Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Clinical Packet
August 8, 2012

Table of Contents

Helpful Hints/Reference Document.....2

External Criteria
Alzheimer's Agents 5
Antidepressants 6
Cerebral Stimulants/Agents Used for ADD/ADHD 7
Anxiolytics/Sedatives/Hypnotics 9
Genitourinary Smooth Muscle Relaxants 10
Antidiabetic Agents 11

Agenda 12

Pharmacotherapy Class Re-Reviews
Pharmacotherapy Review of Alzheimer's Agents 13
Pharmacotherapy Review of Antidepressants 75
Pharmacotherapy Review of Cerebral Stimulants/Agents Used for ADHD 238
Pharmacotherapy Review of Anxiolytics, Sedatives and Hypnotics – Barbiturates 333
Pharmacotherapy Review of Anxiolytics, Sedatives and Hypnotics – Benzodiazepines.....354
Pharmacotherapy Review of Anxiolytics, Sedatives and Hypnotics – Miscellaneous.....412
Pharmacotherapy Review of Genitourinary Smooth Muscle Relaxants.....474

New Drug Review
New Drug Pharmacotherapy Review – Tradjenta® (linagliptin) 561

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
- 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, OTC 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, OTC 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, OTC 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, OTC, 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 ADD/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 ADD/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 ADD/ADHD, either generic, OTC or brand, within the past 6 months.

- If the request is for a *long-acting* cerebral stimulant/agent used for ADD/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 ADD/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 Intuniv®, the patient must also have failed a 30-day treatment trial with immediate-release guanfacine within the past 6 months. In addition, 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. In addition, 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.

- 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 ADD/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.

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.

Antidiabetic 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 two prescribed and preferred antidiabetic agents, either generic, OTC or brand, within the past 12 months, or have a documented allergy or contraindication to all preferred agents in this class.

- If the request is for Avandia®, Avandamet®, or Avandaryl®, the patient must also have failed a 30-day treatment trial with at least two prescribed and preferred antidiabetic agents (of which one is Actos®), either generic, OTC or brand, within the past 6 months.

- If the request is for Symlin®, the patient must also be on insulin therapy and have a hemoglobin A1c greater than 7% despite more than 90 days of insulin therapy.

Stable Therapy

- Approval may be given for 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)

- Antidiabetic agents, excluding Symlin®, 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

August 8, 2012
9:00 a.m. – 12:00 noon

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1. Opening remarks……...……..Chair
2. Approval of May 9, 2012 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® only)
   - Antidepressants – AHFS 281604
   - Cerebral Stimulants/Agents Used for ADHD
     - Central Alpha-Agonists – AHFS 240816 (to include Kapvay® only)
     - Amphetamines – AHFS 282004 (to include Adderall®, Adderall XR®, Desoxyn®, Dexedrine®, Procentra®, and Vyvanse® only)
     - Anorexigenic Agents and Respiratory and Cerebral Stimulants, Miscellaneous – AHFS 282092 (to include Concerta®, Daytrana®, Focalin®, Focalin XR®, Metadate CD®, Metadate ER®, Methylin®, Nuvigil®, Provigil®, Ritalin®, Ritalin LA®, and Ritalin-SR® only)
     - Central Nervous System Agents, Miscellaneous – AHFS 289200 (to include Intuniv®, Strattera®, 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
6. New drug review…University of Massachusetts Medical School Clinical Pharmacy Services
   - Tradjenta® (Dipeptidyl Peptidase-4 (DPP-4) Inhibitors) – AHFS 682005
7. Results of voting announced……...……...…….Chair
8. New business
   - Election of Committee's chair and vice chairperson
9. Next meeting date: November 14, 2012
10. 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
August 8, 2012

I. Overview

Alzheimer's disease is a progressive neurodegenerative disorder in older adults that affects cognition, behavior and activities of daily living.[9] It is the most common form of dementia and the average life expectancy from the onset of symptoms to death is approximately 8 to 10 years.[9-11] Diagnostic features include memory impairment and one or more of the following: aphasia, apraxia, agnosia, and/or disturbance in executive functioning.[9]

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.[10-11] 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.[11]

There are 4 agents approved for the treatment of Alzheimer's disease, including cholinesterase inhibitors (donepezil, galantamine and rivastigmine) and an NMDA receptor antagonist (memantine).[1-8] 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 Alzheimer's agents that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Donepezil, galantamine and rivastigmine are available in a generic formulation. This class was last reviewed in February 2010.

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®*, Aricept ODT®*
Galantamine	extended-release capsule, solution, tablet	Razadyne®*, Razadyne ER®*	galantamine
Rivastigmine	capsule, solution, transdermal patch	Exelon®*	rivastigmine
Central Nervous System Agents, Miscellaneous			
Memantine	solution, tablet	Namenda®	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)
American College of Physicians (ACP)/American Academy of Family Physicians (AAFP): **Current Pharmacologic Treatment of Dementia: A Clinical Practice Guideline[15] (2008)**	• 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 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.
European Federation of Neurological Societies (EFNS): **Recommendations for the Diagnosis and Management of Alzheimer's Disease and other Disorders Associated with Dementia[17] (2007)**	• In patients with Alzheimer's disease (AD), treatment with cholinesterase inhibitors should be considered at the time of diagnosis. • In patients with moderate to severe AD, treatment with memantine can be considered, alone or in combination with a cholinesterase inhibitor. • Realistic expectations for treatment effects and potential side effects should be discussed with the patient and caregivers. • Currently, there is insufficient evidence to consider the use of gingko biloba, anti-inflammatory drugs, selegiline, estrogens, vitamin E or statins in the treatment or prevention of AD.
American Psychiatric Association (APA): **Practice Guideline for the Treatment of Patients with Alzheimer's Disease and other Dementias[18] (2007)**	• 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.

Clinical Guideline	Recommendation(s)
	• 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 4 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 (NSAIDs), 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 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 FDA 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 (AAN): **Practice Parameter: Management of Dementia**[16] **(2003)**	• Significant treatment effects have been demonstrated with several different cholinesterase inhibitors, indicating that the class of agents is consistently better than placebo. However, the disease eventually continues to progress despite treatment, and the average "effect size" is modest. • To date, there have been no head-to-head comparisons of cholinesterase inhibitors, and the main differences between these agents are in the side-effect profiles and the ease of administration (e.g., once or twice versus four times daily dosing). • Vitamin E (1,000 IU twice daily) should be considered in an attempt to slow progression of AD. • There is insufficient evidence to support the use of other antioxidants, anti-inflammatories, or other putative disease-modifying agents specifically to treat AD because of the risk of significant side effects in the absence of demonstrated benefits. • Estrogen should not be prescribed to treat AD.
American Academy of Neurology (AAN): **Practice Parameter: Evaluation and Treatment of Depression, Psychosis, and Dementia in Parkinson Disease**[39] **(2006)**	• For patients with Parkinson's disease (PD) dementia or dementia with Lewy bodies (DLB), rivastigmine is probably effective in improving cognitive function. However, the magnitude of the benefit is modest and tremor may be exacerbated. • For patients with PD 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 PD.

