P=0.03), and the difference in pain intensity was sustained over the 10, 15, 30, 45, and 60 minute evaluation time points. Patient-averaged mean differences in pain relief and TOTPAR scores were also significant at 10 minutes and at all measured time-points to 60 minutes. A total of 49% of those treated with fentanyl had a clinically meaningful reduction in pain intensity at 15 minutes (P<0.001) and 63% had the same degree of pain relief by 30 minutes. The cumulative SPID scores demonstrated that a significantly higher percentage of patients reported a mean reduction in SPID score ≥2 after fentanyl administration vs placebo administration at each evaluation from 10 to 60 minutes post-treatment dose. Overall, 90.6% of episodes treated with fentanyl nasal spray compared to 80.0% of episodes treated with placebo did not require an additional rescue medication within 60 minutes of breakthrough treatment (P<0.001). The overall mean patient-averaged acceptability assessment score was significantly greater for the fentanyl treatment vs placebo at 30 minutes post-treatment (2.63 vs 2.01; P<0.0001) and at 60 minutes post-treatment (2.73 vs 2.02; P<0.0001).
Taylor et al.[37] (2010) Fentanyl nasal spray 100 to 800 µg vs placebo	DB, MC, PC, RCT, XO Adult patients with cancer experiencing at least one to four BTP episodes daily, who were also receiving fixed-dose opioids for pain at a total daily dose	N=114 10 BTP episodes	Primary: Pain intensity score, SPID score, pain relief score Secondary: Overall patient satisfaction, satisfaction with speed of relief and reliability of nasal	Primary: Fentanyl nasal spray significantly decreased pain intensity (≥1 point reduction) at all time intervals (five, 10, 15, 30, 45 and 60 minutes) compared to placebo (P<0.05 at 5 minutes, P<0.0001 at all other intervals). A significant meaningful reduction in pain intensity (≥2 point reduction) was first observed at 10 minutes in 32.9% of fentanyl patients compared to 24.5% of placebo patients (P<0.05) and increased to include 50.8% of fentanyl patients at 30 minutes (P<0.0001 vs placebo). Significant differences were also observed between fentanyl and placebo treated patients in the number of episodes with ≥2 point reduction in SPID

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Fentanyl nasal spray was titrated up to 800 µg until the patient received adequate pain relief for each BTP episode. After titration to an effective dose of fentanyl nasal spray, patients received ten doses of study medication (seven contained fentanyl and three were placebo). Patients could take a maximum of four doses per day with at least four hours between doses.	equivalent to 60 mg of oral morphine		spray, ease of use and convenience of nasal spray	score from 10 to 60 minutes (P<0.01). In addition, the number of episodes with pain relief score changes ≥1 point and ≥2 points was significantly higher in the fentanyl group compared to placebo from 10 to 60 minutes (P<0.0001 and P<0.001, respectively). Secondary: Significantly more patients in the fentanyl group reported a higher overall satisfaction score and satisfaction with speed of relief and reliability compared to placebo (P<0.0001 for all). A total of 68.5 and 69.9% of patients using fentanyl reported they were either satisfied or very satisfied with ease of use and convenience of the nasal spray, respectively.
Christie et al.[38] (1998) Fentanyl transmucosal lozenge 200 µg vs fentanyl transmucosal lozenge 400 µg	DB, dose titration, MC, RCT Adult patients with cancer using transdermal fentanyl for persistent pain	N=62 Duration not reported	Primary: Pain intensity, pain relief, and global satisfaction compared to usual BTP medication Secondary: Dosing requirements	Primary: Pain scores following fentanyl transmucosal on successful days were compared to pain scores on baseline days following usual BTP medication. Scores at zero minutes were not significantly different for the two groups. At 15, 30 and 60 minutes, transmucosal fentanyl produced markedly lower pain intensity scores and higher pain relief scores than the usual BTP medication (P≤0.0002 for each analysis). At 30 minutes, the mean±SD difference between pain intensity scores following usual BTP medication and transmucosal fentanyl was 1.6±1.9. Pain intensity difference values at 15, 30, and 60 minutes were significantly better following transmucosal fentanyl (P≤0.001). The 0 to 15 minute pain intensity difference values for transmucosal fentanyl was

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Fentanyl transmucosal lozenge was titrated up to 1,600 µg until the patient received adequate pain relief for each BTP episode using one Fentanyl transmucosal lozenge unit. On each study day, as many as 4 units could be taken sequentially (one every 30 minutes) for up to two BTP episodes/day. Patients' usual BTP medication included codeine, hydrocodone, hydromorphone, morphine, oxycodone, propoxyphene, tramadol, or no medication.				>2.5 times larger compared to the usual BTP medication (2.35 vs 0.91; P=0.0001), which is consistent with a faster onset of action. Also, transmucosal fentanyl produced a pain relief score at 15 minutes that was >2 times higher compared to the usual BTP medication (1.90 vs 0.82; P=0.001). At 30 minutes, the mean±SD difference between values following each treatment was 0.95±1.20. Global satisfaction ratings were significantly higher following transmucosal fentanyl compared to usual BTP medication (2.6 vs 2.0; P=0.0001). Secondary: Of the 62 patients enrolled, 47 (76%) were successfully titrated to a unit dose of transmucosal fentanyl that effectively treated their BTP. Four patients were unable to control their BTP with the highest transmucosal fentanyl dose of 1,600 µg and 11 patients withdrew from the trial; six of these withdrawals were due to a side effect. Patients who found a successful dose of transmucosal fentanyl were titrated to a mean dose of approximately 600 µg, with no statistically significant difference in the final dose between the patients who began with 200 µg and those who began with 400 µg (667 vs 825 µg, respectively; P=0.58).
Farrar et al.[39] (1998) Fentanyl transmucosal lozenge 200 µg	DB, MC, PC, RCT, XO Patients ≥18 years of age with cancer who had sufficient pain to require at	N=89 Duration not reported	Primary: Pain intensity, pain relief, and use of rescue medication at 15 minute intervals over a 60 minute period	Primary: Transmucosal fentanyl produced significantly larger changes in pain intensity and better pain relief than placebo at all time points (two-sided P<0.0001). Episodes of BTP treated with placebo required the use of rescue medication more often than episodes treated with transmucosal fentanyl

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo Fentanyl transmucosal lozenge was titrated up to 1,600 µg until the patient received adequate pain relief for each BTP episode. After titration to an effective dose of fentanyl transmucosal lozenge, patients were given ten randomly ordered treatment units (seven fentanyl transmucosal lozenge units and three placebo units) in the form of identical lozenges. If adequate pain relief was not achieved with a single dose of transmucosal fentanyl after 30 minutes, patients were instructed to	least the equivalent of 60 mg/day of oral morphine or 50 µg/hour transdermal fentanyl, and had ≥1 BTP episode/day for which they took additional opioids		Secondary: Not reported	(34 vs 15%; RR, 2.27; 95% CI, 1.51 to 3.26; P<0.0001). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
take a dose of their usual BTP medication. Patients' usual BTP medication included hydrocodone, hydromorphone, morphine, oxycodone, and other medications.				
Hanks et al.[40] (2004) Fentanyl transmucosal lozenge 200 µg Fentanyl transmucosal lozenge was titrated up to 1,600 µg until the patient received adequate pain relief for each BTP episode using one transmucosal fentanyl unit. Patients had access to their usual BTP medication. The majority of patients were using IR morphine as	MC, OL Patients stabilized on a long-acting opioid (60 to 1,000 mg/day of oral morphine, 50 to 300 µg/hour of transdermal fentanyl, or 8 to 135 mg/day of oral hydromorphone) for ≥3 days prior to enrollment, but experiencing up to four BTP episodes/day, and achieving at least partial relief from BTP using conventional medication	N=57 Duration not reported	Primary: SPID and TOTPAR up to 60 minutes Secondary: Not reported	Primary: SPID values were significantly higher following transmucosal fentanyl compared to conventional medication at all time points (P<0.001 for all). Transmucosal fentanyl produced better pain relief scores than conventional medication beginning at the 15 minute time point (1.49 vs 0.89; P<0.001) and continuing at the 30, 45, and 60 minute time points (P<0.001 at all time points). TOTPAR values were also significantly higher at each time point evaluated (P<0.001 for all). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
their usual BTP medication. If adequate pain relief was not achieved with a single dose of fentanyl transmucosal lozenge after 30 minutes, patients were instructed to take a dose of their usual BTP medication. The efficacy of their usual BTP medication was documented in a run-in phase and patients then changed to fentanyl transmucosal lozenge.				
Payne et al.[41] (2001) Fentanyl transmucosal lozenge Patients had participated in a previous short-term titration trial	MC, OL Patients requiring either a scheduled oral opioid regimen equivalent to 60 to 1,000 mg/day of oral morphine or 50 to 300 µg/hour of transdermal fentanyl for control of	N=151 1 to 423 days	Primary: Number of successfully treated BTP episodes, global satisfaction rating, side effects Secondary: Not reported	Primary: Ninety-two percent of BTP episodes were considered successful (defined as a BTP episode for which a patient felt that they had achieved satisfactory pain relief using one transmucosal fentanyl unit [i.e., no additional rescue medication for the episode]). The number of patients dropped substantially from months five to eight (N=53) to months nine to 12 (N=19) and months >12 (N=8). Therefore, though the percentage of BTP episodes treated successfully with transmucosal fentanyl dropped from 90 to 85% after month nine, the declining sample size makes it difficult to determine whether this is an actual decrease in efficacy.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
of fentanyl transmucosal lozenge (Christie et al., Portenoy et al., and Farrar et al.). Patients began the study at the fentanyl transmucosal lozenge doses that they had found to be effective in the previous titration trials in which they participated.	persistent pain, experiencing ≥1 BTP episode/day, and achieving at least partial relief of BTP by use of an opioid in the past			Mean global satisfaction ratings were consistently above three, indicating 'very good' to 'excellent' relief. The satisfaction ratings also remained consistent over time. Common adverse events associated with transmucosal fentanyl were somnolence (9%), constipation (8%), nausea (8%), dizziness (8%), and vomiting (5%). Six patients discontinued therapy due to a transmucosal fentanyl-related adverse event. There were no reports of abuse and no concerns about the safety of the drug raised by patients or families. Secondary: Not reported
Portenoy et al.[42] (1999) Fentanyl transmucosal lozenge 200 µg vs fentanyl transmucosal lozenge 400 µg Fentanyl transmucosal lozenge was titrated up to 1,600 µg until the patient received adequate pain relief for each	DB, dose titration, MC, RCT Adult patients with cancer-related pain who were receiving a scheduled oral opioid regimen equivalent to 60 to 1,000 mg of oral morphine/day, experienced ≥1 BTP episode per day between 0700 to 1600 hours on the three days immediately preceding screening, and achieved at least	N=65 Duration not reported	Primary: Pain intensity, pain relief, global assessment of drug performance Secondary: Not reported	Primary: For the 48 patients who were successfully titrated to an effective dose of transmucosal fentanyl, the mean pain intensity immediately before the dose of transmucosal fentanyl was approximately 6 on the 0 to10 numerical scale. After 60 minutes, the pain intensity averaged 1.5. The reduction in pain intensity during the 0 to 15 minute time period after the dose was 56% of the total pain intensity decline. Mean pain relief scores at 15 minutes and 30 minutes after the transmucosal fentanyl dose were 2.1 ('moderate' pain relief) and 2.5 ('moderate' to 'lots' of pain relief), respectively. The global performance of the transmucosal fentanyl during the two successful treatment days was 2.9 on the 0 to 4 verbal rating scale. With the exception of a single pain intensity difference recorded at the 60 minute time point, there were no significant differences between patients randomized to the 200 vs 400 µg starting doses in any of these outcome variables.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
BTP episode using one fentanyl transmucosal lozenge unit. On each study day, as many as four units could be taken sequentially (one every 30 minutes) for up to two BTP episodes/day between 0700 to 1600 hours. Patients' usual BTP medication was used to treat all other BTPs on these study days.	partial relief of this BTP by the use of an oral opioid rescue dose			Secondary: Not reported
Davies et al.[43] (2011) Fentanyl nasal spray vs morphine IR Fentanyl nasal spray was titrated up to 800 µg until the patient reached an effective dose that treated two	DB, DD, MC, XO Patients with a diagnosis of cancer, who were receiving fixed-schedule opioid regimens at a total daily dose ≥60 mg/day oral morphine or equivalent and one to four episodes per day of moderate to severe cancer BTP	N=110 10 BTP episodes	Primary: Pain intensity score, SPID, pain relief score, TOTPAR, onset of clinically meaningful pain relief (≥2 point reduction in pain intensity score), patient acceptability score (overall satisfaction, satisfaction with speed of relief and	Primary: After ten minutes, fentanyl nasal spray had greater pain intensity difference scores and a higher proportion of episodes showing clinically meaningful pain relief compared to morphine IR (P<0.05 for both). After 15 minutes, 52.3% of patients taking fentanyl had a TOTPAR score ≥33% compared to 43.5% of patients taking morphine (P<0.01). This significant difference was maintained until 60 minutes. Patient-averaged acceptability assessment scores were greater for fentanyl nasal spray than for morphine for all questions at 30 minutes (P<0.01) and 60 minutes (P <0.01). More treatment-emergent adverse effects were reported to be associated with fentanyl than with morphine. Only eight patients (six fentanyl and two morphine) experienced adverse effects that resulted in discontinuation of the drug (P values not reported).

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consecutive BTP episodes. After titration to an effective dose, ten episodes of BTP were randomly treated with fentanyl nasal spray and encapsulated placebo or morphine IR and nasal spray placebo (five episodes of each).			satisfaction with reliability), adverse events Secondary: Not reported	Secondary: Not reported
Fallon et al.[44] (2011) Fentanyl nasal spray 100 to 800 µg vs morphine IR Fentanyl nasal spray was titrated up to 800 µg until the patient received adequate pain relief for each BTP episode. IR morphine dose was determined as	DB, DD, MC, RCT, XO Adult patients with cancer that were receiving fixed-schedule opioid regimens at a total daily dose equivalent to ≥60 mg/day oral morphine and experiencing one to four BTP episodes per day	N=110 10 BTP episodes	Primary: Pain intensity difference after 15 minutes Secondary: Patient- and episode-averaged pain intensity difference, SPID, pain intensity score, pain relief score, TOTPAR score, onset of analgesia (≥1 point reduction in pain intensity and pain relief), onset of clinically meaningful pain relief (≥2 point	Primary: The mean (±SD) pain intensity difference score after 15 minutes was 3.02 (±0.21) for fentanyl nasal spray compared to 2.69 (±0.18) for morphine IR (P<0.05). Fentanyl nasal spray had significantly greater pain intensity difference scores compared to morphine IR from 15 minutes through 60 minutes after initial dose (P <0.05). Secondary: After treatment of BTP, fentanyl nasal spray treated episodes had significantly lower pain intensity scores compared to morphine IR treated episodes from 30 minutes through 60 minutes (P<0.05). In addition, patient-averaged pain relief scores were significantly higher from 30 minutes through 60 minutes in patients who took fentanyl nasal spray compared to morphine IR (P≤0.005). Patient-averaged mean difference in TOTPAR were significant from 15 minutes through 60 minutes (P<0.05) favoring fentanyl nasal spray. The proportion of patients experiencing onset of analgesia and clinically meaningful pain relief was significantly greater in the fentanyl nasal spray group compared to the morphine IR group as early as five minutes and ten minutes, respectively (P<0.05 for both).

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one-sixth of the total daily oral morphine dose equivalent of the patient's background opioid medication. After titration to an effective dose, ten episodes of BTP were randomly treated with fentanyl nasal spray and encapsulated placebo or IR morphine and nasal spray placebo (five episodes of each).			reduction in pain intensity and pain relief or 33% reductions in pain intensity and SPID), need for rescue medication	There was no significant difference in the proportion of patients requiring rescue medication within 60 minutes between fentanyl nasal spray and morphine IR. More treatment emergent adverse events occurred in patients using fentanyl nasal spray (P value not reported). Of the 14 serious adverse events reported, 12 occurred following treatment with fentanyl nasal spray.
Webster et al.[45] (2013) Fentanyl buccal tablet vs oxycodone IR <u>OL extension:</u> Fentanyl buccal tablet vs	AC, DB, RCT, XO, followed by OL extension Patients 18 to 80 years of age with ≥3 month history of chronic pain, opioid tolerant (taking ≥60 mg/day of morphine equivalent, average pain intensity of ≤6 on an 11-point scale, and experiencing one to four episodes of	N=211 Two DB phases of 10 BTP episodes OL: 12 weeks	Primary: Difference in pain intensity (0 to 10 numeric scale) before and 15 minutes after medication Secondary: Pain response	Primary: During the double-blind treatment periods, the mean (standard deviation) PID score was significantly greater after fentanyl buccal tablet administration (0.88 [1.20]) than after immediate-release oxycodone (0.76 [1.13]; P<0.001). The mean PID also was significantly greater after fentanyl buccal tablet administration compared with immediate-release oxycodone beginning as early as 10 minutes postdose (P=0.01), and a significant difference was maintained through 60 minutes (P<0.001). Secondary: Mean values of patient assessments of pain response were significantly greater after fentanyl buccal tablet administration than after immediate-release oxycodone administration beginning at 15 minutes (P=0.04) and at all subsequent time points (P<0.01). Patients preferred fentanyl buccal tablet (47%) over oxycodone (35%); 18% had no preference. Patients and clinicians reported consistently better functional improvement and

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any traditional short-acting opioid (SAO) deemed appropriate by their treating physician	BTP daily with at least partial relief with opioids			satisfaction with fentanyl buccal tablet vs short-acting opioids (P<0.05).
Shear et al.[46] (2010) Fentanyl 100 µg transbuccal vs oxycodone-APAP 5-325 mg	DB, RCT Adult patients who presented to the ED with a chief complain of extremity injury	N=60 1 hour	Primary: Time required to achieve a 2-point drop on a 10-point pain scale Secondary: Maximum pain scale reduction and vital signs	Primary: Treatment with fentanyl was associated with faster pain relief onset than oxycodone-APAP (10 vs 35 minutes; P<0.0001). Secondary: Overall, rescue medication was required in 22 subjects; rescue analgesia was more frequently administered to those in the oxycodone-APAP group than in the fentanyl group (17 vs 57; P=0.003). Treatment with fentanyl was associated with faster time to maximum pain reduction than oxycodone-APAP (40 vs 55 minutes; P<0.01). The maximal pain score reduction was greater with fentanyl than oxycodone-APAP (6 vs 3; P=0.0004). Patients receiving fentanyl were more likely to be satisfied with the analgesia provided by the study drug. This was true regardless as to whether preference was measured as a median of the 1 to 5 rating scale (P=0.00001) or as a proportion of subjects indicating either 1 or 2 (meaning strong or probable preference to receive similar analgesia in the future; P<0.001). In the fentanyl group, 100% of patients achieved significant pain reduction compared to 83% of patients in the oxycodone-APAP group, which was not significant (P=0.52). The monitoring of vital signs identified no adverse effects in any subject in either group. No significant side effects occurred in the ED or during the next-day.
Coluzzi et al.[47] (2001)	DB, DD, RCT, XO	N=89	Primary: Pain intensity	Primary: Mean pain intensity differences across all time points significantly favored

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Fentanyl transmucosal lozenge 200 µg vs morphine IR 15 to 60 mg Fentanyl transmucosal lozenge was titrated up to 1,600 µg until the patient received adequate pain relief for each BTP episode. For any non-target BTP episodes, patients used their usual supply of morphine IR.	Adult patients with cancer-related pain who were regularly having one to four BTP episodes/day while using a stable fixed schedule oral opioid regimen equivalent to 60 to1,000 mg/day of oral morphine or 50 to 300 µg/hour of transdermal fentanyl and who were using a successful dose of 15 to 60 mg of morphine IR to treat target BTP	Up to 14 days or 10 BTP episodes	difference at 15, 30, 45 and 60 minutes post dose Secondary: Adverse events	transmucosal fentanyl (P<0.008 for all). Transmucosal fentanyl produced a >33% change in 15 minute pain intensity difference values for 42.3% of the episodes treated compared to 31.8% for morphine IR (P<0.001). Secondary: Most adverse events reported during the study were considered unrelated or unlikely to be related to study medication. The most frequent drug-related adverse events included somnolence, nausea, constipation, and dizziness. Due to the design of the study it is difficult to attribute an adverse event to either of the study medications.
Zeppetella et al.[48] (2006) Opioid analgesics vs placebo or opioid analgesics All RCTs were concerned with the use of	MA (4 RCTs) Patients of any age with cancer and BTP who were treated with opioids for cancer pain	N=393 Duration not reported	Primary: Reduction in pain intensity, adverse effects, attrition, patient satisfaction, and quality of life Secondary: Not reported	Primary: Results from four trials demonstrated that fentanyl transmucosal lozenge was more efficacious to placebo, morphine IR, and previous rescue medication with a WMD of -0.68 (95% CI, -1.03 to -0.34) for pain improvement at 15 minutes and -0.91 (95% CI, -1.23 to -0.59) for pain improvement at 30 minutes. Transmucosal fentanyl was more efficacious in providing pain relief at 15 minutes (WMD, 0.54; 95% CI, 0.40 to 0.69) and 30 minutes (WMD, 0.61; 95% CI, 0.47 to 0.75). Compared to previous rescue medication and placebo, transmucosal fentanyl was also more efficacious for global performance (WMD, 0.76; 95% CI, 0.58 to 0.95). *Fentanyl transmucosal lozenge dose titration:*

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transmucosal fentanyl in the management of BTP. Two trials examined the titration of transmucosal fentanyl, one trial compared transmucosal fentanyl to morphine IR and one trial compared transmucosal fentanyl to placebo. Previous rescue medication included hydrocodone, hydromorphone, morphine, oxycodone, and propoxyphene.				Of the 62 patients on around-the-clock transdermal fentanyl, 47 (76%) were able to titrate transmucosal fentanyl to a safe and effective dose to treat their BTP. Three patients administering around-the-clock transdermal fentanyl withdrew during the titration phase because of treatment-emergent adverse effects and four patients titrated to the 1,600 µg dose without obtaining adequate relief. The mean±SD successful transmucosal fentanyl dose was 587±335 µg. Of the 67 patients on around-the-clock oral opioids, 48 (74%) were able to titrate to a safe and effective dose of transmucosal fentanyl using a single unit to treat their BTP. Eight patients administering around-the-clock oral opioids withdrew during the titration phase because of treatment-emergent adverse effects and five participants titrated to the 1,600 µg dose without adequate obtaining relief. The mean±SD successful transmucosal fentanyl dose was 640±374 µg. It was determined that the optimal dose of transmucosal fentanyl cannot be predicted by the total daily dose of fixed scheduled opioids. The most common adverse events associated with transmucosal fentanyl were somnolence, nausea, dizziness, and vomiting. An OL comparison of transmucosal fentanyl and usual BTP medication demonstrated that transmucosal fentanyl produced significantly better pain relief at all time periods in patients administering around-the-clock transdermal fentanyl or oral opioids (P<0.0001 for both). Patient rated global satisfaction of transmucosal fentanyl was significantly higher compared to usual BTP medication (around-the-clock transdermal fentanyl, 2.6 vs 2.01; P=0.0001 and around-the-clock oral opioids, 2.74 vs 2.09; P=0.0002). Transmucosal fentanyl vs placebo: Of the 130 participants, 93 (72%) were able to titrate and find a safe and effective dose of transmucosal fentanyl using a single unit to treat their BTP. The mean±SD successful transmucosal dose was 789±468 µg. Ninety two patients agreed to enter a DB, randomized phase in which results from 86 patients demonstrated that transmucosal fentanyl produced

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				significantly better pain relief than placebo as evidenced by better pain intensity and pain relief scores for all time points (P<0.0001). Patient rated global performance of transmucosal fentanyl was significantly better compared to placebo (1.98 vs 1.19; P<0.0001) and patients-treated with transmucosal fentanyl required significantly less additional BTP medication (15 vs 34%; P<0.0001). Of the original 92 patients, 74 (80%) chose to continue transmucosal fentanyl following the trial. The most frequent adverse effects included dizziness, nausea, somnolence, constipation, asthenia, confusion, vomiting, and pruritus. *Transmucosal fentanyl vs normal release morphine:* Of the 134 patients, 93 (69%) were able to titrate to a safe and effective dose of transmucosal fentanyl using a single unit to treat their BTP. Five patients titrated up to the 1,600 μg dose without obtaining adequate relief. Transmucosal fentanyl was significantly more efficacious to IR morphine in terms of pain intensity difference (P<0.008) and pain relief (P<0.009) at each time point, and global performance rating (P<0.001). Additionally, significantly more (P<0.001) more BTP episodes treated with transmucosal fentanyl had a >33% change in pain intensity at 15 minutes. Secondary: Not reported
Mercadante et al.[49] (2007) Fentanyl transmucosal lozenge, dose proportional to basal daily opioid dose vs IV morphine, dose proportional to	RCT, XO Adult patients with cancer-related pain, receiving opioids regularly at doses >60 mg/day of oral morphine equivalents, had acceptable pain relief, and presented ≤2 pain flares/day	N=25 Duration not reported	Primary: Pain intensity at zero (T0), 15 (T1), and 30 (T2) minutes post dose; and opioid-related symptoms Secondary: Not reported	Primary: In BTP episodes treated with IV morphine, pain intensity decreased from 6.9 (95% CI, 6.6 to 7.2) to 3.3 (95% CI, 2.7 to 3.8) and 1.7 (95% CI, 1.2 to 2.3) at T1 and T2, respectively. This reduction was >33% in 39 (74%) and in 46 (87%) episodes at T1 and T2, respectively, and >50% in 29 (55%) and in 40 (75%) episodes at T1 and T2, respectively. In BTP episodes treated with transmucosal fentanyl, pain intensity decreased from 6.9 (95% CI, 6.6 to 7.2) to 4.1 (95% CI, 3.6 to 4.7) and 2.4 (95% CI, 1.8 to 2.9) at T1 and T2, respectively. This reduction was >33% in 30 (57%) and 45 (85%) episodes at T1 and T2, respectively, and >50% in 20 (38%) and in 40 (75%) episodes at T1 and T2, respectively. A statistical difference between the two treatments was found at T1

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basal daily opioid dose Patients were planned to receive fentanyl transmucosal lozenge and IV morphine for each couple of BTP episodes between 0700 to 1900 hours. The order of administration was randomized.				(P=0.013), whereas at T2 the difference did not attain a statistical significance (P=0.59). At T1, a decrease of 41.1 and 51.7% in pain intensity was observed after transmucosal fentanyl and IV morphine, respectively (P=0.026). At T2, a decrease of 65.9 and 73.8% in pain intensity was recorded after transmucosal fentanyl and IV morphine, respectively (P=0.136). No differences between the two groups were observed in the number of episodes with a reduction of >33 and >50% at T1 (P=0.66 and P=0.39) and T2 (P=0.23 and P=0.20), respectively. Acute adverse effects occurring after IV morphine and transmucosal fentanyl were comparable and correspond to those commonly observed with opioid therapy. Moderate adverse effects in BTP episodes treated with transmucosal fentanyl and IV morphine were nausea, drowsiness and confusion. Secondary: Not reported
Mercadante et al.[50] (2009) Fentanyl nasal spray 50 to 200 µg vs fentanyl transmucosal lozenge 200 to 1,600 µg Enrolled patients entered a one week screening phase in which background pain intensity, BTP episodes, and use of rescue	OL, XO Patients ≥18 years of age, with a life expectancy ≥3 months, who were experiencing ≥3 BTP episodes/week, but ≤4 BTP episodes/day and receiving stable opioid treatment for background pain (oral hydromorphone, morphine, oxycodone, or transdermal fentanyl) at a dose equivalent to 60 to	N=139 8 to 11 weeks	Primary: Time to onset of 'meaningful' pain relief Secondary: Pain intensity, patient's general impression of drug efficacy and safety	Primary: The median time to onset of 'meaningful' pain relief was 11 minutes for intranasal fentanyl and 16 minutes for transmucosal fentanyl (P value not reported). Secondary: Statistically greater proportions of episodes treated with intranasal fentanyl compared to transmucosal fentanyl achieved ≥33 and ≥50% pain intensity reduction up to 30 minutes post dose. The proportion of BTP episodes treated with intranasal fentanyl and transmucosal fentanyl achieving a pain intensity reduction of ≥33% at five and ten minutes were 25.3 and 6.8% (P<0.001) and 51.0 vs 23.6% (P<0.001), respectively. The proportion of BTP episodes treated with intranasal fentanyl and transmucosal fentanyl achieving a ≥50% pain intensity reduction at 5 and 10 minutes were 12.8 vs 2.1% (P<0.001) and 36.9 vs 9.7% (P<0.001), respectively. The adjusted mean general impression score for treatment of the BTP episode as assessed by the patient at 60 minutes following the

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medication was assessed. Patients were then randomized to receive fentanyl nasal spray followed by fentanyl transmucosal lozenge, or vice versa, and entered a five to eight week titration phase in which an effective dose of the study drug was determined. Patients then entered a <2 week efficacy phase during which six BTP episodes were treated with the identified effective dose of fentanyl nasal spray/ transmucosal lozenge.	500 mg/day of oral morphine for ≥1 month prior to the study			administration of intranasal fentanyl and start of transmucosal fentanyl use respectively was 2.1 (95% CI, 2.0 to 2.3) compared to 2.0 (95% CI, 0.1 to 0.2; P<0.001). Seventy nine (56.8%) patients experienced ≥1 adverse event in the titration and efficacy phase. The only adverse event occurred in ≥5% of patients in either treatment group was nausea.
Vissers et al.[51] (2010) Fentanyl nasal spray vs	MA (six RCT) Adult cancer patients suffering from BTP, treated with opioid analgesics for	N=Not available Duration unknown	Primary: Mean pain intensity difference Secondary: Not reported	Primary: Relative to placebo, fentanyl nasal spray provided a 1.7 (95% CI, 1.4 to 1.9) reduction in pain relief after 15 minutes, while the lozenge provided a 0.4 (95% CI, 0.0 to 0.8) reduction and the buccal tablet provided a 0.5 (95% CI, 0.3 to 0.7) reduction. Differences in pain intensity difference scores favoring fentanyl nasal spray were 1.2 (95% CI, 0.8 to 1.5) relative to the buccal tablet, 1.3 (95% CI, 0.9 to 1.6) relative to the transmucosal

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fentanyl transmucosal lozenge vs fentanyl buccal tablet vs oral morphine vs placebo	management of background pain			lozenge and 1.7 (95% CI, 1.1 to 2.3) relative to oral morphine. The significant difference in mean pain intensity difference scores favoring fentanyl nasal spray was maintained up to 45 minutes compared to the buccal tablet and up to 60 minutes compared to the transmucosal lozenge. According the author's analysis fentanyl nasal spray displayed >99% probability of providing the greatest pain reduction at 15 minutes out of all the interventions in the study. Secondary: Not reported
Velázquez Rivera et al.[52] (2014) Fentanyl sublingual tablet vs oral morphine solution Doses were adjusted individually	DB, RCT Adults ≥18 years of age suffering from cancer pain whose background pain was treated with strong opioids and who had BTP	N=40 30 days	Primary: Pain intensity reduction the VAS, frequency of BTP, and onset of relief Secondary: Patient satisfaction, adverse events	Primary: The mean pain intensity level was consistently better for fentanyl than morphine at all recorded time points with a significance of P=0.001 at day three, and greater (P<0.001) at the other recorded time periods. Sublingual fentanyl provided faster onset of relief (P<0.001) in BTP and improved pain scores with a shorter dose titration period (mean 6.6 ± 3.3 vs 13.3 ± 4.9; P<0.001). Secondary: In the group treated with fentanyl no patient reported dissatisfaction with treatment for BTP, but 37.5% of the patients treated with morphine reported being dissatisfied (31.25%) or very dissatisfied (6.25%). Side effects were similar with both treatments and typical of opioid drugs.
Jandhyala et al.[53] (2013) Fentanyl buccal tablet, sublingual	MA (five studies) Patient population not specified	N=Not available Duration unknown	Primary: Likelihood of more efficacious pain relief (based on pain intensity	Primary: The probability of greater pain relief than placebo during first 60 minutes after dosing was 61% for morphine IR, 97% for fentanyl buccal tablet, 72% for fentanyl sublingual tablet and 66% for fentanyl transmucosal lozenge. The probability of greater pain relief than placebo during first 30

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tablet or transmucosal lozenge vs morphine IR vs placebo			difference) Secondary: Not reported	minutes after dosing was 56% for morphine IR, 83% for fentanyl buccal tablet, 66% for fentanyl sublingual tablet and 73% for fentanyl transmucosal lozenge (P values not reported). Mean pain intensity difference scores 60 minutes after dosing compared to placebo were 0.44 (95% CI, -2.07 to 2.95) for morphine, 1.16 (95% CI, 0.09 to 2.23) for the buccal tablet, 0.81 (95% CI, -1.40 to 3.04) for the sublingual tablet and 0.88 (95% CI, -0.76 to 2.55) for the transmucosal lozenge. The mean pain intensity difference scores compared to morphine IR were 0.75 (95% CI, -1.92 to 3.41) for the buccal tablet, 0.35 (95% CI, -3.00 to 3.63) for the sublingual tablet and 0.48 (95% CI, -1.34 to 2.34) for the transmucosal lozenge. Secondary: Not reported
Joshi et al.[54] (2007) Fentanyl 2 µg/kg IV vs sufentanil 0.2 µg/kg IV vs placebo All study meds administered 10 minutes before chest tube removal.	DB, PC, RCT Patients post-op cardiac surgery, scheduled for chest tube removal	N=141 Single dose	Primary: Pain intensity as assessed by 100 mm VAS pain score 10 minutes before removing chest tubes and five minutes after removing chest tubes Secondary: Level of sedation, heart rate, arterial pressure and respiratory rate	Primary: Mean pain intensity scores 10 minutes before removal of chest tubes in fentanyl, sufentanil and control groups were 23.88, 25.10 and 23.64, respectively. The pain scores five minutes after chest tube removal were reduced to 20.11 in the fentanyl group (P<0.05) vs 13.60 in the sufentanil group (P<0.05). There was an increase to 27.97 in placebo group (P<0.05). The pain scores in sufentanil group were significantly lower compared to fentanyl or the control group. Secondary: Sedation scores remained low in all groups, patients remained alert and none of the patients showed any adverse effects of opioids. Heart rate, arterial pressure and respiratory rate had least variations in sufentanil group vs fentanyl or placebo group.
Motamed et al.[55] (2006)	RCT	N=75	Primary: Maximum post-op	Primary: Post-op pain scores in postoperative care unit were significantly lower in

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Fentanyl 2 to 3 µg/kg IV bolus vs sufentanil 0.2 to 0.3 µg/kg IV bolus vs remifentanil 0.4 to 5 µg/kg IV bolus All trial medications were administered intraoperatively.	Adults scheduled for elective total thyroidectomy	24 hours post-op	pain scores, Secondary: Necessity of morphine injection in both surgical ward and postoperative care unit; incidence of opioid related side effects (nausea/ vomiting, sedation) Secondary: Not reported	the sufentanil and fentanyl group compared to remifentanil group, (P<0.05). Secondary: Necessity and total amount of morphine titration in the postoperative care unit were significantly less in the sufentanil and fentanyl group compared to the remifentanil group (P<0.05). In the surgical ward, maximum pain scores and the incidence and the amount of morphine requirements were not different between groups. No patient had heavy sedation in any of the groups. The incidence of nausea and vomiting was not different between groups. Secondary: Not reported
Chang et al.[56] (2006) Hydromorphone 0.015 mg/kg IV as a single dose vs morphine 0.1 mg/kg IV as a single dose	DB, RCT Patients 21 to 65 years of age who presented to an ED with acute pain (<7 days in duration) warranting use of IV opioids	N=191 Single dose	Primary: Difference between the two groups in pain reduction at 30 minutes Secondary: Adverse effects	Primary: The mean change in pain with hydromorphone was not significantly different from morphine (-5.5 numeric rating scale units' vs -4.1; 95% CI, -2.2 to -0.5). Secondary: Adverse effects were similar in both groups, with the exception of pruritus, which did not occur in the hydromorphone group (0 vs 6%; 95% CI, -11 to -1).
Lazaraki et al.[57] (2007) Midazolam 2 to 5 mg IV vs	RCT Adult patients scheduled for ambulatory colonoscopy	N=126 Single dose	Primary: Patient discomfort as measured on a 0 to 4 scale, and pain on a 0 to 10 scale Secondary:	Primary: Mean discomfort scores were 0.4 in the fentanyl group and 1.0 in the midazolam group (P=0.002). Mean scores for pain and anus-to-cecum time were lower in the fentanyl group than in the midazolam group (2.59 vs 4.43; P=0.002 and 8.7 vs 12.9 minutes; P=0.012, respectively).