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 Alzheimer's Agents[1-8]

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

IV. Pharmacokinetics

The pharmacokinetic parameters of the Alzheimer's agents are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Alzheimer's Agents[1-8]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Parasympathomimetic (Cholinergic Agents)					
Donepezil	100	96	Liver	Renal (57) Feces (9-15)	70
Galantamine	90	18	Liver (75)	Renal (95) Feces (5)	7
Rivastigmine	Oral: 36-72	40	Liver, extensive Brain, extensive	Renal (>90)	Oral: 1.4-1.7 Transdermal: 3
Central Nervous System Agents, Miscellaneous					
Memantine	100	45	Liver, partial	Renal (48-50)	60-80

V. Drug Interactions

There are no significant drug interactions reported with the Alzheimer's agents.[1]

VI. Adverse Drug Events

The most common adverse drug events reported with the Alzheimer's agents are listed in Table 5.

Table 5. Adverse Drug Events (%) Reported with the Alzheimer's Agents[1-8]

Adverse Events	Parasympathomimetic (Cholinergic Agents)			Central Nervous System Agents, Miscellaneous
	Donepezil	Galantamine	Rivastigmine	Memantine
Cardiovascular				
Angina pectoris	-	-	≥1	-
Atrial fibrillation	≥1	-	≥1	-
Bradycardia	≥1	2	≥1	-
Chest pain	1-2	≥1	-	-
Heart failure	-	-	≥1	≥1
Hemorrhage	2	-	-	-
Hypertension	1-3	-	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	-	-	4-5; 3*	≥2
Aphasia	≥1	-	-	-
Bradykinesia	-	-	≥1	-
Cerebrovascular accident	-	-	-	≥1
Confusion	2	-	1-8	6
Convulsion	≥1	-	≥1	-
Delusions	≥1	-	-	-
Depression	2-3	7	1-6; 4*	≥2
Dizziness	2-8	9	6-21; 2-7*	7
Dyskinesia	-	-	≥1	-
Emotional lability	2	-	-	-
Fatigue	5	5	4-9; 2*	2
Gait abnormality	-	-	≥1	≥2
Hallucination	3	-	4	3
Headache	4-10	8	4-17; 3-4*	6
Hostility	3	-	-	-
Hypokinesia	-	-	-	≥1
Insomnia	5-9	5	3-9; 1-4*	≥2
Irritability	≥1	-	-	-
Malaise	-	≥1	5	-
Nervousness	1-3	-	-	-
Paranoid reaction	-	-	≥1	-
Paresthesia	≥1	-	≥1	-
Parkinson's disease worsening	-	-	3	-
Parkinsonism	-	-	2	-
Personality disorder	2	-	-	-
Restlessness	≥1	-	≥1	-

Adverse Events	Parasympathomimetic (Cholinergic Agents)			Central Nervous System Agents, Miscellaneous
	Donepezil	Galantamine	Rivastigmine	Memantine
Somnolence	2	4	4-5	3
Transient ischemic attack	-	-	≥1	≥1
Tremor	≥1	3	4-10; ≥1*	-
Vertigo	≥1	-	≥1; 0-2*	≥1
Wandering	≥1	-	-	-
Dermatological				
Diaphoresis	≥1	-	4	-
Eczema	3	-	-	-
Pruritus	≥1	-	≥1*	-
Rash	≥1	-	≥1	≥1
Skin ulcer	≥1	-	-	-
Urticaria	≥1	-	-	-
Gastrointestinal				
Abdominal pain	≥1	5	4-13; 2-4*	-
Anorexia	4-8	7-9	6-17; 3-9*	≥2
Bloating	≥1	-	-	-
Constipation	≥1	-	5; ≥1*	5
Diarrhea	10	6-12	7-19; 6-10*	≥2
Dyspepsia	≥1	5	1-9	-
Epigastric pain	≥1	-	-	-
Eructation	-	-	2	-
Fecal incontinence	≥1	-	≥1	-
Flatulence	-	≥1	4	-
Gastritis	-	-	≥1; ≥1*	-
Gastrointestinal bleeding	≥1	-	-	-
Nausea	6-11	13-24	29-47; 7-21*	≥2
Toothache	≥1	-	-	-
Vomiting	5-8	6-13	17-31; 6-19*	3
Weight decrease	1-3	5-7	3; 3-8*	≥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	-
LDH increased	≥1	-	-	-
Musculoskeletal				
Arthralgia	-	-	-	≥2
Arthritis	1-2	-	≥1	-
Asthenia	≥1	≥1	2-6; 2-3*	-
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	7-13	-	-	-
Accidental trauma	-	-	1-10	-
Allergy	-	-	≥1	-
Anemia	-	3	≥1; ≥1*	≥1
Dehydration	1-2	-	1-2; ≥1*	-
Ecchymosis	4-5	-	-	-
Edema	≥1	-	≥1	-
Epistaxis	-	-	≥1	-
Fall	-	-	≥1*	≥2
Fever	2	≥1	≥1	-
Flu syndrome	≥1	-	3	≥2
Hot flashes	≥1	-	≥1	-
Infection	1-11	-	-	-
Inflicted injury	-	-	-	≥2
Influenza	≥1	-	-	-
Pain	3-9	-	-	3

- Event not reported
*Transdermal patch

VII. Dosing and Administration

The usual dosing regimens for the Alzheimer's agents are listed in Table 6.

Table 6. Usual Dosing Regimens for the Alzheimer's Agents[1-8]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Parasympathomimetic (Cholinergic Agents)			
Donepezil	Mild-to-Moderate Alzheimer's Disease: 5 to 10 mg once daily Moderate-to-Severe Alzheimer's Disease: 10 to 23 mg once daily	Safety and efficacy in children have not been established.	Orally disintegrating tablet: 5 mg 10 mg Tablet: 5 mg 10 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
			23 mg
Galantamine	Mild-to-Moderate Alzheimer's Disease: Capsule (ER): Initial, 8 mg once daily; maintenance, 16-24 mg/day once daily Solution/tablet (IR): Initial, 4 mg twice daily; maintenance, 16-24 mg/day divided twice daily	Safety and efficacy in children have not been established.	Capsule (ER): 8 mg 16 mg 24 mg Solution (IR): 4 mg/ml Tablet (IR): 4 mg 8 mg 12 mg
Rivastigmine	Mild-to-Moderate Alzheimer's Disease: Capsule/solution: Initial, 1.5 mg twice daily; maintenance, 6-12 mg/day twice daily Transdermal patch: Initial, 4.6 mg/24 hours; maintenance, 9.5 mg/24 hours Mild-to-Moderate Dementia Associated with Parkinson's Disease: Capsule/solution: Initial, 1.5 mg twice daily; maintenance, 3-12 mg/day twice daily Transdermal patch: Initial, 4.6 mg/24 hours; maintenance, 9.5 mg/24 hours	Safety and efficacy in children have not been established.	Capsule: 1.5 mg 3 mg 4.5 mg 6 mg Solution: 2 mg/ml Transdermal patch: 4.6 mg/24 hours 9.5 mg/24 hours
Central Nervous System Agents, Miscellaneous			
Memantine	Moderate-to-Severe Alzheimer's Disease: Initial, 5 mg once daily; maintenance, 20 mg/day divided twice daily	Safety and efficacy in children have not been established.	Solution: 10 mg/5 ml Tablet: 5 mg 10 mg Tablet dose pack: 5 mg-10 mg

ER=extended-release; IR=immediate-release

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the Alzheimer's agents are summarized in Table 7.