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fentanyl 25 to 50 µg IV			Adverse effects and recovery time	Secondary: No adverse events were reported in the fentanyl group, while in the midazolam group, a decrease in oxygen saturation was noted in 35% patients. Mean recovery time was 5.6 minutes in the fentanyl group and 16 minutes in the midazolam group (P=0.014).
Plummer et al.[58] (1997) Morphine PCA 0.75, 1.0 or 1.5 mg bolus vs meperidine PCA 9, 12 or 18 mg bolus	DB, RCT Adult patients scheduled for major abdominal surgery	N=102 Variable duration	Primary: Pain at rest and on sitting Secondary: Incidence of nausea, unusual dreams, performance on standardized tests measuring mood and ability to concentrate	Primary: There was no significant difference in pain while at rest among the treatment groups (P=0.8). There was significantly higher pain relief in morphine group compared to the meperidine group in sitting position (P=0.037). Secondary: There were no differences in the incidence of nausea, unusual dreams, or mood measurements between groups. There was a lower ability to concentrate in the meperidine group.
Sudheer et al.[59] (2007) Morphine PCA (up to 50 mg/4 hours) vs tramadol PCA (up to 200 mg/4 hours) vs codeine 60 mg IM,	RCT Postoperative pain control following elective craniotomy	N=60 Variable duration	Primary: P_aCO_2 four hours after eye opening, analgesia Secondary: Patient satisfaction, adverse effects	Primary: There were no differences between the groups in the change in P_aCO_2 and no change during the study period within each group. Neither the respiratory rate (range of eight to 28 breaths/minute) nor sedation showed differences between groups. Morphine produced significantly better analgesia than tramadol at all-time points (P<0.005) and better analgesia than codeine at four, 12 and 18 hours. Secondary: Patients were more satisfied with morphine than with codeine or tramadol (P<0.001). Vomiting and retching occurred in 50% of patients with tramadol,

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then 60 mg after 1 hour if needed, then 60 mg every 4 hours as needed				compared to 20% with morphine and 29% with codeine.
Poonai et al.[60] (2014) Morphine (0.5 mg/kg orally) every six hours as needed vs ibuprofen (10 mg/kg) every six hours as needed Participants were counselled to take acetaminophen at a dose of 15 mg/kg (max 975 mg) for breakthrough pain	DD, PG, RCT Children 5 to 17 years of age who presented to the pediatric emergency department with a nonoperative, radiographically evident extremity fracture	N=134 24 hours	Primary: Change in pain using the Faces Pain Scale Secondary: Adverse events, APAP use	Primary: Both morphine and ibuprofen resulted in a decrease in pain scores at each dose administration. The between-group difference in pre–post changes in pain scores was not significant. Secondary: There were no significant differences in the percentage of participants requiring APAP for breakthrough pain in the morphine or ibuprofen groups (17 [25.7%] vs 10 [14.7%], P=0.1). Participants in the morphine group had significantly more adverse effects than those in the ibuprofen group (56.1 vs 30.9%, P<0.01).
Kelly et al.[61] (2015) Morphine (0.2 to 0.5 mg/kg per dose every four hours as needed) vs ibuprofen (10 mg/kg per dose every six hours as	PRO, RCT Children 1 to 10 years of age who had sleep disordered breathing who were scheduled for tonsillectomy +/− adenoid removal	N=91 5 days	Primary: Changes in respiratory parameters after surgery Secondary: Pain, adverse drug reactions, tonsillar bleeding	Primary: On the first postoperative night, with respect to oxygen desaturations, 86% of children did not show improvement in the morphine group, whereas 68% of ibuprofen patients did show improvement. The number of desaturation events per hour (preoperative to postoperative) was reduced by a mean of 1.79 ± 7.57 in the ibuprofen group compared with an average increase of 11.17 ± 15.02 in the morphine group with an effect size of 0.96 (P<0.01). Secondary: The mean change in faces pain score from days one to five were 0.80 in the morphine group and 0.21 in the ibuprofen group (P=0.29). The mean change in objective pain scale score was similar between the groups

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needed) All patients were given acetaminophen (10 to 15 mg/kg per dose every four hours as needed)				(P=0.95). Tonsillar bleeding was reported in three children who received ibuprofen and two children who received morphine. Adverse drug events were reported at similar rates by parents in the two groups.
Karaman et al.[62] (2006) Morphine 0.2 mg vs sufentanil 5 µg	DB, RCT Female patients undergoing cesarean section who were receiving bupivacaine in spinal anesthesia	N=54 Single dose	Primary: Quality of anesthesia and postoperative analgesia Secondary: Adverse effects on mother and neonate	Primary: There were no differences between the morphine and sufentanil groups in onset time of sensory block, time to sensory block to T10, time to highest sensory block, highest sensory block level, time to regression of sensory block to T10 level and time to resolution of motor blockade. The time to first request for an analgesic was significantly longer (19.5 vs 6.3 hours) in morphine group (P<0.05). Secondary: Perioperative hemodynamic parameters, sedation scores, nausea/vomiting and pruritus incidences were similar in both groups. Neonatal Apgar scores, neurological and adaptive capacity scores and umbilical blood gas values were similar in both groups.
Friedman et al.[63] (2015) Oxycodone-APAP 5-325 mg vs cyclobenzaprine 5 mg vs placebo	DB, RCT Patients 21 to 64 years of age who presented with nontraumatic, nonradicular, acute low back pain of two weeks' duration or less were eligible for enrollment upon ED discharge if they had a score >5 on the RDQ	N=323 10 days of treatment; 3 months of follow-up	Primary: Improvement in RDQ seven days after ED discharge Secondary: Low back pain (severe, moderate, mild, or none), frequency of medication use, satisfaction with treatment	Primary: At 1-week follow-up, patients randomized to receive naproxen plus placebo improved by a mean of 9.8 (98.3% CI, 7.9 to 11.7) on the RDQ, those randomized to naproxen plus cyclobenzaprine improved by 10.1 (98.3% CI, 7.9 to 12.3), and those randomized to naproxen plus oxycodone-APAP improved by 11.1 (98.3% CI, 9.0 to 13.2). Between group differences in mean RDQ improvement were as follows: cyclobenzaprine vs placebo was 0.3 (98.3% CI, -2.6 to 3.2; P=0.77), oxycodone-APAP vs placebo was 1.3 (98.3% CI, -1.5 to 4.1; P=0.28), and oxycodone-APAP vs cyclobenzaprine was 0.9 (98.3% CI, -2.1 to 3.9; P=0.45). Secondary: At 1-week follow-up, regardless of study group, more than 50% of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
One or two of the randomized medication was taken every eight hours, as needed for low back pain All participants were given 20 tablets of naproxen, 500 mg, to be taken twice a day				patients still required medication for low back pain. Many patients reported moderate or severe, and frequent pain. Despite these outcomes, more than two-thirds of patients reported that they would want to receive the same medications during a subsequent ED visit for acute low back pain.
Kleinert et al.[64] (2008) Tapentadol 25 to 200 mg as a single dose vs morphine 60 mg as a single dose vs ibuprofen 400 mg as a single dose vs placebo	DB, RCT Patients undergoing mandibular third molar extraction and experiencing moderate to severe pain postsurgery	N=400 8 hours	Primary: Mean TOTPAR over eight hours Secondary: Mean TOTPAR over eight hours and onset of analgesia	Primary: Compared to placebo, mean TOTPAR over eight hours was significantly greater for tapentadol 50 mg (P=0.041), 75 mg (P=0.001), 100 mg (P<0.001), and 200 mg (P<0.001); morphine 60 mg (P<0.001); and ibuprofen 400 mg (P<0.001). Secondary: Compared to placebo, mean TOTPAR over four hours was significantly higher for all tapentadol doses ≥50 mg, morphine 60 mg, and ibuprofen 400 mg (P≤0.05). All efficacy variables for tapentadol 100 and 200 mg showed greater analgesia compared to placebo (P≤0.05). The percentages of patients rating study medication treatment as good, very good, or excellent were as follows: tapentadol 25 mg (22%); tapentadol 50 mg (28%); tapentadol 75 mg (35%); tapentadol 100 mg (50%); tapentadol 200 mg (68%); morphine 60 mg (55%); and placebo (12%). Tapentadol 25 mg was not significantly different from placebo in patient global evaluation responses. The efficacy measures demonstrate an onset of analgesia for morphine 60 mg between that of tapentadol 100 and 200 mg doses. These data suggest

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				that morphine 60 mg provides an analgesic dose comparable to a dose of tapentadol between 100 and 200 mg.
Gimbel et al.[65] (2004) Oxymorphone IR 10, 20, or 30 mg vs oxycodone IR 10 mg vs placebo	DB, DR, MC, PC, PG, RCT Men and nonpregnant, nonlacting women 18 to 75 years of age receiving total hip or knee replacement surgery and scoring I to III on the ASA physical status classification system	N=300 First phase: 8 hours Second phase: 48 hours	Primary: TOTPAR, SPID and SPRID at four, six, and eight hours, safety Secondary: Not reported	Primary: Mean TOTPAR scores at four, six, and eight hours for all doses of oxymorphone IR were statistically more efficacious compared to placebo (10 mg; P ≤0.034; 20 and 30 mg; P <0.001). Oxymorphone showed a statistically significant dose-response relationship in a regression model (TOTPAR8) by using the arithmetic dose as the regressor (slope estimate, 0.184; P<0.001; 95% CI, 0.089 to 0.279) and reached an analgesic plateau at the 20-mg dose. Oxymorphone IR at 10, 20, and 30 mg was statistically more efficacious compared to placebo for SPID (P≤0.001 for all doses) and SPRID at four, six, and eight hours (P≤0.007 for 10 mg and P<0.001 for 20 and 30 mg). Although oxycodone IR was generally numerically greater compared to placebo, the differences were not significant for any efficacy measures. The median time to meaningful pain relief was statistically significantly shorter in all of the oxymorphone IR groups (1 hour) than in the placebo group (1.5 hour; P<0.05). Fifty percent pain relief was achieved by 90.2% of patients in the oxymorphone IR 20 mg group (P<0.001), 82.4% of patients in the oxymorphone IR 10 mg group (P=0.022), 77.2% in the oxymorphone IR 30 mg group (P value not significant), and 69.2% in the oxycodone IR 10 mg group (P value not significant). The most frequent occurring adverse events in the oxymorphone IR groups were mild-to-moderate opioid side effects (i.e., nausea, vomiting, somnolence, and pruritus). During the single-dose phase, the incidence of adverse events was more frequent among the oxymorphone IR groups than in the oxycodone IR 10 mg group (39 to 50 vs 27%). In contrast, the incidence was somewhat more frequent in the oxycodone IR 10 mg group (82%) during the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				multiple-dose phase compared to the oxymorphone IR groups (61% to 71%). Secondary: Not reported
Özalevli et al.[66] (2005) Tramadol PCA 0.2 mg/kg bolus vs morphine PCA 0.02 mg/kg bolus	DB, RCT Children 6 to 12 years of age scheduled for tonsillectomy with general anesthesia	N=60 24 hours postoperative	Primary: Pain (as scored on a standardized 10-point scale), sedation (as assessed by a 5-point scale), nausea (as assessed on a 5-point scale) Secondary: Not reported	Primary: Pain scores decreased significantly with time in both groups (P<0.05), but were lower in morphine group vs tramadol group at one, two and four hours (P<0.05). Sedation scores increased with time in both groups (P<0.05), but there were no significant differences in sedation scores between the groups at any time point. Nausea scores were higher in morphine group at four, six and 24 hours (P<0.05). Secondary: Not reported
Silberstein et al.[67] (2005) Tramadol-APAP 75-650 mg vs placebo	DB, PC, PG, RCT Patients with history of migraine of moderate or severe intensity for ≥12 months, with a frequency of 1 to 6 migraine headaches per month in the previous year	N=305 Single dose	Primary: Severity of pain and migraine-related symptoms (photophobia, phonophobia, nausea) as recorded at baseline and at 0.5, one, two, three, four, six, and 24 hours post-dose Secondary: Incidence of adverse events	Primary: Treatment response was higher for tramadol-APAP vs placebo at two hours post-dose (55.8 vs 33.8%; P<0.001) and at every other assessment from 30 minutes (12.3 vs 6.6%) through six hours (64.9 vs 37.7%; all P≤0.022). Subjects in tramadol-APAP group vs placebo group were more likely to be pain-free at two hours (22.1 vs 9.3%), six hours (42.9 vs 25.2%), and 24 hours (52.7 vs 37.9%; all P≤0.007). Two hours post-dose, moderate-to-severe symptoms that were less common for tramadol-APAP vs placebo included photophobia (34.6 vs 52.2%; P=0.003) and phonophobia (34.3 vs 44.9%; P=0.008), but not migraine-related nausea (38.5 vs 29.4%; P=0.681). Secondary: Treatment-related adverse events included nausea (13.4%), dizziness (10.2%), vomiting (7.6%) and somnolence (6.4%). In the placebo group,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				no treatment-related adverse event was reported by more than 2% of subjects.
Palangio et al.[68] (2000) Hydrocodone-ibuprofen 7.5-200 mg 2 tablets vs oxycodone-APAP 5-325 mg 2 tablets vs placebo	DB, PC, PG, RCT Subjects >18 years of age with moderate to severe postoperative obstetric or gynecologic pain	N=180 8 hours	Primary: Pan relief, TOTPAR, SPID scores, time to onset, adverse events Secondary: Not reported	Primary: Mean pan relief scores were similar for hydrocodone-ibuprofen and oxycodone-APAP at 0.5, one, 1.5, two, 2.5, three, four, and seven hours and significantly greater for hydrocodone-ibuprofen than for oxycodone-APAP at five (P=0.003), six (P=0.043), and eight (P=0.044) hours. The mean TOTPAR was similar for hydrocodone-ibuprofen and oxycodone-APAP for the 0- to three- and 0- to four-hour intervals and significantly greater for hydrocodone-ibuprofen than for oxycodone-APAP at the 0- to six-hour (P=0.043) and 0- to eight-hour (P=0.029) intervals. The mean SPID was similar for hydrocodone-ibuprofen and oxycodone-APAP for each interval. The mean SPID was significantly greater for hydrocodone-ibuprofen or oxycodone-APAP than for placebo for each interval (P <0.001). The median estimated time to onset of analgesia was similar for hydrocodone- ibuprofen (12.6 minutes) and oxycodone-APAP (15.4 minutes) and significantly shorter for either of these treatments than for placebo (29.5 minutes; P <0.001 and P=0.006, respectively). Eleven of 61 patients (18.0%) in the hydrocodone-ibuprofen group experienced adverse events, compared to seven of 59 patients (11.9%) in the oxycodone-APAP group and six of 60 (10.0%) in the placebo groups. These findings were not statistically significant. Secondary: Not reported
Palangio et al.[69] (2000) Hydrocodone-ibuprofen 7.5-200 mg (1 tablet) plus	DB, MC, PG, RCT Males and females >18 years of age with a chronic pain condition that	N=469 4 weeks	Primary: Pain relief scores, number of daily doses of study medication, number of daily	Primary: The overall mean pain relief scores for the entire study period were significantly greater in the HI2 group than either the HI1 group (P=0.003) or the CA group (P<0.001). The weekly pain relief scores were significantly greater in the HI2 group

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
1 tablet of placebo every 6 to 8 hours (HI1) vs hydrocodone-ibuprofen 15-400 mg (2 tablets) every 6 to 8 hours (HI2) vs codeine-APAP 60-600 mg (2 tablets) every 6 to 8 hours (CA)	required opioid or opioid-nonopioid combination analgesic therapy		doses of supplemental analgesics, number of patients who discontinued therapy due to an unsatisfactory analgesic response, and global assessment scores Secondary: Not reported	than the HI1 group for weeks one (P<0.001), two (P<0.001), and three (P=0.008). The overall mean number of daily doses of supplemental analgesics was significantly less in the HI2 drop than either the HI1 group (P=0.21) or the CA group (P=0.01). There were no significant differences in the overall weekly mean number of daily doses of supplemental analgesics between the HI1 group and the CA group. The number of patients who discontinued treatment due to an unsatisfactory analgesic response was significantly less in the HI2 group (2/153; 1.3%) than in the CA group (12/160; 7.5%; P=0.08). There were no significant differences in the number of patients who discontinued treatment due to an unsatisfactory analgesic response between the HI1 group (8/156; 5.1%) and either the HI2 group or the CA group. The weekly mean global assessment scores were significantly greater in the HI2 group than the HI1 group for weeks one (P=0.018), two (P=0.005), and four (P=0.013). The weekly mean global assessment scores were significantly greater in the HI2 group than the CA group for weeks one (P<0.001), two (P<0.001), three (P=0.009), and four (P=0.023), and end point (P=0.016). There were no significant differences in the weekly mean global assessment scores between the HI1 group and the CA group. Secondary: Not reported
Marco et al.[70] (2005) Oxycodone-APAP as a combination liquid formulation	DB, PRO, RCT ED patients over the age of 12 with fractures and severe pain, with pain scores >5 on a 0 to	N=73 60 minutes	Primary: Pain score (verbal numeric rating scale) at 30 and 60 minutes Secondary:	Primary: Patients in both groups had pain relief from baseline to 30 minutes (oxycodone-APAP mean change 3.7; 95% CI, 2.9 to 4.6; hydrocodone-APAP mean change 2.5; 95% CI, 1.7 to 3.3) and from baseline to 60 minutes (oxycodone-APAP mean change 4.4; 95% CI, 3.2 to 5.6; hydrocodone-APAP mean change 3.0; 95% CI, 2.1 to 3.9).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs hydrocodone-APAP as a combination liquid formulation	10 scale		Presence and severity of side effects	There was no difference in pain identified between the patients treated with oxycodone-APAP and hydrocodone-APAP at 30 minutes (mean difference between groups -0.6; 95% CI, -1.8 to 0.5) or at 60 minutes (mean difference -0.5; 95% CI, -2.0 to 1.0). Secondary: There was no difference between the groups in nausea, vomiting, itching, or drowsiness; however, the hydrocodone-APAP patients had a higher incidence of subsequent constipation (oxycodone-APAP 0%, hydrocodone-APAP 21%, difference in proportions 21%; 95% CI, 3 to 39%).
Litkowski et al.[71] (2005) Oxycodone-ibuprofen 5-400 mg vs oxycodone-APAP 5-325 mg vs hydrocodone-APAP 7.5-500 mg vs placebo	AC, MC, PC, PG, RCT Men or women >12 years of age who were scheduled to undergo complete removal of >2 ipsilateral, partially or completely impacted third molars	N=249 6 hours	Primary: TOTPAR through six hours after dosing (TOTPAR6), sum of pain intensity differences through six hours (SPID6), and adverse events Secondary: SPID3,TOTPAR3, peak pain relief, peak PID, time to onset of pain relief, time to use of rescue medication, proportion of patients reporting pain half gone, and the patient's global evaluation	Primary: The combination of oxycodone-ibuprofen provided higher pain relief values than any of the other combinations tested or placebo. TOTPAR6 scores were significantly better for each combination treatment compared to placebo (P<0.001). The combination of oxycodone-ibuprofen was associated with a significantly higher TOTPAR6 score compared to oxycodone-APAP, hydrocodone-APAP, and placebo (mean [SD], 14.98 [5.37], 9.53 [6.77], 8.36 [6.68], and 5.05 [6.90], respectively; all, P<0.001). The results for SPID6 were similar, with oxycodone-ibuprofen associated with significantly higher values compared to oxycodone-APAP, hydrocodone-APAP, and placebo (7.78 [4.11], 3.58 [4.64], 3.32 [4.73], and 0.69 [4.85]; all P<0.001). Both oxycodone-APAP and hydrocodone-APAP were associated with significantly higher SPID6 scores compared to placebo (P<0.001 and P=0.002, respectively). The combination of oxycodone-ibuprofen was well tolerated, as evidenced by an overall rate of patients experiencing >1 adverse event that was similar to that for placebo (11.3% [7/62] and 11.1% [7/63], respectively). Rates in the groups receiving oxycodone-APAP and hydrocodone-APAP (27.9% [17/61] and 25.4% [16/63], respectively) were >2-fold higher. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				For TOTPAR3, SPID3, peak pain relief, pain half gone, and the patient's global assessment, oxycodone/ibuprofen was associated with significantly better scores compared to oxycodone-APAP, hydrocodone-APAP, and placebo (all, P<0.001). Peak SPID scores were also significantly higher for oxycodone-ibuprofen compared to oxycodone-APAP (P=0.006). Compared to placebo, oxycodone-APAP and hydrocodone-APAP also were significantly better in terms of TOTPAR3, SPID3, the patient's global assessment (all, P<0.001), and peak pain relief (P<0.001 and P=0.002, respectively). The median time to the onset of pain relief was significantly shorter for oxycodone-ibuprofen compared to hydrocodone-APAP (P=0.002) and placebo (P<0.001). Both oxycodone-APAP and hydrocodone-APAP were associated with significantly shorter median times to the onset of pain relief compared to placebo (P<0.001 and P=0.002, respectively).
Smith et al.[72] (2004) Tramadol-APAP 75-650 mg vs codeine-APAP 30-300 mg vs placebo All study meds were administered	DB, MC, PC, RCT Patients with moderate to severe abdominal or orthopedic postsurgical pain	N=305 6 days	Primary: TOTPAR, SPID, and sum of pain relief and pain intensity differences during the four hours after the first dose of study medication on day one Secondary: Average daily pain intensity scores and average daily pain relief scores reported on days	Primary: Tramadol-APAP was more effective than placebo for TOTPAR, SPID and sum of pain relief and pain intensity differences (P≤0.015); tramadol-APAP and codeine-APAP did not separate (P≥0.281). Secondary: For average daily pain relief, average daily pain intensity, and overall medication assessment, tramadol-APAP was more effective than placebo (P≤0.038). Codeine-APAP did not separate from placebo (P≥0.125). Discontinuation because of adverse events occurred in 8.2% of tramadol-APAP, 10.1% of codeine-APAP and 3.0% of placebo patients. Except for constipation (4.1% tramadol-APAP vs 10.1% codeine-APAP) and vomiting (9.2 vs 14.7%, respectively), adverse events were similar for active treatments.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
as 2 tablets stat, then 1 to 2 tablets every 4 to 6 hours as needed.			one to six; overall rating of study medication by both patients and investigators using a five-point scale; incidence of adverse events	
Hewitt et al.[73] (2007) Tramadol-APAP 75-650 mg vs hydrocodone-APAP 7.5-650 mg vs placebo	RCT Patients 18 to 75 years of age with ankle sprain within previous 48 hours; clinical diagnosis of partial ligament tear, pain on ambulation and ankle swelling.	N=396 5 days	Primary: Pain relief as measured by patient response to two standardized pain relief/pain intensity scales Secondary: Adverse events	Primary: Tramadol-APAP and hydrocodone-APAP provided greater TOTPAR than placebo (P<0.001) during the first four hours, decreased pain intensity during the first four hours and increased average pain relief on days one to five. No efficacy measure was significantly different between the tramadol-APAP and hydrocodone-APAP groups. Secondary: Common adverse events included somnolence, nausea, dizziness, and vomiting.
Zenz et al.[74] (1992) Buprenorphine, dihydrocodeine sustained release, and morphine sustained release	OL Patients receiving chronic opioids for treatment of non-malignant pain	N=100 Variable duration	Primary: Pain reduction with visual analogue scales; patient function using the Karnofsky Performance Status Scale Secondary: Not reported	Primary: Good pain relief was obtained in 51 patients and partial pain relief was reported by 28 patients. Only 21 patients had no beneficial effect from opioid therapy. There was a close correlation between the sum and the peak visual analogue scale values (P<0.0001). Pain reduction was associated with an increase in performance (P<0.0001). Secondary: Not reported
Moyao-Garcia et	DB, PRO, RCT	N=24	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
al.[75] (2009) Nalbuphine 100 µg/kg bolus IV + 0.2 µg/kg/hour continuous infusion vs tramadol 1 mg/kg + 2.0 µg/kg/hour continuous infusion for 72 hours	Children 1 to 12 years of age undergoing scheduled surgery	72 hours	Number of patients requiring dose increments Secondary: Sedation, heart rate, blood pressure, and vomiting	Three patients who received nalbuphine required an extra bolus dose in the 12 hour post-surgery period, vs one child in the tramadol group. There were a similar number of patients in both treatment groups who required an increase in the infusion rate within the 72 hour post-surgery period. Secondary: Sedation was observed in two patients in the nalbuphine group and in one patient in the tramadol group. Vomiting occurred in four children receiving tramadol, and two receiving nalbuphine. No adverse cardiovascular events were detected in either group.
Yeh et al.[76] (2009) Nalbuphine 10 µg/mL IV and morphine 1 mg/mL infusion via PCA vs morphine 1 mg/mL IV infusion via PCA	DB, PRO, RCT Female patients undergoing gynecological surgery	N=174 24 hours	Primary: Pain and medication dose Secondary: Nausea, vomiting, use of antiemetics, pruritus, use of antipruritics, opioid related adverse effects	Primary: Numerical pain rating scores and medication requirements were not significantly different between the treatment groups. Secondary: Nausea was lower in the nalbuphine group than the morphine-only group (45 vs 61%; P=0.03). Other secondary outcomes did not differ between the treatment groups.
Levine et al.[77] (1988) Pentazocine 60 mg IV vs	DB, RCT Patients undergoing surgery for the removal of impacted third molars	N=105 Single dose	Primary: Pain intensity using a visual-analogue scale Secondary: Not reported	Primary: The mean pain intensity was increased in the group receiving placebo. Mean pain intensity was decreased in the groups that received either morphine (8 and 15 mg; P<0.05 and P<0.01, respectively) or pentazocine (60 mg; P<0.05) as a single agent. The combination of low-dose naloxone and pentazocine produced

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
naloxone 0.4 mg IV vs morphine 8 or 15 mg IV vs naloxone 0.4 mg + morphine 8 mg IV vs naloxone 0.4 mg + pentazocine 60 mg IV vs placebo				significantly greater analgesia than either low-dose naloxone (P<0.01), pentazocine (P<0.01), or even high-dose morphine administered alone (P<0.01). The combination of low-dose naloxone and 8 mg morphine produced less analgesia when compared to the same dose of morphine alone (P<0.05) or with high-dose morphine (P<0.01) but not when compared to low-dose naloxone administered alone. The mean pain intensity measured at three hours and 10 minutes after injection of single analgesic agents was not significantly decreased compared to placebo. The analgesia produced by the combination of low-dose naloxone and 8 mg morphine did not differ significantly from the analgesia produced by the same dose of morphine. The combination of low-dose naloxone and pentazocine produced significant analgesia when compared to either agent alone (both P<0.01). By three hours and 10 minutes after injection, only the group of patients receiving low-dose naloxone plus pentazocine still reported significant analgesia. Secondary: Not reported
Petti[78] (1985) Pentazocine 25 mg and APAP 650 mg vs codeine 30 mg and APAP 300 mg vs propoxyphene	PC, PG, SB Patients with moderate postoperative pain	N=129 6 hours	Primary: Intensity of pain and degree of pain relief Secondary: Not reported	Primary: Pentazocine and APAP was significantly better than placebo and equivalent to codeine and APAP and propoxyphene and APAP in patients with moderate postoperative pain. No adverse events were reported with APAP and pentazocine, APAP and propoxyphene napsylate, or placebo. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
napsylate 100 mg and APAP 650 mg vs placebo				
Chronic Pain				
Le Loët et al.[79] (2005) Fentanyl 25 µg/hour transdermal every 72 hours	MC, OL Patients ≥50 years of age with OA of knee or hip who were waiting for a knee or hip replacement; all patients required supplementary analgesia because of moderate/severe pain not adequately controlled with APAP, NSAIDs, COX-2 inhibitors or weak opioids.	N=159 28 days	Primary: Pain control Secondary: Pain assessment; pain intensity; treatment assessment; quality of life; functionality using the WOMAC; adverse events	Primary: At baseline, 25% of patients reported very poor pain control, 48% poor pain control and 25% moderate pain control. After the first week of treatment, 74% of patients reported adequate pain control, 37% reported moderate pain control, 29% reported good pain control and 8% reported excellent pain control. Adequate pain control was reported by 80 and 88% patients on days 14 and 28, respectively. At endpoint, 83% of patients considered their pain controlled, with 37% reporting moderate pain control, 38% reporting good pain control, and 8% reporting excellent pain control. Secondary: The mean reduction in 'pain right now' was 2.6 points (from 6.1 to 3.5) from baseline to endpoint. A significant reduction in 'pain right now' was reported as early as 24 hours after baseline (1.3 points, from 6.0 to 4.7). The mean score for degree of pain was significantly decreased at each time point (P<0.001). While at baseline, 58% reported severe/extreme pain, 4% reported mild pain and only two patients were without pain. By study endpoint, 41% reported moderate pain, 30% reported mild pain and 7% reported no pain. In their assessment of treatment, 63% of patients rated fentanyl positively with respect to pain control and 84% would recommend fentanyl for their type of pain. A total of 93% of patients thought it easy/extremely easy to use; 85% were very/somewhat pleased by the way it's used, and 53%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				considered side effects were not an issue. In assessing how they had felt over the past week, the percentage of all patients who answered good or very good increased during the study from 7 to 32% at week 4, and their scores at all time points were significantly better than before treatment (P<0.001). By the end of the study, help with basic activities was required by only 28% of patients, with 49% relying less on their helper. For the 122 patients who completed the quality of life questionnaire, there were statistically significant improvements in all domains from baseline to endpoint, including overall physical health (P<0.001) and mental health (P<0.05). The mean score for all 24 questions from the three WOMAC summary parameters (pain, stiffness and physical functioning) improved significantly from baseline to endpoint for all groups (P<0.001). The percentage of patients who reported no pain, stiffness or physical difficulties increased for all items. Mean overall WOMAC score improved significantly (P<0.001) from baseline to endpoint. Adverse events were reported by 65% of patients during the treatment period. The study medication was permanently stopped in 25% (39) of cases, particularly because of nausea (53%), vomiting (47%) and dizziness (18%). No falls or fractures were reported; no deaths occurred.
Weinstein et al.[80] (2009) Fentanyl transbuccal tablet	OL Opioid tolerant adults with cancer pain and a life expectancy of ≥2 months	N=232 ≥12 months	Primary: Adverse event monitoring, physical examination, and clinical laboratory tests Secondary: Patient-assessed comparison of fentanyl vs	Primary: Ninety percent of patients reported at least one adverse event during the fentanyl titration and maintenance phases. The most common adverse events during the titration phase were dizziness, nausea, somnolence, and headache. The most common adverse events during the maintenance phase were nausea, vomiting, fatigue, constipation, peripheral edema, and anemia although study investigators did not consider peripheral edema and anemia to be related to the study drug. Abnormal hematology findings were consistent with the patient's medical history and no meaningful trends were observed in laboratory values.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			previous supplemental medication, Global Medication Performance questionnaire, dose changes over time	A successful fentanyl buccal tablet dose was identified by 71% of patients during the titration phase. Only three (1%) patients discontinued the study because of lack of fentanyl efficacy during the maintenance phase. Fentanyl buccal tablets were generally well tolerated by patients with chronic cancer pain. Secondary: Patients favored fentanyl compared to previous breakthrough medication (88 vs 12%). Patients rated fentanyl between “good” and “very good” on average for the Global Medication Performance questionnaire. The final fentanyl dose was the same as the initial successful dose for 69% of patients.
Mercadante et al.[81] (2010) Fentanyl transdermal patch 12 µg/hour and titrated every 2 to 3 days as necessary Oral morphine at a dose of 5 mg was allowed for BTP.	OL Opioid-naïve patients with advanced cancer and moderate pain	N=46 4 weeks	Primary: Pain intensity, time to dose stabilization, and quality of life Secondary: Not reported	Primary: Pain control was achieved within a mean of 1.7 days after the start of transdermal fentanyl therapy. Pain intensity significantly decreased from baseline through the remaining weekly evaluations (P<0.001). Significant differences in fentanyl doses were observed after week two and were almost doubled at week four. The mean calculated fentanyl escalation index were 4.04% and 0.012 mg. No differences in fentanyl escalation index were found when considering the pain mechanism and primary cancer. There were no significant changes in opioid, related symptoms and quality of life between weekly evaluations. The pain mechanism did not significantly affect the changes in pain intensity and doses of fentanyl. Transdermal fentanyl was well tolerated, with only five of 36 patients (13.8%) who discontinued fentanyl for alternative treatments or poor compliance. Secondary: Not reported
Agarwal et al.[82]	OL, PRO	N=53	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2007) Fentanyl transdermal system 25 to 150 µg/hour replaced every 72 hours	Patients >18 years of age with neuropathic pain persisting for >3 months	16 weeks	Change in pain intensity and daily activity Secondary: Pain relief, cognition, physical function and mood	The average pain reduction across the population using pain diary data was -2.94±0.27. Thirty patients (57%) reported >30% improvement in pain and 21 patients (40%) reported >50% change in pain intensity. Decreases in pain scores for the subgroups were; peripheral neuropathy, -3.40±0.44; CRPS-1, 2.40±0.40 and postamputation pain, -2.70±0.47. There was a trend toward a greater reduction in pain intensity in the peripheral neuropathy group compared to the CRPS-1 (P=0.06) and postamputation (P=0.07) groups among the ITT population. Among completers, fentanyl was more effective in reducing pain in the peripheral neuropathy subjects compared to the other two groups of patients (P<0.04). The average increase in daily activity from baseline was significant with fentanyl treatment (P<0.001). Overall, 32.5% of patients experienced both a >30.0% decrease in pain intensity and a >30.0% increase in activity. The effect of fentanyl on activity was that 62% of subjects experienced a >15% increase in activity levels compared to baseline, 20% showed minimal or no change (±15%) in activity, and 18% showed a >15% reduction in activity. The average increase in activity in the three subgroups was 42.6, 37.5 and 33.3%, respectively, in patients with peripheral neuropathy, CRPS, and postamputation pain. Secondary: The change in the grooved pegboard test for the entire population was -1.46±5.80 seconds and -5.9±12.2 seconds for the dominant and non-dominant hands (P value not significant). The change in MPI-Interference for the whole group was 0.20±0.94 (P value not significant), and the change in MPI-Activity was -0.03±0.80 (not significant). The difference in the BDI was 0.03±0.32 (P value not significant).
Finkel et al.[83] (2005) Fentanyl	MC, OL, SA Patients 2 to 16 years of age with	N=199 15 days (with 3 month	Primary: Global assessment of pain treatment; changes in pain	Primary: The most common starting dose of fentanyl was 25 µg/hour, which was required by 90 patients (45.2%). The lowest starting dose, 12.5 µg/hour, was considered appropriate for 59 patients (29.6%). The average duration

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transdermal system 12.5 to 100 µg/hour applied every 3 days	moderate to severe chronic pain due to malignant or nonmalignant disease	extension)	level, PPS, and CHQ and safety Secondary: Not reported	of treatment with fentanyl in the primary treatment period was 14.80±0.25 days in the ITT patient group. A total of 84.9% of patients received at least one rescue medication, with a mean oral morphine equivalent of 1.35±0.16 mg/kg during the primary treatment period. The average daily pain intensity levels reported by parents/guardians using the numeric pain scale for the ITT population decreased steadily throughout the study period from 3.50±0.23 at baseline to 2.60±0.21 by day 16. Parent/guardian-rated improvements in mean PPS scores were observed from baseline (41.22±1.68) to the data collection endpoint (53.80±1.91), resulting in a mean change of 11.5%. At the end of month one of the extension phase (n=36), parents reported improvement in 11/12 domains assessed by the CHQ with the largest improvement noted in bodily pain (29.52±4.52; baseline, 18.14). Other domains demonstrating an improvement of greater than five points from baseline include mental health (8.28±2.76; baseline, 54.33), family activities (6.96±3.19; baseline, 43.04), role emotional behavior (12.36±6.08; baseline, 34.72), physical function (7.15±2.71; baseline, 23.65) and role physical (13.82±5.76; baseline, 17.07). At the end of month three, participating patients continued to demonstrate sustained improvements in 11/12 domains. One hundred eighty patients (90.5%) reported at least one adverse event during treatment. The most frequent adverse events were fever (n=71 patients), emesis (n=66 patients), nausea (n=42 patients), headache (n=37 patients) and abdominal pain (n=34 patients). Secondary: Not reported
Park et al.[84] (2011) Fentanyl transdermal patch	OL, PRO Patients ≥19 years of age, with overall good health, and	N=65 12 weeks	Primary: Percentage of change in pain intensity from before the	Primary: Changes in average pain intensity, evaluated by investigators, decreased from a level of 6.70 to 2.58 (61.5%) at trial end. The average individual pain intensity, evaluated by the patients, decreased from 7.02 to 2.86 (59.3%; P<0.001). The pain intensities evaluated by the patients, at rest