Table 7. 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.[19] (2003) Donepezil 5 mg/day	OS Patients with Alzheimer's disease	N=1,115 Variable duration	Primary: Time to nursing home placement	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 9-12 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.
Burns et al.[50] (2007) Donepezil 5-10 mg/day	OL, MC 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 (AE)	Primary: Mean changes in ADAS-cog scores of all patients were improved by approximately 2 points after 6 weeks (cumulative week 36) and 1 point after 12 weeks (cumulative week 42), with improvement compared with the start of open-label 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 open-label treatment. From 24 weeks, ADAS-cog scores declined over the remainder of the study. At the end of 132 weeks of open-label treatment (162 weeks total follow-up), the change from double-blind baseline was 15.6 points for all patients. No difference was seen between patients who had previously received placebo in the double-blind 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 open-label treatment and then slowly declined for the remainder of the study period (up to cumulative week 162). Mean IDDD total scores were maintained over the first 24 weeks of open-

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				label 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 open-label extension, QoLS scores were improved compared to baseline, with a mean change of 3.03. The scores remained above the baseline level at weeks 6 and 12 of open-label treatment. At the end of 132 weeks of open-label treatment, the decline from the baseline for the double-blind study was -46.2. Overall, 85% of patients experienced at least one treatment-emergent adverse event (AE). The most common AEs included diarrhea (12%), nausea (11%), infection (11%) and accidental injury (10%). Nonfatal all-causality and treatment-related serious AEs were reported for 25% and 7% of patients, respectively. Seventeen patients died during the study or within 4 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 5 of treatment and another due to a suspected myocardial infarction on day 55, were considered by the investigators to be possibly related to donepezil.
Hashimoto et al.[91] (2009) Donepezil 5 mg/day	PRO, OS Patients with Alzheimer's disease	N=416 12 weeks	Primary: Japanese version of the Zarit Caregiver Burden Interview (J-ZBI), MMSE, BPSD	Primary: There were significant changes in mean scores on the J-ZBI (-1.9; P<0.01) and 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. There was no significant decrease in the time spent supervising AD patients. In patients with BPSD, there was a significant decrease in J-ZBI scores over the 12 weeks (P=0.013). In patients without BPSD, the decrease in the J-ZBI score was not significant (P=0.418).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Homma et al.[80] (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 1–12 and diagnosis confirmed by neuroimaging)	N=189 52 weeks	Primary: SIB, ADCS-ADL-sev, and BEHAVE-AD	Primary: The mean change in SIB scores during the open-label 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 open-label study) was –6.1. The mean change in SIB declined more rapidly after 24 weeks. A gradual deterioration in the ADCS-ADL-sev was observed during the open-label study, reflecting disease progression. The change from baseline to weeks 24 and 52 were –2.0 and –5.3, respectively. For the BEHAVE-AD, little change was observed during the open-label 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 (AE). Severe AEs were reported by 15 patients (7.9%) and serious AEs were reported by 33 patients (17.5%). The most common AEs were nasopharyngitis, diarrhea, nausea and vomiting.
Courtney et al.[20] (2004) Donepezil 5-10 mg/day vs placebo	DB, RCT Patients with Alzheimer's disease	N=565 156 weeks	Primary: MMSE, BADLS, time to entering institution	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 2 years. No significant benefits were seen with donepezil compared with placebo in institutionalization (42% vs 44% at 3 years; P=0.4) or progression of disability (58% vs 59% at 3 years; P=0.4). The relative risk of entering institutional care in the donepezil group compared with placebo was 0.97 (95% CI: 0.72 to 1.30; P=0.8); the relative risk of progression of disability or entering institutional care was 0.96 (95% CI: 0.74 to 1.24; P=0.7). Similarly, no significant differences were seen between donepezil and placebo in behavioral and psychological symptoms, caregiver psychopathology, adverse events or deaths, or between 5 mg and 10 mg

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				donepezil.
Winblad et al.[24] (2006) RCT Donepezil 10 mg/day vs placebo OL 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 open-label 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 3-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 3-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) Donepezil 5 mg/day vs donepezil 10 mg/day vs placebo	DB, MC, PC, RCT Patients with mild-to-moderate Alzheimer's disease	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 to adverse effects were 7%, 6%, and 16% in the placebo, 5 mg 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 mg and 10 mg treatment showed no statistical difference in improvements.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Winblad et al.[23] (2006) Donepezil 10 mg/day vs placebo	DB, PC, PG Patients ≥50 years of age with severe Alzheimer's disease (MMSE score of 1-10 and a FAST rating of stage 5-7c)	N=248 6 months	Primary: SIB and Modified ADCS-ADL-severe Secondary: MMSE, NPI, and CGI-I	Primary: At 6 months, patients assigned donepezil had significantly better mean change from baseline scores than those taking placebo on both SIB and ADCS-ADL-severe (all P<0.05). Secondary: CGI-I scores and the mean change from screening scores on the MMSE at 6- 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.[22] (2007) Donepezil 10 mg/day vs placebo	DB, MC, PC, RCT Patients ≥50 years of age with severe Alzheimer's disease (MMSE score of 1-12, modified Hachinski Ischemic score ≤6, and FAST score of ≥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 not significant (P=0.3574). On the NPI, donepezil was not significantly different from placebo (P=0.4612). The donepezil group showed significant improvement from screening to endpoint on the MMSE compared with 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.[61] (2008) Donepezil 5-10 mg/day	RCT, MC, DB, PC Japanese patients ≥50 years of age with severe	N=302 24 weeks	Primary: SIB and CIBIC-Plus Secondary:	Primary: Donepezil 5 mg/day 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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	Alzheimer's disease (modified Hachinski Ischemic Score ≤6, FAST ≥6, MMSE score of 1–12 and diagnosis confirmed by neuroimaging)		ADCS-ADL-sev and BEHAVE-AD	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 7 categories of change as well as the 3 collapsed categories of improved, no change and worsened. In the 7-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 (AEs) were reported by 73.3% of placebo patients, 78.2% of donepezil 5 mg/day patients and 83.3% of donepezil 10 mg/day patients. There was no significant difference in AEs between the donepezil groups and the placebo group. The most common AEs reported are consistent with the known cholinergic side effects of donepezil. Serious AEs 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 7 days after completion) and arrhythmia (donepezil 10 mg/day group).
Birks et al.[21]	MA	N=5,796	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2006) Donepezil 5-10 mg/day vs placebo	Patients with Alzheimer's disease	(24 trials) 12-60 weeks	ADAS-Cog, MMSE, CIBIC-Plus, ADL, withdrawals and adverse events	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 mg/day 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 mg/day and 10 mg/day treatment groups as compared to placebo are: anorexia, diarrhea, and muscle cramps.
Wallin et al.[25] (2007) Donepezil 5-10 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	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 4-9 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 2 months, 34% of patients were considered improved, 59% unchanged and 7% were worse. At 6 months, 28% of patients were

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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 6 months was 1.01, at 12 months 2.19, and at 36 months 6.18.
Farlow et al.[107] (2010) Donepezil 10 mg/day vs donepezil 23 mg/day	DB, RCT, MC 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	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 AD compared to less impaired patients (SIB, +1.6 vs -1.5, respectively; P<0.001; CIBIC+, 4.31 vs 4.42; P=0.028). TEAEs 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 TEAEs were nausea (6.1%), vomiting (5%) and diarrhea (3.2%). Severe TEAEs 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 TEAEs were nausea (1.9%), vomiting (0.8%) and diarrhea (1.5%). Severe TEAEs that were reported included nausea (0.2%) and dizziness (0.2%).
Ferris et al.[108] (2011)	DB, RCT, MC (post-hoc analysis)	N=1,467 24 weeks	Primary: SIB-Language scale (SIB-L) and	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Donepezil 10 mg/day vs donepezil 23 mg/day	Patients 45 to 90 years of age with moderate-to-severe Alzheimer's disease who took donepezil 10 mg/day ≥12 weeks		21-item SIB-derived language scale (SIB[lang]) Secondary: Correlation of SIB-L and SIB[lang] with ADCS-ADL-sev, CIBIS-plus/CIBIC-plus, and MMSE	mg/day (SIB-L treatment difference 0.8, P=0.0013; SIB[lang] treatment difference 0.8, P=0.0009). Secondary: At week 24, SIB-L and SIB[lang] scores were moderately correlated with scores on the ADCS-ADL-sev and CIBIS-plus. Results were similar in both moderate (MMSE 17-20) and severe (MMSE 0-16) Alzheimer's disease patients.
Farlow et al.[109] (2011) Donepezil 10 mg/day vs donepezil 23 mg/day	DB, RCT, MC (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	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 AEs 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). AEs 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 AEs 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 AEs 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).
Wilcock et al.[51] (2003) Donepezil 10	MC, PG, RCT Patients with Alzheimer's disease	N=182 52 weeks	Primary: BrADL Secondary:	Primary: BrADL total score showed no significant difference between treatment groups in mean change from baseline to week 52.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/day vs galantamine 24 mg/day			MMSE, ADAS-Cog, NPI	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 not significant, whereas galantamine treated patients with MMSE scores of 12-18 demonstrated an increase (worsening) in the ADAS-Cog score of 1.61 +/- 0.80 versus baseline, compared with an increase of 4.08 +/- 0.84 for patients treated with donepezil. More caregivers of patients receiving galantamine reported reductions in burden compared with donepezil. Changes from baseline in NPI were similar for both treatments.
Jones et al.[52] (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	Primary: Physicians and caregivers reported statistically significant greater satisfaction/ ease of use with donepezil compared to galantamine at weeks 4 and 12. Significantly greater improvements in cognition were observed for donepezil versus galantamine on the ADAS-Cog at week 12 and at endpoint. Activities of daily living improved significantly in the donepezil group compared with the galantamine group at weeks 4 and 12 (P<0.05). Forty-six percent of galantamine patients reported gastrointestinal adverse events versus 25% of donepezil patients.
Mossello et al.[54] (2004) Donepezil 5-10 mg/day vs	OL, OS Patients with mild-to-moderate Alzheimer's disease	N=407 9 months	Primary: MMSE, ADL and IADL	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%;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
galantamine 16-24 mg/day vs rivastigmine 6-12 mg/day				P=0.01).
Aguglia et al.[55] (2004) Donepezil vs galantamine vs rivastigmine	OL Patients with Alzheimer's disease	N=242 6 months	Primary: MMSE, ADAS-Cog, ADL and IADL	Primary: There were no statistical differences on changes in the MMSE, ADAS-Cog, ADL or IADL measures amongst the 3 groups. There were no differences on changes in the IADL measure among the 3 groups. 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.
Lopez-Pousa et al.[56] (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	Primary: All 3 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Rodda et al.[88] (2009) Donepezil 5-10 mg/day vs galantamine 8-24 mg/day vs rivastigmine 9-17.4 mg/day	RETRO Patients with Alzheimer's disease being treated with donepezil, rivastigmine or galantamine monotherapy	N=6,110 12-170 weeks	Primary: Neuropsychiatric Inventory (NPI) and behavioral and psychological symptoms of dementia (BPSD)	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 open label treatment phase. Of these 4 positive studies, two specified a minimum level of behavioral disturbance at baseline and used behavioral scores as a primary outcome. Ten studies did not find a significant improvement in BPSD with the medications reviewed, though the majority were not specifically designed or powered to detect changes in neuropsychiatric outcomes.
Modrego et al.[92] (2010) Donepezil 10 mg/day vs memantine 20 mg/day	SB, PG, RCT Patients with mild-to-moderate Alzheimer's disease	N=63 6 months	Primary: ADAS-cog, NPI, DAD, changes in N-acetylaspartate (NAA) metabolite levels	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, NAA/Cr ratio in the PCG correlated significantly with the ADAS-cog (P=0.02) and MEC (P=0.02). The NAA/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 NAA/Cr ratios (P=0.004). None of the baseline metabolite levels predicted response to treatment in any of the examined areas.
Howard et al.[89] (2012) Donepezil 10	MC, DB, RCT Community-based patients with	N=295 52 weeks	Primary: Standardized Mini-Mental State Examination	Primary: Mean donepezil vs placebo SMMSE 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/day vs memantine 20 mg/day vs donepezil 10 mg/day and memantine 20 mg/day vs placebo	moderate-to-severe Alzheimer's disease who were taking donepezil 10 mg/day for ≥3 months		(SMME) and Bristol Activities of Daily Living Scale (BADLS) scores Secondary: NPI, DEMQOL-Proxy, caregiver health status assessed by General Health Questionnaire 12 (GHQ-12)	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 6 week assessment than at later time points. From 6 weeks onward, differences were roughly parallel. Mean donepezil + memantine vs placebo + memantine SMMSE 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 not significant. Both donepezil and memantine demonstrated benefits on both SMMSE 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 SMMSE 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 with discontinuation of donepezil therapy (2.3 points lower with continuation; 95% CI, -1.1 to 5.7; P=0.08). Donepezil + memantine vs donepezil 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 GHQ-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%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				CI, -0.1 to 0.9; P=0.03), though significance was not reached to allow for multiple secondary outcomes.
Wilkinson et al.[53] (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	Primary: More patients taking donepezil completed the study (89.3%) compared to the rivastigmine group (69.1%; P=0.009). Approximately 10% of the donepezil group and 21.8% of the rivastigmine group discontinued treatment due to adverse events. Approximately 87% 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 4 and 12.
Wilkinson et al.[90] (2009) Donepezil 5 mg/day vs donepezil 10 mg/day vs placebo	MA Patients with mild-to-moderate Alzheimer's disease	N=906 (3 trials) 24 weeks	Primary: MMSE	Primary: A significantly greater percentage of placebo patients than donepezil-treated patients met the specified criteria for all 3 definitions of clinical worsening (COG, COG+G, and COG+G+F). The odds ratios for clinical worsening were significantly reduced for donepezil-treated patients compared with 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, 18–26) and more moderate (MMSE, 10–17) subgroups were analyzed separately.
Raskind et al.[29] (2004) Galantamine 24 mg/day	OL Patients with mild-to-moderate Alzheimer's disease	N=194 36 months	Primary: ADAS-Cog, adverse events	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