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
12.5 µg/hour, dose could be increased by 12.5 or 25 µg/hour	complaining of chronic pain of the spine and limbs that scored >4 points on a numerical rating scale 72 hours prior to baseline data		administration of the study drug to 12 weeks Secondary: Degree of satisfaction, patient's function/sleep interference, dose, safety	and when moving, were decreased from 5.40 to 1.95 (63.9%; P<0.0001). Secondary: Within three visits, the sum of patients who answered "very satisfied" or "satisfied" was 76.8, 83.7, and 93.0%, respectively. Differences in the sums of the rates of 'very satisfied' and "satisfied" measured in week four and the rates on the last visit constituted a significant increase (P<0.05). The determinants of the patient's satisfaction with pain treatment were (in order of frequency): efficacy of pain treatment is good, satisfied overall, and convenient. Investigators' satisfaction with the pain treatment was also evaluated and the sum of the rates of "very satisfied" and "satisfied" on each visit was 83.7, 83.7, and 86.0%. Following treatment, each function of daily life, walking, and eating due to pain showed a decrease as follows: from 7.30 to 3.07, from 6.58 to 2.86, and from 3.33 to 0.35, respectively (P<0.001). Rate of patients whose sleep was not disturbed increased from 32.6% in the first evaluation to 86.1% in the fifth evaluation (P<0.0001). The average dose administered was 13.95 µg/hour upon initial administration and 42.59 µg/hour at the termination of the trial (P<0.001). In 55 patients, more than one adverse event was observed during the trial. Nausea was observed in 32 patients, dizziness in 28 patients, drowsiness in 20 patients, constipation in 11 patients, and vomiting in 10 patients. In general all events were mild. There were 18 patients who discontinued the trial due to adverse events.
Langford et al.[85] (2006) Fentanyl transdermal system 25 to 100 µg/hour every 72 hours vs	MC, PC, RCT Patients ≥40 years of age meeting the ACR diagnostic criteria for hip or knee OA and requiring joint replacement surgery, with	N=399 6 weeks	Primary: Pain relief Secondary: Function and individual aspects of pain relief affecting mobility and quality of life	Primary: Fentanyl was associated with significantly better pain relief ($AUCMB_{avg}$ -20.0±1.4 vs -14.6±1.4; P=0.007). Secondary: WOMAC scores for pain, stiffness and physical function improved significantly from baseline to study end in both groups. The overall WOMAC score and the pain score were significantly better in the fentanyl group (P=0.009 and P=0.001), while stiffness and physical functioning scores showed non-significant trends in favor of fentanyl (P=0.051 and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo	moderate to severe pain that was not adequately controlled with weak opioids			P=0.064). Significantly more patients who received fentanyl than those who received placebo reported that the transdermal systems definitely met their overall expectations (28 vs 17%; P=0.003). When asked to compare the study medication with previous treatments, significantly more patients who received fentanyl considered it to provide much better or somewhat better relief than other pain medication (fentanyl, 60% vs placebo, 35%; P<0.001). Not all of the individual domains of the SF-36 quality of life assessment showed significant improvements from baseline, although the physical functioning, pain index, and physical component scores improved significantly in both groups (all P<0.05 vs baseline). Scores on the SF-36 pain index were significantly better for patients receiving fentanyl (P=0.047), whereas changes in the mental component scores showed a small, but statistically significant, benefit in those receiving placebo (1.1±0.7; P=0.041).
Morley et al.[86] (2003) Methadone 10 to 20 mg/day vs placebo In Phase 1 of the study patients were instructed to take methadone 5 mg BID or placebo on odd days and take no medication on even days (20 days total).	DB, RCT, XO Patients 18 to 80 years of age with a history of >3 months of nonmalignant neuropathic pain (defined as 'pain initiated or caused by a primary lesion or dysfunction of the nervous system') who had not been satisfactorily relieved by other interventions or by current or previous	N=19 40 days	Primary: Analgesic effectiveness and adverse events Secondary: Not reported	Primary: When compared to placebo in Phase 2, methadone 20 mg/day significantly reduced VAS maximum pain intensity by 16.00 (P=0.013) and VAS average pain intensity by 11.85 (P=0.020) and increased VAS pain relief by 2.16 (P=0.015). Analgesic effects, by lowering VAS maximum pain intensity and increasing VAS pain relief, were also seen in Phase 1 on days in which methadone 10 mg/day was administered but failed to reach statistical significance (P=0.065 and P=0.67, respectively). Significant analgesic effects on rest days were only seen in Phase 2. Compared to placebo, there was lowering of VAS maximum pain intensity by 12.02 (P=0.010), a lowering of VAS average pain intensity by 10.46 (P=0.026), and an increase in VAS pain relief by 0.94 (P=0.025). During Phase 1, one patient withdrew because of severe nausea, dizziness, and sweating. Six patients withdrew from Phase 2 due to severe nausea, dizziness, vomiting, and sweating; and disorientation with severe headaches. Four patients in Phase 1 and 2 reported no adverse events and all adverse events were reported as mild to moderate in patients who

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In Phase 2 of the study, patients were instructed to take methadone 10 mg BID or placebo on odd days and to take no medication on even days (20 days total).	drug regimens			completed the trial. Secondary: Not reported
Fleishmann et al.[87] (2001) Tramadol up to 400 mg/daily vs placebo	DB, MC, PC, PG, RCT Patients aged 35 to 75 with symptomatic (painful) OA of the knee for ≥1 year and had used NSAIDs for ≥3 months	N=129 3 months	Primary: Efficacy (as measured by pain intensity, relief, patient and investigator overall assessments, discontinuation, time to failure, and WOMAC OA index scores) Secondary: Tolerability and adverse events	Primary: The mean final pain intensity score was not statistically different between groups (P=0.082). However, pain intensity scores improved progressively from baseline through day 91 for patients in both groups, and the mean final pain intensity score was 15% lower in the tramadol group (2.10) than in the placebo group (2.48; P=0.045). The mean final pain relief score for tramadol patients was significantly higher than that of the placebo patients (0.43 vs -0.57; P=0.004). The patient overall assessment score was significantly higher for tramadol than for placebo (P=0.038). The investigator overall assessment was also significantly more positive for tramadol than for placebo (P=0.001). A total of 26 tramadol-treated patients (41.3%) and 43 placebo patients (65.2%) discontinued the study because of drug ineffectiveness. Time to failure of effectiveness, as assessed by duration of therapy, was substantially shorter for the placebo group (median=19 days) compared with the tramadol group (median=57 days; P=0.042). Patients who received tramadol had significantly better scores for pain (P=0.012), stiffness (P=0.028), and physical function (P=0.033) (each category of the WOMAC score) than patients who received placebo. The mean final overall score was 17.5% lower in the tramadol group than in the placebo group (4.16 vs 5.04; P=0.015).

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				Secondary: No clinically significant trends in vital signs were noted among tramadol patients. The most common side effects were nausea, constipation, dizziness, pruritus, and headache.
Ruoff et al.[88] (2003) Tramadol-APAP 37.5-325 mg up to 8 tablets daily vs placebo	DB, MC, PC, PG, RCT Men and non-pregnant women 25 to 75 years of age, in general good health, ambulatory, and with lower back pain such that daily medication was needed for ≥3 months	N=318 3 months	Primary: PVA score at final visit Secondary: Scores on the PRRS, SF-MPQ, RDQ, SF-36, discontinuation due to insufficient pain relief, and overall assessments of medication by patients and investigators	Primary: The tramadol-APAP group had a significantly lower final mean PVA score compared with the placebo group (P=0.015). The mean final PVA score was 44.4 mm in the tramadol-APAP group (down from baseline 71.1) and 52.3 mm in the placebo group (from baseline 68.8). Secondary: The tramadol-APAP group exhibited a significantly higher mean PRRS score than the placebo group (1.8 vs 1.1; P<0.001). The tramadol-APAP group exhibited greater improvement from baseline on every category of the SF-MPQ compared with the placebo group. The mean change was statistically significant for the sensory component (P=0.011), present pain index (P=0.011), and total score (P=0.021). In the categorical responder analysis, 54.7% of the tramadol-APAP group had ≥30% reduction in PVA scores compared with 39.5% of the placebo group (P=0.011), and 44.1% of the tramadol-APAP group had ≥50% reduction in PVA scores compared with 32.5% of the placebo group (P=0.044). The tramadol-APAP group had a significantly greater improvement in bothersomeness score (RDQ; P=0.027) and total score (RDQ; P=0.023) compared with the placebo group. For every subcategory of the SF-36, mean improvements from baseline were greater in the tramadol-APAP group than in the placebo group. These changes were statistically significant for the subcategories of role-physical (P=0.005), bodily pain (P=0.046), role-emotional (P=0.001), mental health (P=0.026), reported health transition (P=0.038), mental component summary (P=0.008). The overall assessments of study medication by patients (P<0.001) and

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				investigators (P=0.002) were significantly more positive for the tramadol-APAP group than for the placebo group. The incidence of efficacy failures was significantly lower in the tramadol-APAP group compared with the placebo group (19.3 vs 37.6%; P<0.001).
Beaulieu et al.[89] (2007) Tramadol ER 200-400 mg/ daily vs tramadol IR 50-100 mg every 4 to 6 hours vs placebo	DB, DD, RCT, XO Men and non-pregnant women aged 18 to 75 years with chronic (>1 month) noncancerous pain	N=122 8 weeks	Primary: Pain intensity (measured by VAS and ordinal scales) Secondary: Tolerability	Primary: Mean pain intensity scores did not differ during the first two weeks of treatment in each phase, however, there was a significant difference between ER and IR tramadol during the second two weeks of treatment in each phase. In the completers' population, during the second two weeks of each phase, the mean (SD) VAS scores were 29.9 (20.5) and 36.2 (20.4) mm for ER and IR tramadol, respectively (P<0.001). The mean (SD) ordinal scores were 1.41 (0.7) and 1.64 (0.6), respectively (P<0.001). In the ITT population, during the second two weeks of each phase the mean (SD) VAS scores were 32.5 (22.9) and 38.5 (21.2) mm for ER and IR tramadol, respectively (P<0.003). The mean (SD) ordinal scores were 1.50 (0.80) and 1.72 (0.70), respectively (P<0.002). In the completers' population, over the course of the entire study, the mean (SD) VAS pain intensity scores recorded in the daily diary were 34.1 (18.7) and 38.2 (20.0) mm (P=0.01) and the mean (SD) ordinal scores were 1.56 (0.50) and 1.72 (0.60) (P<0.003) during ER and IR tramadol treatment, respectively. Secondary: The most common adverse events and the numbers of patients reporting them during ER and IR tramadol treatment, respectively, were as follows: nausea (n=24, n=13), dizziness (n=20, n=9), constipation (n=18, n=10), somnolence (n=12, n=10), asthenia (n=11, n=9), headache (n=10, n=9), sweating (n=9, n=8), and vomiting (n=5, n=6). When the most common adverse events were analyzed individually, the only difference was for nausea, which occurred significantly more often in the ER tramadol group (P<0.021).

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Allan et al.[90] (2001) Morphine (MS Contin®) 10 to 200 mg for 4 weeks vs fentanyl transdermal system 25 to 100 µg/hour for 4 weeks	MC, OL, RCT, XO Patients >18 years of age with chronic non-cancer pain requiring continuous treatment with potent opioids for six weeks preceding the trial, who achieved moderate pain control with a stable dose of oral opioid for seven days before the trial	N=256 8 weeks	Primary: Patient preference Secondary: Pain control and treatment assessment, rescue drug use, SF-36 quality of life, and safety	Primary: Preference could not be assessed in 39 of 251 patients, leaving a total of 212 patients for analysis. A higher proportion of patients preferred or very much preferred fentanyl to morphine (138 [65%] vs 59 [28%]; P<0.001). Preference for fentanyl was not significantly different in patients with nociceptive, neuropathic or mixed nociceptive and neuropathic pain. The predominant reason for preferring fentanyl was better pain relief. Secondary: Patients treated with fentanyl reported on average lower pain intensity scores than those treated with morphine (57.8 [range, 33.1 to 82.5] vs 62.9 [range, 41.2 to 84.6]; P<0.001), irrespective of the order of treatment. More patients receiving fentanyl considered their pain control to be good or very good vs those receiving morphine (35 vs 23%; P=0.002). Investigators' opinion of global efficacy for fentanyl was good or very good in 58% (131/225) of patients compared to 33% (75/224) of patients receiving morphine (P<0.001). The corresponding percentages from the patient assessments were 60% for fentanyl and 36% for morphine (P<0.001). Analysis of the consumption of rescue drug during the last three weeks of each treatment period showed that the mean (SD) consumption was significantly higher with fentanyl than with morphine (29.4 [33.0] mg vs 23.6 [32.0] mg; P<0.001). A significant period effect was also observed: the higher consumption during fentanyl treatment was more apparent in the second trial period (32.4 [38.5] mg) than the first (26.3 [26.0] mg), where the consumption of the rescue drug remained essentially the same over the two treatment periods in the morphine group (23.7 [35.3] mg vs 23.6 [27.3] mg). Patients receiving fentanyl had higher overall quality of life scores than patients receiving morphine in each of eight categories measured by the SF-36. Differences were significant in bodily pain (P<0.001), vitality (P<0.001), social functioning (P=0.002), and mental health (P=0.020). The overall incidence of treatment related adverse events was similar in

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				both groups as was the proportion of patients with adverse events. Fentanyl was associated with a higher incidence of nausea (26 vs 18%) but less constipation (16 vs 22%).
van Seventer et al.[91] (2003) Fentanyl 25 µg/hour transdermal every 3 days vs morphine ER 30 mg every 12 hours	MC, RCT Patients with moderate-to-severe cancer-related pain	N=131 4 weeks	Primary: Analgesia Secondary: Constipation; tolerability; safety	Primary: There was similar pain control and improved sleep quality between two treatment groups. Secondary: Fewer patients in the fentanyl group reported constipation during the trial. This finding was statistically significant after one week of treatment (27 vs 57%; P=0.003). Transdermal fentanyl was better tolerated than oral morphine. A higher number of patients taking morphine dropped out due to adverse events (36% morphine vs 4% fentanyl). Patient assessment favored fentanyl treatment in terms of a significantly lower rate of troublesome side-effects ('quite a bit' to 'very much' troublesome side-effects in 14 vs 36% of patients; P=0.003) and less interruption of daily activities (absence of any interruption of daily activities in 88 vs 63% of patients; P=0.012).
Bruera et al.[92] (2004) Methadone 7.5 mg every 12 hours, in addition to methadone 5 mg every 4 hours as needed for BTP vs slow-release morphine 15 mg every 12 hours, in	DB, MC, PG, RCT Patients with poor control of pain caused by advanced cancer necessitating initiation of strong opioids; normal renal function; life expectancy of ≥4 weeks; normal cognition and written informed consent	N=103 4 weeks	Primary: Difference in pain intensity Secondary: Change in toxicity and patient-reported global benefit	Primary: Evaluation of trends by day eight revealed that the proportion of patients with a ≥20% improvement in pain expression was similar for both groups, with 75.5% (95% CI, 62.0 to 89.0) and 75.9% (95% CI, 63.0 to 89.0). By Day 29, there was no significant difference between methadone and morphine for the proportion of treatment responders (49%; 95% CI, 31 to 64 vs 56%; 95% CI, 41 to 70; P=0.50). Secondary: The proportion of patients in the methadone and morphine groups who reported a ≥20% worsening of composite toxicity was similar (67%; 95% CI, 53 to 82 vs 67%; 95% CI, 53 to 80; P=0.94). There was also no significant difference between the methadone and morphine groups for patient-reported global benefit scores (53%; 95% CI,

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addition to IR morphine 5 mg every 4 hours as needed for BTP				38 to 68 vs 61%; 95% CI, 47 to 75; P=0.41).
De Conno et al.[93] (2008) Morphine 5 mg IR every 4 hours, if taking Step 1 analgesics or morphine 10 mg IR every 4 hours, if taking Step 2 analgesics Patients currently receiving treatment with WHO Step I or Step II analgesics.	OL Cancer patients ≥18 years of age, never treated with strong opioids, and with pain score of >5 points on a 0 to 11 point standard scale for ≥24 hours	N=159 5 days	Primary: Proportion of time with pain control (reduction of ≥50% with respect to the baseline pain score) during the titration phase Secondary: Adverse events	Primary: Pain control was observed for 75% (95% CI, 70 to 80) of the follow-up period in the intent-to-treat population. Overall, 50 and 75% of patients achieved pain control eight to 24 hours after starting 5 and 10 mg morphine therapy respectively. Mean pain score was 7.63 points at baseline, and decreased to 2.43 and 1.67 points (both P<0.001) at days three and five respectively. Secondary: The most commonly reported adverse events were somnolence (24% of patients), constipation (22%), vomiting (13%), nausea (10%) and confusion (7%).
Reid et al.[94] (2006) Oxycodone vs morphine vs hydromorphone	MA Patients with moderate to severe cancer pain	N=1,013 Variable duration	Primary: Pain relief, as assessed on two standardized verbal/visual pain scoring methods Secondary: Patient acceptance, quality of life and adverse events	Primary: Mean pain scores did not differ between oxycodone and control drugs (P=0.8). Pain scores were higher for oxycodone compared to morphine (0.20; 95% CI, -0.04 to 0.44) and lower compared to hydromorphone (-0.36; 95% CI, -0.71 to 0.00), although these effect sizes were small. The investigators estimated that for oxycodone compared to morphine or hydromorphone, the pooled standardized differences represented only 2 to 3 mm on a 100-mm VAS, and suggested such standardized differences are unlikely to be clinically important or meaningful to patients. Secondary: No differences in patient preference or quality of life were demonstrated,

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				although one study suggested that nighttime acceptability of morphine was better than that of oxycodone. The point estimates for the pooled data comparing oxycodone with control groups were 0.75 (95% CI, 0.51 to1.10) for nausea and 0.2 (95% CI, 0.49 to1.06) for vomiting. Estimates of the association of oxycodone with dry mouth and drowsiness varied widely across trials. When the MA was repeated using only data from the trials with morphine as the control treatment, the pooled OR favored oxycodone for dry mouth and drowsiness. As many as 90% of patients experienced opioid-related adverse effects in each trial.
Schwartz et al.[95] (2011) Tapentadol ER 100 to 250 mg BID (fixed, optimal dose identified for patients during OL phase of trial) vs placebo Initial treatment with tapentadol ER 50 mg BID for 3 days; then titrated to tapentadol ER 100 mg BID for 3 days (minimum study dose for maintenance); subsequent titration in 50 mg	DB, PC, PG, RCT Adults ≥18 years with Type 1 or 2 diabetes and painful diabetic peripheral neuropathy for ≥6 months with a history of analgesic use for diabetic peripheral neuropathy and dissatisfaction with current treatment (opioid daily doses equivalent to < 160 mg of oral morphine), an average pain intensity score ≥5 on an 11-point rating scale, and effective method of birth control (if applicable)	N=395 (A total of 588 received study drug through OL titration phase; a total of 395 were randomized to DB phase of the study) 12 weeks (maintenance phase after a 3-week titration phase)	Primary: The change from baseline in average pain intensity over the last week (week-12) of the maintenance phase Secondary: Proportion of patients with improvements in pain intensity of at least 30 and 50% at week 12 (i.e., responder rate), PGIC at weeks two, six, and 12, and safety measures	Primary: The least square mean change in average pain intensity from the start of DB treatment to week 12 was 1.4 in the placebo group, indicating a worsening in pain intensity, and 0.0 in the tapentadol ER group, indicating no change in pain intensity. The least square mean difference between tapentadol ER and placebo was -1.3 (95% CI, -1.70 to -0.92; P<0.001). Secondary: The mean changes in average pain intensity scores (on 11-point rating scale) from baseline to week-12 were similar between males and females who received tapentadol ER, for those <65 years of age and those >65 years who received tapentadol ER, as well as those who were opioid-naïve and opioid-experienced. From pre-titration to week 12 of maintenance treatment, at least a 30% improvement in pain intensity was observed in 53.6% of tapentadol ER-treated patients and 42.2% of placebo-treated patients (P=0.017). At least a 50% improvement in pain intensity from pre-titration to week-12 was observed in 37.8% of tapentadol ER-treated patients and 27.6% of placebo-treated patients. There was a statistically significant difference in the distribution of responder rates for patients with any degree of improvement (pre-titration to week-12) between the tapentadol ER and placebo groups (P=0.032).

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increments every 3 days (within dose range of 100 to 250 mg BID). APAP ≤2,000 mg/day was permitted during the OL phase, except during the last 4 days.				Of the patients who achieved ≥ 30% improvement in pain intensity (titration phase) and were randomized to tapentadol ER treatment, 60.8% maintained ≥30% improvement through week 12 (maintenance phase); whereas 34.0% of patients who had not achieved at least a 30% improvement in pain intensity (titration phase) and were randomized to tapentadol ER reached ≥30% improvement from pre-titration by week 12 of the maintenance period. Of those patients who were randomized to placebo after achieving ≥30%improvement in pain intensity (titration phase), 48.7% of patients maintained ≥30% improvement through the maintenance phase, while only 17.5% of patients who were randomized to placebo and had not reached ≥30% improvement (titration phase) achieved ≥30% improvement in pain intensity during the maintenance phase. Among patients who achieved ≥50% improvement in pain intensity (titration phase) and were randomized to treatment with tapentadol ER, 59.1% of patients maintained ≥50% improvement through week 12 (maintenance phase); whereas 18.0% of patients who had not achieved ≥50% improvement (titration phase) and were randomized to tapentadol ER reached ≥50% improvement from pre-titration by week 12 of the maintenance period. Among patients who were randomized to placebo after achieving ≥50% improvement in pain intensity (titration phase), 36.4% of patients maintained ≥50% improvement through the maintenance phase, while only 16.5% of those randomized to placebo and had not reached ≥50% improvement during titration reached ≥50% improvement during the maintenance phase. A total of 64.4% of tapentadol ER-treated patients and 38.4% of placebo-treated patients reported on the PGIC scale that their overall status was “very much improved” or “much improved” (P<0.001). The overall incidence of adverse events (maintenance phase) was 70.9% among the tapentadol ER group and 51.8% among the placebo group. The most commonly reported events among the active treatment group were

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				nausea, anxiety, diarrhea, and dizziness. During the maintenance phase, the overall incidence of adverse events was similar between males and females, those ages <65 years and >65 years, and among opioid-naïve and opioid-experienced individuals who received tapentadol ER. Treatment-emergent serious adverse events occurred in 1.4% of tapentadol ER-treated patients in the titration phase; and among 5.1% of the tapentadol ER-treated patients and 1.6% of placebo-treated patients in the maintenance phase.
Hartrick et al.[96] (2009) Tapentadol 50 to 75 mg every 4 to 6 hours vs oxycodone 10 mg every 4 to 6 hours vs placebo	DB, RCT Patients 18 to 80 years of age who were candidates for primary joint replacement surgery as a result of end-stage degenerative joint disease	N=674 10 days	Primary: SPID over five days Secondary: Two- and 10-day SPID: two-,five-, and 10-day TOTPAR, and the sum of TOTPAR and pain intensity difference (SPRID)	Primary: After five days, both tapentadol treatment groups had a significant reduction in pain intensity compared to placebo (P<0.001). A significant difference was also seen between oxycodone and placebo (P<0.001). Secondary: Both tapentadol treatment groups had significant reductions in pain intensity compared to placebo, with increasing two- and 10-day SPID values (all, P<0.001). Significant reductions in pain intensity were also seen in the oxycodone group compared to placebo (all, P<0.001). The proportion of patients with a decrease in pain intensity of ≥30% at day five were 43% in the tapentadol 50 mg group (P=0.018 vs placebo), 41% in the tapentadol 75 mg group (P=0.033 vs placebo), 40% in the oxycodone group (P value not significant), and 30% in the placebo group. The corresponding responder rates of patients with a decrease in pain intensity of at least 50% at day five were 27% (APAP=0.003 vs placebo), 26% (P=0.002 vs placebo), 25% (P=0.007 vs placebo), and 13%. At the end of the study, overall status was rated as very much improved or much improved by 49 and 42% of patients in the tapentadol 50 and 75 mg groups, respectively (both, P<0.001 vs placebo), 41% of those in the oxycodone group (P=0.005 vs placebo), and 21% of those in the placebo group. Adverse effects were reported by 52% of patients in the tapentadol 50 mg

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				group, 71% of patients in the tapentadol 75 mg group, 84% of patients in the oxycodone group, and 32% of patients in the placebo group. The most frequently reported adverse effects were dizziness, nausea, vomiting, somnolence, constipation, pruritus, and fatigue. No serious adverse events were reported in the tapentadol groups.
Afilalo et al.[97] (2010) Tapentadol ER 100 mg BID vs placebo vs oxycodone CR 20 mg BID Initial treatment with tapentadol ER 50 mg BID or oxycodone CR 10 mg BID for 3 days; then doses were increased to tapentadol ER 100 mg BID or oxycodone CR 20 mg BID (minimum study doses); at 3-day intervals doses were increased in increments of tapentadol ER 50 mg or oxycodone	AC, DB, MC, PC, RCT Patients ≥40 years of age with a diagnosis of OA of the knee (per ACR criteria) functional capacity class I-III, and pain at reference joint requiring analgesics (both non-opioid and opioid doses ≤ 160 mg oral morphine daily) for ≥3 months, who were dissatisfied with their current analgesic regimen, and had a baseline pain intensity score ≥5 during the 3 days prior to randomization	N=1,030 12 weeks (maintenance phase after a 3-week titration phase)	Primary: Change in average pain intensity at week-12 of the maintenance period compared to baseline Secondary: Change in average pain intensity over the entire 12-week maintenance period compared to baseline	Primary: Significant pain relief was achieved with tapentadol ER vs placebo at study endpoint. The least square mean difference was - 0.7 (95% CI, -1.04, -0.33) at week 12 of the maintenance period compared to placebo. Secondary: The least square mean difference was -0.7 (95% CI, -1.00 to -0.33) for the overall maintenance period for tapentadol compared to placebo (P-values not reported). The average pain intensity rating with oxycodone CR was reduced significantly compared to placebo from baseline for the overall maintenance period (least square mean difference vs placebo, -0.3; 95% CI, -0.67 to 0.00), but was not statistically significantly lower at week-12 of the maintenance period (-0.3; 95% CI, -0.68 to 0.02); P-values not reported. The percentage of patients who achieved ≥30% reduction from baseline in average pain intensity at week-12 of the maintenance period was not significantly different between tapentadol ER and placebo (43.0 vs 35.9%; P=0.058), but was significantly lower for oxycodone CR compared to placebo (24.9 vs 35.9%; P=0.002). Treatment with tapentadol ER resulted in a significantly higher percentage of patients achieving ≥50% reduction in average pain intensity from baseline at week-12 of the maintenance period vs treatment with placebo (32.0 vs 24.3%; P=0.027). Conversely, treatment with oxycodone CR resulted in a significantly lower percentage of patients achieving at least a 50% reduction in average pain intensity from baseline at week-12 of the maintenance period vs treatment with placebo (17.3 vs 24.3%; P=0.023). Tapentadol ER was significantly better than placebo at week-12 on the

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CR 10 mg (max daily doses: tapentadol ER 250 mg BID or oxycodone CR 50 mg BID). APAP ≤1,000 mg/day (max of 3 consecutive days) was permitted.				WOMAC global scale with a least square mean difference of -0.21 (95% CI, -0.357 to -0.065; P=0.0047) compared to the least square mean difference between oxycodone CR and placebo -0.18 (95% CI, -0.343 to -0.010; P=0.0381). The pain subscale for tapentadol ER compared to placebo was a least square mean difference of -0.27 (95% CI, -0.422 to -0.126; P<0.001) compared to the least square mean difference between oxycodone CR and placebo of -0.17 (95% CI, -0.338 to -0.000; P=0.051). The physical function subscale at week-12 was significantly improved with tapentadol ER and placebo (least square mean difference of -0.21; 95% CI, -0.357 to -0.060; P=0.006), whereas the least square mean difference between oxycodone CR and placebo was -0.20 (95% CI, -0.373 to -0.034; P=0.019). The stiffness subscale assessment was improved with tapentadol ER compared to placebo with a least square mean difference of -0.17 (95% CI, -0.377 to -0.002; P=0.053); however the difference was not statistically significant. Conversely, the least square mean difference between oxycodone ER and placebo was -0.10 (95% CI, -0.292 to 0.096; P=0.321), which also was not statistically significant. The incidence of adverse events was 61.1% with placebo, 75.9% with tapentadol ER, and 87.4% with oxycodone CR. The most common events (≥10% in any group) in the active treatment groups were nausea, constipation, vomiting, dizziness, headache, somnolence, fatigue and pruritus. The majority of reported events were mild to moderate in severity. Events leading to discontinuation occurred in 6.5% of patients treated with placebo, 19.2% of patients treated with tapentadol ER, and 42.7% of patients treated with oxycodone ER. Gastrointestinal-related events were the most common events in both active treatment groups.
Buynak et al.[98] (2010) Tapentadol ER 100 mg BID	AC, DB, MC, PC, PRO, RCT Patients ≥18 years with a history of	N=981 12 weeks (maintenance phase after a	Primary: Change from baseline in mean pain intensity at week-12 of the	Primary: Throughout the 12-week maintenance period, average pain intensity scores improved in both the tapentadol ER and oxycodone CR groups relative to placebo.

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vs oxycodone CR 20 mg BID vs placebo Initial treatment with tapentadol ER 50 mg BID or oxycodone CR 10 mg BID for 3 days; then doses were increased to tapentadol ER 100 mg BID or oxycodone CR 20 mg BID (minimum study doses); at 3-day intervals doses were increased in increments of tapentadol ER 50 mg or oxycodone CR 10 mg (max daily doses: tapentadol ER 250 mg BID or oxycodone CR 50 mg BID). APAP ≤1,000 mg/day (max of 3 consecutive days)	non-malignant low back pain for ≥3 months who were dissatisfied with their current treatment, had a baseline pain intensity ≥5 on an 11-point rating scale after washout, and whose previous opioid daily doses, if applicable, were equivalent to ≤160 mg of oral morphine	3-week titration phase)	maintenance period Secondary: Change from baseline in mean pain intensity over the entire 12-week maintenance period, proportion of patients with ≥30 and ≥50% reduction in pain intensity at week-12 of maintenance, PGIC score, BPI survey, SF-36 health survey	The mean (SD) change in pain intensity from baseline to week 12 was -2.9 (2.66) for tapentadol ER and -2.1 (2.33) for placebo resulting in a least square mean difference vs placebo of -0.8 (95% CI, -1.22 to -0.47; P<0.001). The mean change in pain intensity from baseline over the entire maintenance period was -2.8 (2.50) for tapentadol ER and -2.1 (2.20) for placebo, corresponding to a least square mean difference vs placebo of -0.7 (95% CI, -1.06 to -0.35; P<0.001). Secondary: The mean pain intensity was also reduced for the oxycodone CR group. Compared to the placebo group at week 12 the least square mean difference was -0.9 (95% CI, -1.24 to -0.49; P<0.001); and over the entire maintenance period the least square mean difference was -0.8 (95% CI, -1.16 to -0.46; P<0.001). Reductions in mean pain intensity were significantly greater with tapentadol ER than with placebo at week-12 of the maintenance period both for patients with moderate and severe baseline pain intensity. Significantly greater reductions in mean pain intensity with tapentadol ER compared to placebo were also observed for the overall maintenance period in patients with both moderate baseline pain intensity and severe baseline pain intensity. Reductions in mean pain intensity were also significantly greater with oxycodone CR than with placebo for patients with moderate and severe baseline pain intensity at both week 12 of the maintenance period and for the overall maintenance period. The overall distribution of responders at week 12 of the maintenance period was significantly different between the tapentadol ER group and the placebo group (P=0.004), with a higher percentage of patients showing improvements in pain scores in the tapentadol ER group than in the placebo group. The overall distribution of responders at week 12 in the oxycodone CR group, however, was not significantly different from the placebo group (P=0.090).

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was permitted.				A total of 39.7% of patients treated with tapentadol ER compared to 27.1% of patients treated with placebo responded with ≥30% improvement in pain intensity at week-12 compared to baseline (P<0.001). A total of 27.0% of patients treated with tapentadol ER compared to 18.9% of patients treated with placebo responded with 50% improvement in pain intensity at week-12 compared to baseline (P<0.016). The percentage of patients in the oxycodone CR group with ≥30% improvement in pain intensity at week-12 compared to baseline was 30.4% (P=0.365) and did not differ significantly from placebo (percent among placebo group not reported). Conversely, the percentage of patients in the oxycodone CR group with ≥50% improvement in pain intensity at week-12 compared to baseline was 23.3% (P=0.174) and did not differ significantly from placebo (percent among placebo group not reported). At endpoint, there was a significant difference in PGIC ratings for both tapentadol ER (P< 0.001) and oxycodone CR (P<0.001) compared to placebo. Compared to placebo, both tapentadol ER and oxycodone CR showed significant reductions from baseline to week-12 in the BPI total score, the pain interference subscale score, and the pain subscale score. The percentage of patients with “any pain today other than everyday kinds of pain” on the BPI survey at baseline was 88.6, 85.6, and 86.1% for the placebo group, tapentadol ER group, and oxycodone CR group, respectively. At week 12, the percentage scores decreased to 80.7% for the placebo group, 69.8% for the tapentadol ER group, and 67.3% for the oxycodone CR group. The percentage of patients who reported “at least 50% pain relief during the past week” was similar for all three treatment groups at baseline for the placebo, tapentadol ER, and oxycodone ER groups (23.4, 24.7, and 20.9%,

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				respectively). These results increased to 59.7, 75.4, and 80.0% among the placebo, tapentadol ER, and placebo groups, respectively at week 12. Treatment with both tapentadol ER and oxycodone CR significantly improved physical health status compared to placebo, as reflected by the physical component summary score. The mean changes at week-12 from baseline on the SF-36 survey for four of eight measures (physical functioning, role-physical, bodily pain, and vitality) were significantly improved in the tapentadol ER group compared to the placebo group. The mean changes from baseline were significantly improved for role-physical and bodily pain scores among the oxycodone CR group compared to the placebo group. No clinically important changes in laboratory values, vital signs, or electrocardiogram findings were attributed to treatment. Overall, at least one adverse event was reported by 59.6, 75.5, and 84.8% of patients in the placebo, tapentadol ER, and oxycodone CR groups, respectively. The most commonly reported events (reported by >10% in any treatment group) were nausea, constipation, headache, vomiting, dizziness, pruritus, and somnolence, the majority of which were categorized as mild to moderate in intensity across all treatment groups. In the oxycodone CR group, the incidence of vomiting, constipation, and pruritus was nearly double incidence in the tapentadol ER group.
Wild et al.[99] (2010) Tapentadol 100 to 250 mg BID vs oxycodone CR 20	AC, MC, OL, PG, RCT Men and (non-pregnant) women ≥18 years of age with a diagnosis of moderate to severe knee or hip OA pain	N=1,121 51 weeks (maintenance phase)	Primary: Safety and tolerability Secondary: Change in mean pain intensity score	Primary: The proportion of patients who completed treatment in the tapentadol ER and oxycodone CR groups were 46.2 and 35.0%, respectively, with the most common reason for discontinuation in both treatment groups being adverse events (22.1% for tapentadol ER vs 36.8% for oxycodone ER). Overall, 85.7% of patients in the tapentadol ER group and 90.6% of patients in the oxycodone CR group experienced at least one adverse event. The most commonly reported events (reported by >10% in either

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to 50 mg BID Initial treatment with tapentadol ER 50 mg BID or oxycodone CR 10 mg BID for 3 days; then doses were increased to tapentadol ER 100 mg BID or oxycodone CR 20 mg BID for 4 days (minimum study doses); at 3-day intervals doses were increased in increments of tapentadol ER 50 mg BID or oxycodone CR 10 mg BID (max daily doses: tapentadol ER 250 mg BID or oxycodone CR 50 mg BID). Occasional pain relief with NSAIDs, aspirin doses ≤325 mg/day for cardiac prophylaxis, and APAP ≤1,000 mg/day (up to a max of 7	or low back pain (non-malignant) with a ≥ 3 month history of pain, who were dissatisfied with current analgesic therapy, and had a pain intensity score ≥4 on an 11-point rating scale after therapy washout			treatment group) were constipation, nausea, dizziness, somnolence, vomiting, headache, fatigue, and pruritus. The incidences of constipation (22.6 vs 38.6%), nausea (18.1 vs 33.2%), and vomiting (7.0 vs 13.5%) were lower in the tapentadol ER group than in the oxycodone CR group, respectively. The incidence of pruritus was 5.4% among the tapentadol ER-treated patients and 10.3% among oxycodone-treated patients. No clinically relevant treatment-related effects on laboratory values, vital signs, or electrocardiogram parameters were observed. Adverse events led to discontinuation in 22.1% of patients in the tapentadol ER group and 36.8% of patients in the oxycodone CR group. The incidence of gastrointestinal events (i.e., nausea, vomiting, or constipation) that led to discontinuation was lower in the tapentadol ER group than in the oxycodone CR group (8.6 vs 21.5%, respectively). The incidence of serious adverse events was low in both the tapentadol ER and oxycodone CR groups (5.5 vs 4.0%, respectively). Among those who reported constipation, the mean change from baseline to endpoint was lower for patients in the tapentadol ER group than for those in the oxycodone CR group as well as for the overall rectal and overall stool subscale scores. Secondary: Baseline mean pain intensity scores at endpoint among the tapentadol ER and oxycodone CR groups decreased to 4.4 and 4.5 from the baseline scores of 7.6 and 7.6, respectively. Ratings on the global assessment of study medication of “excellent,” “very good,” or “good” among the tapentadol ER and oxycodone CR groups were reported by the majority of patients (75.1 and 72.3%, respectively) and investigators (77.3 and 72.3%, respectively). The most commonly reported rating on the PGIC at endpoint was “much improved” for both the tapentadol ER and oxycodone CR groups (35.7

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
consecutive days and no more that 14 out of 30 days) were permitted.				and 32.8%, respectively). A rating of "very much improved" or "much improved" was reported by 48.1 and 41.2%, respectively.
Fricke et al.[100] Tramadol 50 mg vs. tramadol-APAP 37.5-325 mg vs placebo	DB, PC, RCT Men and women aged 18 to 75 who underwent elective outpatient surgery for extraction of at least two upper or lower impacted third molars	N=456 1 dose	Primary: Efficacy (measured by hourly PAR and pain intensity scores) Secondary: PID and PAR at each time point, time to onset of perceptible/ meaningful PAR, time to rescue analgesia, and adverse events	Primary: Tramadol-APAP was more efficacious to tramadol (P<0.001) or placebo (P<0.001) for all the primary efficacy endpoints, regardless of the time interval examined. Tramadol was numerically more efficacious to placebo but was not statistically different from placebo for any of the endpoints. Mean PAR scores were greater at all time points after a dose of tramadol-APAP compared with tramadol (P<0.001) or placebo (P<0.001). Tramadol was significantly more effective than placebo for mean PAR scores at hour two (P=0.022), but not at other times. Mean PID scores also demonstrated greater improvement throughout the study in the tramadol-APAP group compared with the tramadol (P<0.001) or placebo (P<0.001) group. Secondary: Tramadol-APAP-treated patients reported meaningful PAR more rapidly than tramadol-treated (P<0.001) or placebo-treated (P<0.001) patients. Tramadol-treated patients reported meaningful PAR more rapidly than placebo-treated patients (P=0.035). Tramadol-APAP also had significantly faster onset of action than tramadol (P<0.001) or placebo (P<0.001) with respect to perceptible PAR, but tramadol did not demonstrate significantly faster onset of perceptible PAR than placebo (P=0.805). The overall incidences of adverse events were 54% in the tramadol-APAP group, 64% in the tramadol group, and 39% in the placebo group. Nausea was significantly less common in the tramadol/APAP group (33%) than the tramadol group (46%; P=0.019).
Rodriguez et al.[101] (2007)	DB, RCT Patients with	N=177 3 weeks	Primary: Analgesic efficacy	Primary: There was no significant difference in the analgesic efficacy of the three opioids (P=0.69).