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				treatment. Almost 80% of patients who received galantamine for 36 months seemed to demonstrate cognitive benefits compared with those predicted for untreated patients.
Rockwood et al.[41] (2008) Galantamine 24 mg/day	OL Patients with mild-to-moderate Alzheimer's disease	N=240 48 months	Primary: ADAS-Cog, DAD, adverse events	Primary: The mean ADAS-Cog worsened from 22.6 at baseline to 31.3 at 48 months. The DAD declined from 73.4 to 36.1. The K-means analysis confirmed three clusters of patients; one cluster (n=82) had the lowest rate of progression, another had persistent progression (n=75) and a third was intermediate (n=82). Patients with the least progression started with the highest cognitive function which was stable for 24 months. The intermediate group was stable for ~12 months, whereas the group with persistent decline was stable for about only 6 months. The DAD was relatively stability for all groups for about 12 months, after which decline was similar in shape. Of 240 patients, 51 (21%) withdrew between months 36–48 (nine died and 12 with adverse events). Seven percent of adverse events were rated as 'severe' including falls (5%), pathological fractures (5%), aggressive reactions (4.4%), cerebrovascular disorder (4.4%), injuries (4.4%), and pneumonia (4.4).
Wallin et al.[110] (2011) Galantamine 24 mg/day	PRO, OL, MC Patients with Alzheimer's disease and no previous cholinesterase inhibitor therapy	N=280 36 months	Primary: MMSE, ADAS-cog, IADL, CIBIC Secondary: Subgroup analysis by K-means cluster analysis	Primary: From baseline to 36 months, MMSE decreased from 23.3 to 21.74. The MMSE score was significantly better at 2 months (P<0.001) and at 6 months (P=0.006) compared with baseline, and was stable at 12 months (P=0.616) compared with baseline. The total mean decline in MMSE score from baseline after 3 years of treatment was 2.6 From baseline to 36 months, ADAS-cog increased from 16.85 to 19.39. The total change in ADAS-cog score after 3 years of treatment was 5.6 points above baseline values. The ADAS-cog scores at 6 months were not different from baseline (P=0.248), but deteriorated after that.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Mean IADL scores demonstrated deteriorated at all time points compared to baseline (12.76 to 17.13). According to CIBIC scores at 2 months, 93% of patients remaining in the study were "improved or unchanged", at months 6, 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 with cluster 2 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.[60] (2006) Galantamine 2-50 mg/day	OL, OS, PRO Patients with mild-to-moderate Alzheimer's disease	N=345 6 months	Primary: MMSE, ADAS-Cog, CIBIC-Plus, IADL	Primary: For the MMSE 65% of PP patients had an increased score at the 3-month assessment as compared to baseline with an overall 92% response rate. A total of 70% of PP patients had an increased score at the 6-month assessment as compared to baseline with an overall 91% response rate. A total of 44% of ITT patients had an increased score at the 6-month assessment as compared to baseline. For ADAS-Cog at 6 months, 86% of the PP patients and 33% of the ITT patients had a decrease in ADAS-Cog score. For CIBIC-Plus at 3 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 improved. For CIBIC-Plus at 6 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 6 months. Most PP patients had no change in IADL scores or behavior at 3 and 6 months.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Cummings et al.[30] (2004) Galantamine 8-24 mg/day vs placebo	DB, PC, RCT Patients with mild-to-moderate Alzheimer's disease	N=978 21 weeks	Primary: NPI, caregiver distress related to patients' behavior	Primary: NPI scores worsened with placebo, whereas patients treated with 16 or 24 mg/day of galantamine had no change in NPI scores. 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.
Scarpini et al.[48] (2011) Phase 1 Galantamine 8-16 mg/day Phase 2 Galantamine 16 mg/day vs placebo	Phase 1 OL, MC Phase 2 DB, RCT, MC Mild to moderate Alzheimer's disease in patients ≥50 yo (MMSE 11 – 24)	N=393 36 months	Primary: ADAS-cog/11 deterioration ≥4 points Secondary: CIBIC-plus, AEs	Phase1 Primary: Cognitive functions improved significantly on the ADAS-cog/11 scale with galantamine treatment at month 7 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 open label 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 AEs, of which the most common was gastrointestinal disorders (21.3%), nervous system disorders (9.8%), and psychiatric disorders (19.7%). Serious AEs were reported in 12.2%. Phase 2 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: There were no significant differences between the treatment groups

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				concerning mean values of the CIBIC-plus scale. A total of 34.1% of patients receiving galantamine and 27% of patients receiving placebo experienced AEs. The most common AEs were nervous system disorders (6.6%) and psychiatric disorders (5.3%). Serious AEs were reported in 14.5% of galantamine-treated patients compared to 6.3% of patients in the placebo group.
Kavanagh et al.[94] (2011) Galantamine 16-24 mg/day vs placebo	RCT, OL, PA 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 (2-5 months after reaching maintenance doses)	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.
Burns et al.[70] (2009) Galantamine 24 mg/day vs placebo	RCT, DB, MC, PC Patients aged 40–95 years with severe dementia of the Alzheimer type or probable Alzheimer's disease (MMSE 5–12 points)	N=407 6 months	Primary: SIB, MDS-ADL, and adverse events	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). 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

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				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.
Wilcock et al.[32] (2000) Galantamine 24 mg/day vs galantamine 32 mg/day vs placebo	DB, RCT Patients with mild-to-moderate Alzheimer's disease	N=653 6 months	Primary: ADAS-Cog, adverse events	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 mg and 32 mg dose groups, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Dunbar et al.[33] (2006) Galantamine IR 8-16 or 24 mg/day vs galantamine ER 8-16 or 24 mg/day vs placebo	DB, MC, PC, RCT (Post-hoc analysis) Patients with mild-to-moderate Alzheimer's disease	N=965 7 months	Primary: Nausea and vomiting	Primary: Nausea reports were as follows: 16.9% of the galantamine ER group, 13.8% of galantamine IR group, and 5% 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 (P=0.01). For galantamine ER versus placebo and galantamine ER versus galantamine IR, no significant differences were seen (P=NS). 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.
Brodaty et al.[34] (2005) Galantamine IR 8-16 or 24 mg/day vs galantamine ER 8-16 or 24 mg/day vs placebo	DB, MC, RCT Patients with mild-to-moderate Alzheimer's disease	N=971 6 months	Primary: ADAS-cog/11, CIBIC-Plus Secondary: ADCS-ADL, NPI, ADAS-cog/13, non-memory ADAS-cog/ memory, ADAS-Cog	Primary: Compared to placebo, galantamine ER was significantly more effective with improvement from baseline in ADAS-cog/11 scores (OC 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 IR 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 ER group versus placebo (OC, P=0.003; 95% CI: 0.85 to 4.03; LOCF, P<0.001; 95% CI: 1.09 to 3.91).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The OC analysis was numerically better in treatment response while the LOCF analysis was statistically better for the galantamine group compared to placebo (OC, P=0.088; 95% CI: –0.21 to 2.99; LOCF, P=0.018; 95% CI: 0.22 to 3.04). In galantamine ER and galantamine IR groups versus placebo, OC NPI scores were not statistically significant but instead numerically significant (OC, 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.
Van Puyvelde et al.[93] (2011) Galantamine vs donepezil or rivastigmine (safety control group [SCG])	PRO, MC, OS 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	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 SCG 9.7%); severe: galantamine 11.3% vs SCG 12.9%. A total of 84.5% of patients treated with galantamine continued their treatment after 6 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%), 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).
Loy et al.[31] (2006)	MA	N=6,805 (10 trials)	Primary: CIBIC-plus,	Primary: Statistically significant difference was seen on the global rating scales for