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Codeine-APAP vs hydrocodone-APAP vs tramadol	persistent moderate or severe cancer-associated pain		Secondary: Adverse effects	Secondary: Tramadol produced higher rates of adverse events than codeine and hydrocodone, including vomiting, dizziness, loss of appetite, and weakness (P<0.05).
Mullican et al.[102] (2001) Tramadol-APAP 37.5-325 mg once to twice every 4 to 6 hours vs codeine-APAP 30-300 mg once to twice every 4 to 6 hours	AC, DB, DD, PG, RCT Men and non-pregnant women >18 years of age with chronic nonmalignant low back pain, OA pain, or both	N=462 4 weeks	Primary: Efficacy (measured by patient reported pain relief and pain intensity using Likert scales, and overall efficacy as reported by investigators) Secondary: Safety	Primary: Mean TOTPAR scores were comparable between the two groups at each weekly observation. Mean SPID scores were similar for tramadol-APAP and codeine-APAP at each visit. The maximum number of doses required in a single day for pain relief was a mean of 5.5 tablets of tramadol-APAP and 5.7 capsules of codeine-APAP. The percentage of patients requiring supplemental ibuprofen at any point was comparable between the two groups and ranged from 21 to 30% for each week of the study. The mean duration of therapy was 25.5 days for tramadol-APAP and 25.0 days for codeine-APAP. Secondary: The overall rates of treatment-emergent adverse events were comparable for the two groups. 71% of the tramadol-APAP and 76% of the codeine-APAP treated patients reported adverse events. Somnolence (24% [37/153] and constipation (21% [32/153]) were significantly more common in the codeine-APAP group than in the tramadol group (17% [54/309] and 11% [35/309]; P=0.05 and P<0.01, respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Fricke et al.[103] (2002) Tramadol-APAP 37.5-325 mg vs tramadol-APAP 75-650 mg vs hydrocodone-APAP 10-650 mg vs placebo	AC, DB, PC, PG, SC Men and women 16 to 75 years of age who experiencing moderate or severe pain within 5 hours after surgical removal of > 2 impacted third molars and associated bone	N=200 8 hours	Primary: Efficacy based on TOTPAR, SPID, and SPRID measures Secondary: Efficacy measured by PAR, PID, and PRID scores; onset and duration of pain relief, time to re-medication with a supplemental analgesic agent; and patients' overall assessment of medication	Primary: For TOTPAR, SPID, and SPRID, tramadol-APAP 75-650 mg and hydrocodone-APAP provided statistically superior pain relief during all three intervals (0 to four, four to eight, and 0 to eight hours) compared to placebo (P<0.024), but were not significantly different from each other. There was a statistically significant dose response for tramadol-APAP compared to placebo (two tramadol-APAP tablets >1 tablet >placebo) on all three primary efficacy variables during all three time periods (P<0.001, 0 to four and 0 to eight hours; P<0.018, four to eight hours) Secondary: The median times to onset of pain relief were 34.0 and 33.3 minutes in the tramadol-APAP 75-650 mg and tramadol-APAP 37.5-325 mg groups, respectively, and 25.4 minutes in the hydrocodone-APAP group (P<0.001, active treatments vs placebo). There was no significant difference between tramadol-APAP 75-650 mg and hydrocodone-APAP in terms of duration of pain relief as measured by the areas under the curve for PAR, PID, and PRID over the second half of the study (four to eight hours). Both treatments had significantly longer duration of activity than placebo (TOTPAR; P<0.018; SPID; P<0.024; SPRID; P<0.019). Fewer patients required supplemental analgesic medication during the eight-hour observation period in the tramadol-APAP 75-650 mg (78.0%) and hydrocodone-APAP (84.0%) groups compared to the tramadol-APAP 37.5-325 mg (94.0%) and placebo (94.0%) groups. The median time to re-medication with a supplemental analgesic was shortest in the placebo group (78.5 minutes), followed by tramadol-APAP 37.5-325 mg (113.0 minutes), tramadol-APAP 75-650 mg (169.0 minutes), and hydrocodone-APAP (204.0) minutes. The time to remedication was significantly longer for all active treatments compared to placebo (tramadol-APAP 75-650 mg and hydrocodone-APAP; P<0.001; tramadol-APAP 37.5-325 mg; P=0.036).

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				Patients' mean overall assessment of study medication was statistically superior in all active-treatment groups compared to placebo (P<0.001).
Furlan et al.[104] (2006) Weak opioids: Tramadol, propoxyphene, codeine Strong opioids: morphine, oxycodone	MA Patients with nociceptive pain (OA, rheumatoid arthritis or back pain), neuropathic pain (postherpetic neuralgia, diabetic neuropathy or phantom limb pain), fibromyalgia, and mixed pain	N=6,019 1 to 16 weeks	Primary: Pain relief; improvement in functional outcome, based upon standardized indices and scoring methods Secondary: Adverse events	Primary: Opioids were more effective than placebo for both pain and functional outcomes in patients with nociceptive pain, neuropathic pain or fibromyalgia. Strong opioids were significantly more effective than naproxen and nortriptyline for pain relief, but not for functional outcomes. Weak opioids did not significantly outperform NSAIDs or tricyclic antidepressants for either pain relief or functional outcomes. Tramadol reduced pain and improved functional outcomes in patients with fibromyalgia. Secondary: Among the side effects of opioids, only constipation and nausea were clinically and statistically significant.
Steiner et al.[105] (2011) Buprenorphine transdermal system 5 or 20 µg/hour every 7 days vs oxycodone immediate-release 10 mg every 6 hours	AC, DB, DD, MC, PG, RCT Patients ≥18 years of age with clinical diagnosis of low back pain for ≥3 months, taking between 30 to 80 mg of oral morphine sulfate or opioid equivalent daily, at least 4 days a week, for ≥30 days prior to visit 1	N=1,160 12 weeks	Primary: Average pain score over the last 24 hours on an 11-point numerical pain scale ranging from 0 (no pain) to 10 (pain as bad as you can imagine) at weeks four, eight and 12 Secondary: Treatment differences with respect to less sleep disturbances and the daily	Primary: The protocol-specified analysis of the primary efficacy variable, in which missing values were not imputed, resulted in a statistically significant treatment difference of -0.67 between buprenorphine 20 and 5 µg/hour in favor of buprenorphine 20 µg/hour (P<0.001). The treatment difference of -0.75 between oxycodone IR and buprenorphine 5 µg/hour in favor of oxycodone IR was also statistically significant (P<0.001). The four sensitivity analyses of the primary efficacy variable resulted in statistically significant treatment differences in favor of buprenorphine 20 µg/hour and oxycodone IR compared to buprenorphine 5 µg/hour. Secondary: Treatment with buprenorphine 20 µg/hour led to statistically significant treatment differences with respect to less sleep disturbance (P<0.001) and decreased use of supplemental analgesic medication (P=0.006) compared to buprenorphine 5 µg/hour.

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			number of tablets of supplemental analgesic medication during DB period, and the Oswestry Disability Index at weeks four, eight, and 12	The difference between buprenorphine 20 µg/hour and 5 µg/hour with respect to the Oswestry Disability Index was not statistically significant (P value not reported).
Karlsson et al.[106] (2009) Buprenorphine transdermal system 5, 10, 15 or 20 µg/hour every 7 days vs tramadol prolonged-release 150 to 400 mg/day orally divided in two doses	AC, MC, OL, PG, RCT Patients ≥18 years of age with a clinical diagnosis of OA of the hip and/or knee with suboptimal analgesia in the primary osteoarthritic joint in the week before visit 1	N=135 12 weeks	Primary: Mean weekly Box Scale-11 pain score ranging from 0 (no pain) to 10 (pain as bad as you can imagine) Secondary: Daily number of tablets of supplemental analgesic medication, sleep disturbance and quality of sleep assessment, patient-investigator-rated and global assessment of pain relief, patient preference and safety	Primary: In the ITT analysis, the least squares mean change from baseline in Box Scale-11 pain score at week 12 was -2.26 for buprenorphine and -2.09 for tramadol prolonged-release. The difference between the two treatment groups was -0.17 (95% CI, -0.89 to 0.54; P value not reported), which was within the non-inferiority margin, showing that buprenorphine was non-inferior to tramadol prolonged-release. Secondary: The mean number of supplemental analgesic medication used during the study was 206.4 tablets for buprenorphine and 203.7 tablets for tramadol prolonged-release. The difference between the two treatment groups did not reach statistical significance (P value not reported). There were no statistically significant differences in sleep disturbance and quality of sleep between the buprenorphine and tramadol prolonged-release groups (P value not reported). There were statistically significant differences in favor of buprenorphine compared to tramadol prolonged-release with regard to patient- and investigator-rated global assessment of pain relief (P=0.039 and P=0.020, respectively). Ninety of 128 patients (70.3%; 95% CI, 62 to 78) preferred a once-weekly patch as a basic analgesic treatment for OA pain in the future. There were no differences between the two treatment groups in the total number of reported adverse events (P value not reported). The most

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				commonly observed adverse events in the buprenorphine group were nausea (30.4%), constipation (18.8%) and dizziness (15.9%).
Felden et al.[107] (2011) Hydromorphone vs morphine	MA (11 RCTs) Patients with acute or chronic pain	N=1,215 Duration not specified	Primary: Pain relief and adverse events Secondary: Not reported	Primary: Hydromorphone was associated with greater acute pain relief compared to morphine (pooled standard mean difference, -0.226; P=0.006). No differences were observed for the treatment of chronic pain relief (P=0.889). The overall incidences of nausea, vomiting and pruritus were comparable between the two opioids. When the four studies on chronic pain were analyzed separately, hydromorphone was associated with less nausea (P=0.005) and vomiting (P=0.001). Secondary: Not reported.
Opioid Dependence				
Johnson et al.[108] (1992) Buprenorphine 8 mg daily vs methadone 60 mg daily vs methadone 20 mg daily	DB, PG, RCT Adults seeking treatment for opioid dependence	N=162 17-week maintenance phase, followed by a 8-week detoxification phase	Primary: Retention time in treatment, urine samples negative for opioids, and failure to maintain abstinence Secondary: Not reported	Primary: During the maintenance phase, the retention rates were significantly greater for buprenorphine (42%) than for methadone 20 mg/day (20%; P<0.04). During the maintenance phase, the percentage of urine samples negative for opioids was significantly greater for buprenorphine (53%; P<0.001) and methadone 60 mg/day (44%; P<0.04), than for methadone 20 mg/day (29%). Failure to maintain abstinence during the maintenance phase was significantly greater for methadone 20 mg/day, than for buprenorphine (P<0.03). During the detoxification phase, there were no differences between the treatment groups with regards to urine samples negative for opioids. During the 25 week study period, retention rates for buprenorphine (30%; P<0.01) and methadone 60 mg/day (20%; P<0.05) were significantly greater than for methadone 20 mg/day (6%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				All treatments were well tolerated, with similar profiles of self-reported adverse effects. The percentages of patients who received counseling did not differ between groups. Secondary: Not reported
Petitjean et al.[109] (1992) Buprenorphine sublingual tablets (flexible dosing schedule) vs methadone (flexible dosing schedule)	DB, RCT Patients seeking treatment for opioid dependence	N=58 6 weeks	Primary: Treatment retention rate, urine samples positive for opiates, substance use Secondary: Not reported	Primary: The retention rate was significantly better in the methadone group than in the buprenorphine group (90 vs 56%, respectively; P<0.001). There were similar proportions of opioid positive urine samples in both treatment groups (buprenorphine, 62%; methadone, 59%) and positive urine specimens, as well as mean heroin craving scores decreased significantly over time (P=0.035 and P<0.001). The proportion of cocaine-positive toxicology results did not differ between groups. At week six, the mean stabilization doses were 10.5 mg/day for buprenorphine and 69.8 mg/day for methadone. Secondary: Not reported
Strain et al.[110] (1994) Buprenorphine sublingual tablets (flexible dosing schedule) vs methadone (flexible dosing	DB, DD, RCT Patients seeking treatment for opioid dependence	N=164 26 weeks	Primary: Treatment retention rate, medication and counseling compliance, urine samples positive for opiates Secondary: Not reported	Primary: Buprenorphine (mean dose ~9 mg/day) and methadone (mean dose 54 mg/day) were equally effective in sustaining retention in treatment, compliance with medication, and counseling regimens. In both groups, 56% of patients remained in the treatment program through the 16-week flexible dosing period. Opioid-positive urine sample rates were 55 and 47% for buprenorphine and methadone groups, respectively. Cocaine-positive urine sample rates were 70 and 58%, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
schedule)				Secondary: Not reported
Ling et al.[111] (1996) Buprenorphine 8 mg daily vs methadone 30 mg daily vs methadone 80 mg daily	DB, RCT Patients seeking treatment for opioid dependence	N=225 1 year	Primary: Urine toxicology, retention, craving, and withdrawal symptoms Secondary: Not reported	Primary: Patients receiving high-dose methadone maintenance therapy performed significantly better on measures of retention, opioid use, and opioid craving than either the low-dose methadone group or the buprenorphine group. Performance on measures of retention, opioid use, and opioid craving were not significantly different between the low-dose methadone group or the buprenorphine group. Secondary: Not reported
Schottenfeld et al.[112] (1997) Buprenorphine 4 mg daily vs buprenorphine 12 mg daily vs methadone 20 mg daily vs methadone 65 mg	DB, RCT Patients seeking treatment for opioid dependence	N=116 24 weeks	Primary: Retention in treatment and illicit opioid and cocaine use Secondary: Not reported	Primary: There were significant effects of maintenance treatment on rates of illicit opioid use, but no significant differences in treatment retention or the rates of cocaine use. The rates of opioid-positive toxicology tests were lowest for treatment with 65 mg of methadone (45%), followed by 12 mg of buprenorphine (58%), 20 mg of methadone (72%), and 4 mg of buprenorphine (77%), with significant contrasts found between 65 mg of methadone and both lower-dose treatments and between 12 mg of buprenorphine and both lower-dose treatments. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
daily				
Soyka et al.[113] (2008) Buprenorphine (mean daily dose 9 to 12 mg) vs methadone (mean daily dose 44 to 50 mg)	RCT Opioid-dependent patients who had been without opioid substitution therapy	N=140 6 months	Primary: Retention rate; substance use; predictors of outcome Secondary: Not reported	Primary: There was an overall retention rate of 52.1%. There was no significant difference between buprenorphine-treated patients and methadone-treated patients (55.3 vs 48.4%). Substance use decreased significantly over time in both groups and was non-significantly lower in the buprenorphine group. Predictors of outcome were length of continuous opioid use and age at onset of opioid use (significant in the buprenorphine group only). Mean dosage and other parameters were not significant predictors of outcome. The intensity of withdrawal symptoms showed the strongest correlation with drop-out. Secondary: Not reported
Gibson et al.[114] (2008) Buprenorphine vs methadone	RCT Heroin-dependent patients ≥18 years of age	N=405 10 years	Primary: Mortality Secondary: Not reported	Primary: There was an overall mortality rate of 8.84 deaths per 1,000 person-years of follow-up. Increased exposure to episodes of opioid treatment longer than seven days reduced the risk of mortality. There was no difference in mortality among methadone vs buprenorphine participants. More dependent, heavier users of heroin at baseline had a lower risk of death, and also higher exposure to opioid treatment. Older patients on buprenorphine had significantly improved survival. Secondary: Not reported
Maremmani et al.[115] (2007)	OL Patients involved in	N=213 12 months	Primary: Opioid use, psychiatric status,	Primary: There were significant improvements in opioid use, psychiatric status, and quality of life between the 3rd and 12th months for buprenorphine-treated

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Buprenorphine vs methadone	a long-term treatment program with buprenorphine or methadone		quality of life Secondary: Not reported	and methadone-treated patients. Secondary: Not reported
Jones et al.[116] (2010) Buprenorphine 2 to 32 mg per day vs methadone 20 to 140 mg per day	DB, DD, MC, RCT Opioid-dependent women 18 to 41 years of age with a singleton pregnancy between 6 and 30 weeks	N=175 ≥10 days	Primary: Neonates requiring neonate abstinence syndrome therapy, total morphine needed, length of hospital stay, and head circumference Secondary: Not reported	Primary: Percentage neonates requiring neonate abstinence syndrome treatment, peak neonate abstinence syndrome scores, or head circumference did not differ significantly between groups. Neonates exposed to buprenorphine required an average 89% less morphine (1.1 and 10.4 mg; P<0.0091) than did neonates exposed to morphine. Neonates exposed to buprenorphine required an average 43% less time in hospital (10.0 vs 17.5 days; P<0.0091). The methadone group had higher rates of nonserious maternal events overall (P=0.003) and of nonserious cardiac events in particular (P=0.01). No differences in serious adverse events were detected in mothers or nonserious adverse events in neonates. Secondary: Not reported
Cornish et al.[117] (2010) Buprenorphine vs methadone	MC, OS, PRO Opioid dependent patients <60 years of age	N=5,577 585 days	Primary: All cause mortality Secondary: Duration of therapy effect on mortality	Primary: Three percent of patients died while receiving treatment, or within a year of receiving the last prescription. Of these, 35% died while on treatment. Overall, the risk of death during opiate substitution treatment was lower than the risk of death while off treatment. Crude mortality rates off therapy nearly doubled (1.3 vs 0.7 per 100-person years). Standardized mortality rates were 5.3 (95% CI, 4.0 to 6.8) on treatment vs 10.9 (95% CI, 9.0 to13.1). After adjustment for age, sex, calendar period, and comorbidity, the mortality rate ratio was 2.3 (95% CI, 1.7 to 3.1). The risk of death increased eight to nine-fold in the month immediately

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				after the end of opiate substitution therapy, which did not vary according to medication, dosing within standard thresholds, or planned cessation. There was no difference in the overall mortality rate between patients who received methadone and those who received buprenorphine. Secondary: Substitution therapy has a greater than 85% chance of reducing overall mortality when average duration of treatment is at least 12 months.
Pinto et al.[118] (2010) Buprenorphine vs methadone	OS, PRO Cohort of opioid-dependent patients new to substitution therapy	N=361 6 months	Primary: Retention in treatment at six months or successful detoxification based on patient selected substitution therapy Secondary: Not reported	Primary: A total of 63% of patients chose methadone and 37% chose buprenorphine. At six months, 50% of buprenorphine patients compared to 70% of methadone patients had favorable outcomes (OR, 0.43; 95% CI, 0.20 to 0.59; P<0.001). Methadone patients were more likely to remain on therapy than those on buprenorphine (HR, 2.08; 95% CI, 1.49 to 2.94). Retention was the primary factor in favorable outcomes at six months. Buprenorphine patients were more likely to not use illicit opiates (OR, 2.13; 95% CI, 1.509 to 3.027; P<0.001) and to achieve detoxification. A total of 28% of patients selecting buprenorphine reported they would not have accessed treatment with methadone therapy. Secondary: Not reported
Farré et al.[119] (2002) Buprenorphine ≥8 mg daily (high dose vs buprenorphine <8	MA Patients seeking treatment for opioid dependence	N=1,944 (13 trials) Variable duration	Primary: Retention rate and reduction of opioid use Secondary: Not reported	Primary: High doses of methadone were more effective than low doses of methadone in the reduction of illicit opioid use (OR, 1.72; 95% CI, 1.26 to 2.36). High doses of methadone were significantly more effective than low doses of buprenorphine (<8 mg/day) for retention rates and illicit opioid use, but similar to high doses of buprenorphine (≥8 mg/day). Patients treated with levo-acetylmethadol had more risk of failure of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg daily (low dose) vs methadone ≥50 mg daily (high dose) vs methadone <50 mg daily (low dose) vs levo-acetylmethadol				retention than those receiving high doses of methadone (OR, 1.92; 95% CI 1.32 to 2.78). Secondary: Not reported
Mattick et al.[120] (2008) Buprenorphine vs methadone vs placebo	MA Patients dependent on heroin or other opioids	N=4,497 (24 trials) Variable duration	Primary: Treatment retention, suppression of opioid use, use of other substances Secondary: Not reported	Primary: <u>Flexible Dose Buprenorphine vs Flexible Dose Methadone</u> Methadone was more likely to retain patients than buprenorphine (RR, 0.85; 95% CI, 0.73 to 0.98). There was no significant difference between the treatment groups with regards to heroin use (95% CI, -0.26 to 0.02), cocaine use (95% CI, -0.03 to 0.25), or benzodiazepine use (95% CI, -0.04 to 0.26). <u>Low Dose Buprenorphine vs Low Dose Methadone</u> Low dose methadone was more likely to retain patients than low dose buprenorphine (RR, 0.67; 95% CI, 0.52 to 0.87). There was no significant difference between the treatment groups with regards to morphine use (95% CI, -0.87 to 0.16), heroin use (95% CI, -0.38 to 0.96), cocaine use (95% CI, -0.43 to 0.59), or benzodiazepine use (95% CI, -0.33 to 0.38). <u>Low Dose Buprenorphine vs Medium Dose Methadone</u> There was a statistical difference in retention in treatment RR, 0.67; (95%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				CI, 0.55 to 0.81) favoring medium dose methadone. Medium dose methadone was more effective than low dose buprenorphine in suppressing heroin use as indexed by the extent of morphine positive urine, one study (95% CI, 0.33 to 1.42). There was no significant difference among the treatment groups in heroin use (95% CI, -0.48 to 0.68) or cocaine use (95% CI, -0.60 to 0.44). <u>Medium Dose Buprenorphine vs Low Dose Methadone</u> There was one study which favored low dose methadone in terms of retention, and the remaining three studies showed no statistically significant difference. There was no significant difference among the treatment groups in cocaine use (95% CI, -0.14 to 0.89). <u>Medium Dose Buprenorphine vs Medium Dose Methadone</u> Two of the six studies suggest that medium doses of buprenorphine are less likely to retain patients than medium dose methadone and the remainder showed no statistical significant difference. Medium dose buprenorphine was significantly less able to suppress heroin use, three studies (95% CI, 0.05 to 0.50). There was no significant difference among the treatment groups in cocaine use (95% CI, -0.30 to 0.74). <u>Low Dose Buprenorphine Maintenance vs Placebo</u> There was a benefit for low dose buprenorphine above placebo in terms of retaining patients in treatment (RR, 1.50; 95% CI, 1.19 to 1.88). Low dose buprenorphine patients had no less heroin use as indexed by morphine positive urines (95% CI, -0.80 to 1.01). There was no significant difference among the treatment groups in cocaine use (95% CI, -0.10 to 0.62) or benzodiazepine use (95% CI, -0.33 to 0.38). <u>Medium Dose Buprenorphine Maintenance vs Placebo</u>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There was a benefit for buprenorphine above placebo in terms of retaining patients in treatment (RR, 1.74; 95% CI, 1.06 to 2.87). Patients in the buprenorphine group had less heroin use as indexed by morphine positive urines (95% CI, -0.47 to 0.10). For cocaine use, there was an advantage for placebo in one study (95% CI, 0.05 to 0.94). For benzodiazepine use, buprenorphine was more effective than placebo in one study (95% CI, -1.27 to -0.36). <u>High Dose Buprenorphine Maintenance vs Placebo</u> There was a benefit for buprenorphine above placebo in terms of retaining patients in treatment (RR, 1.74; 95% CI, 1.02 to 2.96). Patients in the buprenorphine group had less heroin use when receiving 16mg of buprenorphine than placebo patients (95% CI, -0.95 to -0.51). There was no significant difference among the treatment groups in cocaine use (95% CI, -0.20 to 0.36) or benzodiazepine use (95% CI, -0.52 to 0.02). Secondary: Not reported
Kakko et al.[121] (2007) Buprenorphine-naloxone (stepped treatment) vs methadone (maintenance treatment)	RCT Patients >20 years of age with heroin dependence for >1 year	N=96 24-day induction phase, followed by a 6 month follow-up phase	Primary: Retention in treatment Secondary: Completer analyses of problem severity (Addiction Severity Index); proportion of urine samples free of illicit drugs	Primary: The six-month retention was 78% with buprenorphine-naloxone stepped treatment and methadone maintenance therapy being virtually identical (adjusted OR, 1.02; 95% CI, 0.65 to 1.60). The proportion of urine samples free of illicit opiates over time increased and ultimately reached approximately 80% in both arms at the end of the study (P=0.00003). No difference between the two groups was found (P=0.87). Secondary: Problem severity as measured by the Addiction Severity Index decreased over time (P<0.000001). No difference between the treatment arms was found (P=0.90).
Kamien et al.[122] (2008)	DB, DD, RCT Patients ≥18 years	N=268 17 weeks	Primary: Amount of opioid abstinence	Primary: The percentage of opioid-free urine samples over time did not differ significantly among drug groups (P=0.81) or among drug doses (P=0.46).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Buprenorphine-naloxone 8-2 mg daily vs buprenorphine-naloxone 16-4 mg daily vs methadone 45 to 90 mg daily	of age who met criteria for opioid dependence and who were using heroin or prescription opioids or receiving methadone maintenance treatment		achieved over time Secondary: Proportion of patients who achieved 12 consecutive opioid-negative samples, proportion of patients with successful inductions, medication compliance, non-opioid illicit drug use, and treatment retention	Secondary: The proportion of patients who had at least 12 consecutive opioid-negative urine samples were as follows: 10% (buprenorphine-naloxone 8-2 mg) 17% (buprenorphine-naloxone 16-4 mg), 12% (methadone 45 mg), and 16% (methadone 90 mg). The percentage of patients with at least 12 consecutive opioid-negative urine samples differed by dose (8 vs 16 mg buprenorphine-naloxone; P<0.001, 45 vs 90 mg methadone; P=0.02), but not by drug (8 mg buprenorphine-naloxone vs 45 mg methadone; P=0.18, 16 mg buprenorphine-naloxone vs 90 mg methadone; P=0.22). Those receiving higher doses of methadone or buprenorphine-naloxone were more likely to have at least 12 consecutive opioid-negative urine samples than those receiving lower doses. Successful inductions occurred in 80.5, 81.0, 82.7 and 82.9% of the patients receiving buprenorphine-naloxone 8-2 mg, buprenorphine-naloxone 16-4 mg, methadone 45 and 90 mg, respectively. There were no significant differences among the treatment groups (P=0.22 to P=0.98). Medication compliance did not differ significantly among the treatment groups (P=0.41). Non-opioid drug use did not change significantly over time, nor did it differ significantly across groups (P=0.32 to P=0.83). Treatment retention did not differ significantly in the low dose groups (P=0.09) or in the high dose groups (P=0.28).
Strain et al.[123] (2000) Buprenorphine 4 mg to 16 mg per day vs buprenorphine-	DB, DD, PC Adults with active opioid abuse, but not physically dependent	N=7	Primary: Peak drug effect; physiologic and psychomotor measures Secondary: Not reported	Primary: Dose-related increases in ratings of Drug Effects, High, Good Effects, and Liking were seen for hydromorphone, for buprenorphine, and for the combination of buprenorphine-naloxone. The predominant effects were seen with the highest doses tested (hydromorphone 4 mg, buprenorphine-naloxone 8-2 and 16-4 mg, and buprenorphine 8 and 16 mg). None of the treatments produced significant changes in ratings of Bad Effects or Sick. For ratings of Drug Effects, only the two higher doses of buprenorphine alone (8 and 16 mg) produced significantly increased ratings compared to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
naloxone sublingual tablets 1-0.25, 2-0.5, 4-1, 8-2, 16-4 mg per day vs hydromorphone 2 and 4 mg IM vs placebo				placebo (P<0.05 and P<0.01, respectively). The combination dose of 8-2 mg and 16-4 produced ratings of drug effects that were lower than those produced by the buprenorphine dose of 8 mg. The differences between buprenorphine alone and buprenorphine-naloxone doses were not statistically significant for these or any other measures. None of the treatments produced significant changes on measures of blood pressure, heart rate, or respiratory rate. There were no significant differences in psychomotor effects among the treatments. Secondary: Not reported

Drug abbreviations: BID=twice daily, CR=controlled release, ER=extended-release, IM=intramuscular, IR=immediate release, IV=intravenous, SR=sustained-release
Study abbreviations: AC=active control, CI=confidence interval, DB=double-blind, DD=double dummy, DR=dose ranging, ES=extension study, HR=hazard ratio, ITT=intention-to-treat, MA=meta-analysis, MC=multicenter, MD=multi-dose, OL=open label, OR=odds ratio, OS=observational study, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RR=relative risk, SA=single-arm, SC=single center, SD=standard deviation, SE=standard error, SEM=standard error of mean, WMD=weighted mean difference, XO=crossover
Miscellaneous abbreviations: APAP=acetaminophen, ASA=American Society of Anesthesiologists, AUCMBavg=average area under the curve of VAS scores overtime between baseline and end of study, BPI=Brief Pain Inventory, BTP=breakthrough pain, CGI=Clinical Global Impression, CHQ=Child Health Questionnaire, COX-2=cyclooxygenase 2, CRPS=Complex Regional Pain Syndrome, ED=emergency department, MPI=multidimensional pain inventory, NSAIDs=non-steroidal anti-inflammatory drugs, OA=osteoarthritis, PAR=hourly pain relief, PaCO2=partial pressure of arterial carbon dioxide, PCA=patient-controlled analgesia, PDI=Pain Disability Index, PGIC=Patient's Global Impression of Change, PID=Pain Intensity Differences, PPS=Play Performance Scale, PRRS=pain relief rating scale, PVA=pain visual analog scale, RDQ=Roland disability questionnaire, SF-36=Short-Form health survey 36 questions, SPID=Summed Pain Intensity Differences, TOTPAR=Total Pain Relief, VAS=visual analog scale, WHO=World Health Organization, WOMAC index=Western Ontario and McMaster Universities Index

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription.

Table 24. Relative Cost of the Opiate Agonists

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Alfentanil	injection^	Alfenta®*	$$$	$-$$
Codeine	tablet	N/A	N/A	$
Fentanyl	buccal lozenge, buccal tablet, injection, nasal spray, sublingual spray, sublingual tablet, transdermal patch	Abstral®, Actiq®*, Duragesic®*, Fentora®, Lazanda®, Sublimaze®*, Subsys®	$$$$$	$$$
Hydromorphone	injection, liquid, rectal suppository, tablet	Dilaudid®*	$$-$$$$$	$
Levorphanol	tablet	N/A	N/A	$$$
Meperidine	injection, solution, tablet	Demerol®*	$$$	$
Methadone	injection, oral concentrate, solution, tablet	Dolophine®*, Methadose®*	$$$	$$$
Morphine	epidural, injection, rectal	Astramorph-PF®, Duramorph®, Infumorph®	$$$$-$$$$$	$$$

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
	suppository, solution, tablet			
Oxycodone	capsule, oral concentrate, solution, tablet	Oxecta®, Roxicodone®*	$$$-$$$$$	$$
Oxymorphone	injection, tablet	Opana®*	$$$$$	$$$$$
Remifentanil	injection^	Ultiva®	$$$-$$$$$	N/A
Sufentanil	injection^	Sufenta®*	$$$-$$$$$	
Tapentadol	extended-release tablet, tablet	Nucynta®, Nucynta ER®	$$$$$	N/A
Tramadol	extended-release capsule, extended-release tablet, tablet	Conzip ER®*, Ultram®*, Ultram ER®*	$$$-$$$$$	$
Combination Products				
Codeine and acetaminophen	elixir, suspension, tablet	Capital w/Codeine®, Tylenol-Codeine No.3®*, Tylenol-Codeine No.4®*	$-$$$	$
Codeine, butalbital, acetaminophen, and caffeine	capsule	Fioricet With Codeine®*	$$$$	$$$
Codeine, butalbital, aspirin, and caffeine	capsule	Fiorinal With Codeine®*	$$-$$$	$
Dihydrocodeine, acetaminophen, and caffeine	capsule	N/A	N/A	$$$$
Dihydrocodeine, aspirin, and caffeine	capsule	Synalgos-DC®*	$$$	$$$$
Hydrocodone and acetaminophen	solution, tablet	Hycet®*, Lorcet HD®*, Lorcet Plus®*, Lortab®*, Norco®*, Verdrocet®*, Vicodin®*, Vicodin ES®*, Vicodin HP®*, Xodol®*, Zamicet®*	$$$-$$$$	$
Hydrocodone and ibuprofen	tablet	Ibudone®*, Reprexain®*, Vicoprofen®*, Xylon®*	$$-$$$	$$
Opium and belladonna	rectal suppository	N/A	N/A	$$$$$
Oxycodone and acetaminophen	extended-release tablet, solution, tablet	Percocet®*, Primlev®, Xartemis XR®	$$$$-$$$$$	$
Oxycodone and aspirin	tablet	Percodan®*	$$$	$$
Oxycodone and ibuprofen	tablet	N/A	N/A	$
Tramadol and acetaminophen	tablet	Ultracet®*	$$-$$$$$	$

*Generic is available in at least one dosage form or strength.
^Product is primarily administered in an institution.
N/A=Not available

X. Conclusions

Currently, there is no standard treatment regimen that will satisfy the needs of all patients with pain. The opiate agonists are considered to be the most potent analgesics available and are frequently prescribed for the treatment of acute pain, chronic pain, and palliative care. They are available in a variety of dosage forms as single entity

agents, as well as in combination with acetaminophen, aspirin, butalbital, caffeine, and ibuprofen. All of the products are available in a generic formulation, with the exception of remifentanil and tapentadol.

Patients with cancer often suffer from pain due to tumor infiltration, which significantly affects their quality of life. For the treatment of cancer pain, guidelines recommend the use of an opiate agonist in patients with moderate to severe pain. For patients with continuous pain, it is appropriate to prescribe opioids around-the-clock and provide supplemental doses for breakthrough pain. Long-acting formulations are recommended in patients whose pain is controlled on stable doses of short-acting opioids, or for patients who require >4 breakthrough doses per day. Guidelines do not give preference to one opiate agonist over another for the treatment of cancer pain.[18,20]

For the treatment of chronic noncancer pain, guidelines recommend the use of an opiate agonist in patients with moderate to severe pain.[19,21,23,24] The selection of therapy should be based on patient preference, ease of administration, prior treatment trials, tolerance, adverse events, and risk for misuse or abuse.[21,23,14] The Veterans Health Administration, Department of Defense guidelines recommend that an opiate agonist with a long duration of action be used in patients experiencing continuous chronic pain.[23] However, the American Pain Society/American Academy of Pain Medicine guidelines state that there is insufficient evidence to recommend short-acting vs long-acting opioids, or as needed vs around-the-clock dosing of opioids.[24] Guidelines do not give preference to one opiate agonist over another for the treatment of noncancer pain, although it is generally agreed that morphine is a reasonable initial agent.[19,21,23,24] The efficacy of the opiate agonists for the acute treatment of noncancer pain has been demonstrated in short-term trials; however, the available evidence is variable for the long-term (>6 months) treatment of chronic noncancer pain.[28-107]

Interventions for opioid-related conditions (dependence, abuse, intoxication, and withdrawal) include psychosocial therapy and pharmacotherapy. The selection of therapy should be based on patient preference, past response to therapy, probability of achieving and maintaining abstinence, and the effects of continued use of opioids.[9] For the maintenance treatment of opioid dependence, guidelines recommend the use of methadone or the combination product buprenorphine and naloxone as first-line therapy.[9,25-27] Maintenance treatment with methadone has been shown to decrease illicit opioid use, decrease morbidity and mortality, decrease criminal activity, improve health status and social functioning, and reduce the spread of Human Immunodeficiency Virus infection among intravenous drug users. Studies directly comparing methadone to buprenorphine (with or without naloxone) have shown mixed results, which is thought to be due to differences in the dosing regimens used.[9,107-123] Serious adverse events have occurred in patients receiving methadone, including death, respiratory depression and cardiac arrhythmias.[4-6] These adverse events may have been caused by unintentional overdoses, drug interactions, and/or cardiac toxicities (QT prolongation and Torsades de Pointes).[124] Methadone's pharmacokinetic properties, as well as high inter-patient variability in its absorption, metabolism, and analgesic potency, require an individualized approach to prescribing.[4-6]

Within the past several years, the Food and Drug Administration (FDA) notified healthcare providers about an increased risk of suicide with tramadol.[10] An additional safety communication regarding the risks of using tramadol in children aged 17 years and younger was released in September 2015. The FDA is reviewing available information on the rare but serious risk of slowed or difficult breathing and will communicate final conclusions when the review is complete.[11]They also recommended against the continued prescribing and use of propoxyphene-containing products and asked manufacturers to voluntarily remove these products from the United States market.[12] The FDA has also asked manufacturers to limit the amount of acetaminophen in prescription drug products (which are predominantly combinations of acetaminophen and opioids) to 325 mg per dosage form to make these products safer for patient to use, has asked health care professionals to discontinue prescribing and dispensing prescription combination drug products with over 325 mg of acetaminophen, and has made efforts to reduce the misuse and abuse of extended release/long acting opioids.[13-15]

In September 2013, the FDA announced labeling changes for all extended-release and long-acting opioids, and the changes were finalized in April 2014. Safety labeling across the class now includes an updated indication stating that these agents are indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or otherwise inadequate. The FDA requires a new boxed warning regarding the risk of neonatal opioid withdrawal syndrome when these agents are used during pregnancy, and also requires the manufacturers of extended-release and long-acting opioids to conduct postmarket studies further

assessing the known risks of misuse, abuse, hyperalgesia, addiction, overdose, and death. These changes are incorporated into the Risk Evaluation and Mitigation Strategy (REMS) program.[16]

There is insufficient evidence to support that one brand opiate agonist is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand opiate agonists within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand opiate agonist is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

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