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Galantamine 8-36 mg/day vs placebo	Patients with mild cognitive impairment or Alzheimer's disease	12 weeks to 2 years	ADAS-Cog, ADCS-ADL, DAD, NPI	patients treated with galantamine, at all durations and all doses but 8 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 6 months than 3 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.
Herrmann et al.[106] (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, 7 patients decreased psychotropic medication use during the study, while 3 increased usage; Most remained the same for psychotropic usage.
Bakchine et al.[81] (2007) Memantine 20 mg/day	RCT, DB, PC, MC Patients ≥50 years of age with mild-to-moderate Alzheimer's disease	N=470 24 weeks	Primary: ADAS-cog total score and CIBIC-Plus Secondary:	Primary: There were no significant differences in the ADAS-cog total score with memantine and placebo at week 24 (-1.93 and -1.08, respectively; P=0.156). There were no significant differences in the CIBIC-plus total score with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	(MMSE score 11-23)		NPI and ADCS-ADL_{23}	memantine and placebo at week 24 (4.12 and 4.19, respectively; P=0.523). Secondary: There were no significant differences in the NPI total score with memantine and placebo at week 12 (-1.37 and -1.02, respectively; P=0.671) or week 24 (-1.45 and -2.73, respectively; P=0.159). There were no significant differences in the ADCS-ADL_{23} total score with memantine and placebo at week 12 (-0.67 and -0.19, respectively; P=0.480) or week 24 (-1.99 and -2.08, respectively; P=0.912). The incidence of adverse events was similar in both treatment groups. The majority of the adverse events were considered by the investigator to be mild to moderate. A total of 8 patients died during the study or within 30 days after the last dose of study drug. None of the events leading to death were considered related to treatment.
Reisberg et al.[35] (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.[36] (1999) Memantine 10 mg/day vs	DB, PC Patients with severe dementia (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 AD population alone also yielded statistically significant results in favor of patients receiving memantine, by either the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				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.
Porsteinsson et al.[83] (2008) Memantine 20 mg/day plus cholinesterase inhibitor vs cholinesterase inhibitor plus placebo	RCT, DB, PC, PG Patients ≥50 years of age with mild-to-moderate Alzheimer's disease (MMSE score of 10-22) and concomitant treatment with a cholinesterase inhibitor for ≥6 months	N=433 24 weeks	Primary: ADAS-cog and CIBIC-Plus Secondary: ADCS-ADL_{23}, NPI, MMSE, RUD	Primary: There were no significant differences between treatment groups on the ADAS-cog or CIBIC-Plus throughout the study except week 8 on the CIBIC-Plus. The ADAS-cog least squares (LS) mean treatment difference at study endpoint was -0.7 (95% CI -1.8 to 0.4; P=0.184). The treatment difference for the CIBIC-Plus was 0.0 (95% CI -0.2 to 0.2; P=0.843). Secondary: There were no significant differences between the treatment groups on the ADCS-ADL_{23} or NPI throughout the study except week 4 on the ADCS-ADL_{23}. At study endpoint, LS mean differences were -0.2 for the ADCS-ADL_{23} (95% CI -1.64 to 1.29; P=0.816), 0.3 for the NPI (95% CI -1.69 to 2.36; P=0.743), and 0.5 for the MMSE (95% CI -0.13 to 1.09; P=0.123).
Tariot et al.[26] (2004) Memantine 20 mg/day vs donepezil	DB, MC, PC, RCT Patients with moderate-to-severe Alzheimer's disease who received donepezil therapy	N=404 24 weeks	Primary: SIB, ADCS-ADL, CIBIC-Plus, BGP	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				memantine-donepezil resulted in sustained cognitive performance above baseline compared with 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%.
Cumming et al.[27] (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	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).
Winblad et al.[37] (2007) Memantine 20 mg/day vs placebo	MA Patients with moderate-to-severe Alzheimer's disease	N=1,826 (4 trials) 24-28 weeks	Primary: CIBIC-Plus, SIB, ADAS-Cog, ADCS-ADL, NPI	Primary: There was a statistically significant advantage for the memantine group 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).
Wilkinson et al.[38] (2007) Memantine 20 mg/day vs	MA Patients with moderate-to-severe Alzheimer's disease	N=1,826 24-28 weeks	Primary: ADAS-Cog, SIB, CIBIC-Pus, ADCS-ADL	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				
McShane et al.[62] (2006) Memantine 10-30 mg/day vs placebo	MA Patients with mild-to-moderate or moderate-to-severe Alzheimer's disease; patients with mild-to-moderate vascular dementia	N=3,731 (15 trials) Variable duration	Primary: CIBIC-Plus, SIB, ADAS-Cog, ADCS-ADL, NPI	Primary: Significant improvement at 6 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 6 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).
Burns et al.[40] (2004) Rivastigmine	RETRO Patients with moderate-to-severe Alzheimer's disease	N=2,126 (3 trials) 6 months	Primary: Effectiveness	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 progressive deterioration scale, and items of the BEHAV-AD assessed efficacy. Rivastigmine showed the same pattern of adverse events as in other studies, but the relative risk of dropping out due to adverse events was lower than in patients with milder AD.
Dantoine et al.[47] (2006) Rivastigmine 3-12 mg/day Addition of memantine 5-20 mg/day was allowed for non-responders of	MC, OL Patients ≥50 years of age with probable Alzheimer's disease (MMSE scores <18 or GDS scores >4), previously treated for at least 6 months with donepezil 5-10 mg/day or	N=202 <u>Phase 1</u> 16 weeks of rivastigmine monotherapy <u>Phase 2</u> 12 weeks of rivastigmine plus	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
rivastigmine at the end of week 16.	galantamine 16-24 mg/day and considered not stabilized	memantine		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).
Gauthier et al.[97] (2010) Rivastigmine 3 to 12 mg/day	PRO, OL, MC, OS Patients with mild-moderate Alzheimer's disease	N=3,800 12 months	Primary: Physician-assessed abbreviated CGI-C, MMSE, psychotropic medication use	Primary: At 6 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% 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 6 and 12 months demonstrated a larger percentage of patients with improvement vs deterioration. At 6 months, 54% of patients overall demonstrated no change. At 12 months, 52% of patients overall demonstrated no change.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				MMSE scores were 20.8 at baseline, 21.5 after 3 months, 21.3 after 6 months, and 21.3 after 12 months. At baseline, 61.3% of patients were not taking a psychotropic medication. At 6 months, the proportion of patients not taking any psychotropic medications increased to 70.8%; at 12 months, it was 84.7%.
Rosler et al.[42] (1999) Rivastigmine 1-4 mg/day vs rivastigmine 6-12 mg/day vs placebo	DB, MC, PC, RCT Patients 50-85 years of age with Alzheimer's disease (MMSE scores 10-26)	N=725 26 weeks	Primary: 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 with 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 6-12 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).
Bullock et al.[86] (2005) Rivastigmine 3-12 mg/day vs	RCT, DB, MC Patients 50-85 years of age with moderate to moderately-severe Alzheimer's disease (MMSE score 10-	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 which there was a between-treatment difference of 2.1 points after 2 years

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
donepezil 5-10 mg/day	20)			(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).
Sadowsky et al.[104] (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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(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 not significant. 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.
Articus et al.[96] (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 Secondary: Tolerability, week 24 MMSE, ADCS-CGIC, TMT-A, ADCS-ADL, ADCPQ, Zarit Burden Interview Score	Primary: In the ITT population, 80.8% of patients (95% CI, 75.0–86.5%) were treated for at least 8 weeks with rivastigmine. A total of 74.2% of patients (95% CI, 67.8–80.5%) were treated for at least 8 weeks and completed the study. A total of 74.2% of patients treated rivastigmine patch were able to reach and maintain the maximum dose for at least 8 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), ADCS-ADL (1.3), and TMT-A (-8.9). 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.[72] (2009)	OL Patients 50-85 years	N=870 28 weeks	Primary: Safety and tolerability	Primary: During the first 4 weeks of the open-label extension, patients formerly randomized to rivastigmine treatment (capsule or patch) reported fewer

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Rivastigmine patch 9.5 mg/24 hours to 17.4 mg/24 hours	of age with Alzheimer's disease (MMSE scores 10-20)	(weeks 25-52 of open-label extension)	Secondary: ADAS-cog	adverse events (AEs) 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 AEs during the open-label extension (weeks 25 to 52), with nausea and vomiting being reported most frequently (15.7% and 14.3%, respectively). During the open-label 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 AEs occurred in 1.0% of patients during the first 4 weeks of the open-label 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 SAEs were gastrointestinal disorders (2.0%), infections and infestations (2.0%), cardiac disorders (1.7%), and nervous system disorders (1.5%). Eight deaths occurred during the open-label extension phase and a further 2 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Cummings et al.[102] (2010) Rivastimine patch 9.5 mg/24 hours vs rivastigmine patch 17.4 mg/24 hours vs placebo	PRO, RCT, DB, PC 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 28 weeks	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 (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 double-blind 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.
Blesa González et al.[112] (2011) Rivastigmine 6-12 mg/day (RO) vs rivastigmine patch titrated to 9.5 mg/24 hours (RPT) vs	MC, RCT, OL 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 AEs Secondary: Overall tolerance, local tolerance for those patients on patches, satisfaction level, and cognitive state by MMSE	Primary: Gastrointestinal AEs 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 AEs were noted in 11 cases, 2 in RPT patients, 6 in RP patients, and 3 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 AEs reported in 11.6% of patients in the RPT group vs 17% of patients in the RP group (P=0.4055). All skin AEs were reported as slight or moderate intensity.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
rivastigmine patch 9.5 mg/24 hours (RP)				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 1 and 3 month visits.
Winblad et al.[44] (2007) Rivastigmine patch 9.5 mg/24 hours vs rivastigmine patch 17.4 mg/24 hours vs rivastigmine 12 mg/day vs placebo	RCT, PC Patients 50-85 years of age with Alzheimer's disease (MMSE scores 10-20)	N=1,195 24 weeks	Primary: ADAS-Cog subscale, ADCS-CGIC Secondary: ADCS-ADL, MMSE, NPI, Ten Point Clock-drawing Test, and Trail-making Test part A	Primary: Patients in all rivastigmine groups (patch and capsule) showed significant improvements compared with placebo at week 24 with respect to ADAS-Cog and the ADCS-CGIC (all P<0.05 vs placebo). 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.
Winblad et al.[43] (2007) Rivastigmine patch 9.5 mg/24 hours vs	RCT, DB, DD, MC Patients 50-85 years of age with Alzheimer's disease (MMSE scores 10-20)	N=1,195 24 weeks	Primary: ADAS-Cog, ADCS-CGIC Secondary: ADCS-ADL scale; NPI, MMSE, Ten Point Clock-	Primary: Patients receiving rivastigmine patches or capsules showed significant benefits compared with 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 9.5 mg/24 hours patch and capsule group (all P<0.05 vs placebo). The 17.4 mg/24 hours patch did not achieve statistical significance

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
rivastigmine patch 17.4 mg/24 hours vs rivastigmine 12 mg/day vs placebo			drawing Test, Trail Making Test Part A	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.[45] (2007) Rivastigmine patch 9.5 mg/24 hours vs rivastigmine patch 17.4 mg/24 hours vs rivastigmine 12 mg/day vs placebo	RCT, DB, DD, MC Patients 50-85 years of age with Alzheimer's disease (MMSE scores 10-20)	N=1,059 24 weeks	Primary: ADCPQ	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).
Farlow et al.[101] (2011) Rivastigmine patch 9.5 mg/24 hours vs	RETRO Patients with mild-to-severe Alzheimer's disease	N=1,050 24 weeks	Primary: ADAS-cog, ADCS-CGIC, and ADCS-ADL	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
rivastigmine patch 17.4 mg/24 hours vs rivastigmine 12 mg/day vs placebo				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.
Molinuevo et al.[99] (2012) Rivastigmine patch 9.5 mg/24 hours vs rivastigmine 3-12 mg/day	PRO, MC, OS 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 3 and 6 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 3 months was 73.6% and at 6 months was 85.9% (P<0.0001). Secondary: Modification of AD treatment was the only intervention that substantially improved adherence at 3 months (P<0.0001). At the 6 month visit, psychoeducation was the only effective strategy that reached statistical

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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%).
Olin et al.[103] (2010) Rivastigmine 6-12 mg/day and memantine 20 mg/day	PRO, MC, OL Patients ≥50 years of age with moderate-to-severe Alzheimer's disease (MMSE ≥10 to ≤20)	N=116 26 weeks	Primary: Safety and tolerability Secondary: ADCS-CGIC, ADCS-ADL measured	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% 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.
Choi et al.[105] (2011)	MC, RCT, OL Patients with mild-	N=172 24 weeks	Primary: Tolerability	Primary: The incidence of adverse events (53.4% vs 50.6%) and discontinuation due to AEs (6.8% vs 4.8%) was not different between patients with and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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	to-moderate Alzheimer's disease		Secondary: Efficacy as measured by CMAI-K, ADAS-cog, K-MMSE, FAB, CGA-NPI, ADCS-ADL and CDR-SB scores	without memantine, respectively. The most common AEs 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.[87] (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 AEs (73.3% vs 67.5%) and SAEs (10.4% vs 7.1%) were both slightly higher in patients receiving concomitant memantine, but the differences were not significant (95% CIs, -5.2 to 16.9 and -3.6 to 10.1 for AEs and SEAs, respectively). The most frequent AEs 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 significant worsening in patients receiving memantine compared with those not receiving memantine (mean change from baseline rivastigmine + memantine vs rivastigmine monotherapy: -5.3 vs -2.0; P=0.043).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Birks et al.[85] (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	Primary: <u>Cognitive function</u> The meta-analysis, using weighted mean differences (WMD), demonstrated benefit on cognitive function as measured by ADAS-Cog test scores for rivastigmine compared with placebo as follows: rivastigmine 1-4 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 6-12 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). An additional analysis of ADAS-Cog dichotomized into those showing less than 4 points improvement and those showing 4 or more points improvement at 26 weeks shows benefit for cognitive function for the 6-12 mg daily of rivastigmine compared to placebo (83% did not show 4 points improvement compared to 89%; OR 0.6, 95% CI 0.4 to 0.8). There was no difference for the 1- 4 mg/day dose compared to placebo (88% did not show 4 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 with placebo as follows: rivastigmine 1-4 mg/day at 26 weeks (WMD 0.43, 95% CI, 0.08 to 0.78, P=0.02) and rivastigmine 6-12 mg/day at 26 weeks (WMD 0.82, 95% CI, 0.56 to 1.08, P<0.00001). One study used the Severe Impairment Battery (SIB), which shows benefit associated with higher dose rivastigmine compared with 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 with placebo as follows: rivastigmine 6-12 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 1-4

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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 6-12 mg/day compared with 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 1-4 mg daily rivastigmine compared to placebo. <u>Activities of daily living</u> The PDS showed an improvement associated with rivastigmine compared to placebo as follows: rivastigmine 6-12 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 showed benefit for rivastigmine 6-12 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 1-4 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 6-12 mg/day at 12weeks (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 (1-4 mg/day) and placebo groups. There were significant differences between the higher dose rivastigmine (6-12 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,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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 (1-4 mg/day) and placebo groups. There were significant differences between the higher dose rivastigmine (6-12 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 6-12 mg/day group by the end of the titration period, and by 26 weeks for the number of patients suffering nausea, vomiting, diarrhea, anorexia, headache, syncope, abdominal pain and dizziness. There were significant differences in favor of placebo, for the rivastigmine 1-4 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.
Feldman et al.[95] (2009) Cholinesterase inhibitors	PRO, OS Alzheimer's disease patients with and without cerebrovascular disease (CVD)	N=548 7 years	Primary: Time to nursing home placement (NHP) 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, 38.0-48.0 months). Secondary: Factors noted to reduce the risk of being admitted to a nursing home included higher baseline DAD and MMSE scores, AD 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 AChEI -29%).
Trinh et al.[57] (2003) Cholinesterase inhibitors vs placebo	MA Patients with mild-to-moderate Alzheimer's disease	29 trials Variable duration	Primary: NPI, ADAS-noncog, ADL and IADL	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 ADLs numerically but not

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				significantly better than placebo (95% CI: 0.0 to 0.19). Cholinesterase inhibitors improved IADLs statistically compared to placebo (95% CI: 0.01 to 0.17).
Lanctot et al.[58] (2003) Cholinesterase inhibitors vs placebo	MA Patients with Alzheimer's disease	N=7,954 (16 trials) Variable 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, 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 1 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 1 additional patient to experience an adverse event was 12 (95% CI: 10 to 18).
Birks et al.[59] (2006) Cholinesterase inhibitors vs placebo	MA Patients with mild, moderate or severe dementia due to Alzheimer's disease	N=7,298 ≥6 months	Primary: CIBIC-Plus, GBS, GDS, ADAS-Cog, MMSE, SIB, NPI, ADL scored by PDS and DAD Secondary: Withdrawals adverse events	Primary: <u>Cholinesterase inhibitor vs placebo (12 trials)</u> 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). No significant difference was seen in GBS between the cholinesterase inhibitor and placebo groups at 1 year. Significant improvement in ADAS-Cog was found for patients treated with donepezil, galantamine, or rivastigmine over placebo (MD, –2.66, 95% CI: –3.02 to –2.31; P<0.00001). Significant benefit was seen in MMSE for patients treated with a cholinesterase inhibitor over placebo (MD, 1.37, 95% CI: 1.13 to 1.61, P<0.00001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Significant benefit was seen in ADL-PDS and DAD for patients treated with a cholinesterase inhibitor over placebo (MD, 2.40, 95% CI: 1.55 to 3.37, P<0.00001 for PDS; and MD, 4.39, 95% CI: 1.96 to 6.81, P=0.0004 for DAD). Significant benefit was seen in NPI for patients treated with a cholinesterase inhibitor over placebo (MD, –2.44, 95% CI: –4.12 to –0.76; P=0.004). <u>Donepezil vs rivastigmine (1 trial)</u> There was no statistically significant difference between the treatment groups for cognitive function, ADL scales, behavior disturbances, and global assessment. Secondary: <u>Cholinesterase inhibitor vs placebo (12 trials)</u> Significantly more patients treated with a cholinesterase inhibitor (29%) withdrew prior to 6 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). <u>Donepezil vs rivastigmine (1 trial)</u> 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				No significant difference between treatment groups for serious adverse events was noted.
Hansen et al.[82] (2008) Cholinesterase inhibitors	MA Patients with Alzheimer's disease	26 trials Variable duration	Primary: Cognition (ADAS-cog), function, behavior (NPI), global assessment of change (CIBIC+ and CGI-C)	Primary: Cognition (14 studies) The pooled weighted mean difference 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. Function (14 studies) 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. Behavior (7 studies) The pooled weighted mean difference 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. Global assessment of change (9 studies) The pooled relative risk of responding for active treatment compared with 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.
Kim et al.[111] (2011) Cholinesterase inhibitors	MA Cognitively impaired older adults	54 trials Variable duration	Primary: Falls, syncope, fracture and accidental injury reported	Primary: AChEI usage was associated with the greatest risk of syncope compared to placebo (OR, 1.53; 95% CI, 1.02-2.30), but not with any other events: falls (OR, 0.88; 95% CI, 0.74-1.04); fracture (OR, 1.39; 95% CI, 0.75-2.56); accidental injury (OR, 1.13; 95% CI, 0.87-1.45). Memantine was associated with fewer fractures (OR, 0.21; 95% CI, 0.05-0.85), but not with other events: falls (OR, 0.92; 95% CI, 0.72-1.18), syncope (OR, 1.04; 95% CI, 0.35-3.04); accidental injury (OR, 0.80; 95% CI, 0.56-1.12). There were no differential effects noted according to type and severity of cognitive impairment, residential status, or length of follow-up.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Parkinson's Disease				
Emre et al.[63] (2004) Rivastigmine 3-12 mg/day; average dose 8.6 mg/day vs placebo	DB, MC, PC, R Patients ≥50 years of age with mild-to-moderate dementia developed 2 years after the diagnosis of Parkinson's disease	N=541 24 weeks	Primary: 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	Primary: 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. A total of 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.[64] (2005) Rivastigmine 3-12 mg/day, average dose 8.6 mg/day vs placebo	DB, MC, PC, R Patients ≥50 years of age with Parkinson's disease and mild-to-moderate dementia	N=487 24 weeks	Primary: Power of attention, continuity of attention, cognitive reaction time, reaction time variability	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) versus 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).
Schmitt et al.[98] (2010) Rivastigmine 3 to 12 mg/day	RCT, MC, DB, PC Patients with Parkinson's disease dementia	N=541 24 weeks	Primary: Executive function (EF) as assessed by Delis-Kaplan Executive Function System (D-KEFS)	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			measures	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 not significant. 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 EF tests were not statistically significant.
Olin et al.[100] (2010) Rivastigmine 3 to 12 mg/day vs placebo	MC, RCT, DB, PC Patients ≥50 years of age with Parkinson's disease dementia	N=541 24 weeks	Primary: Tolerability and efficacy as measured by ADCS-ADL	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.
Maidment et al.[65] (2006) Rivastigmine 3-12 mg/day vs placebo	MA Patients with Parkinson's disease and mild-to-moderate dementia	N=541 24 weeks	Primary: ADAS-Cog, ADCS-CGIC Secondary: MMSE, ADCS-ADL, NPI, CDR, D-KEFS, Ten Point Clock-drawing Test, UPDRS, adverse events	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 rivastigmine over placebo (WMD, –0.50, 95% CI: –0.77 to –0.23, P=0.0004). A total of 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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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 D-KEFS, results significantly favored patients treated with rivastigmine over placebo (WMD, 2.80, 95% CI: 1.47 to 4.13, P<0.0001). For CDR no statistically significant difference was found (P=0.25). 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).

*Product not available in the United States
Study abbreviations: AC=active control, CI=confidence interval, DB=double blind, DD=double dummy, ER=extended release, IR=immediate release, MA=meta analysis, MC=multicenter, NS=not significant, OC=observational case, OL=open label, OR=odds ratio, OS=observational study, PA=pooled analysis, PC=placebo controlled, PG=parallel group, PRO=prospective, R=randomized, RCT=randomized controlled trial, RETRO=retrospective, SB=Single-blind, SD=standard deviation, SE=standard error, 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, EXIT-25=Executive Interview, 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, NINCDS-ADRDA=National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association, NPI=Neuropsychiatric Inventory, NPI-10=10-item Neuropsychiatric Inventory, 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.[67] 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.[68] Wilkinson et al. found no difference in tolerability when patients were switched from donepezil to galantamine using either a 4-day washout period or a 7-day washout period.[69] Sadowsky et al. evaluated immediate switch (no washout) or delayed switch (7-day washout) from oral donepezil to transdermal rivastigmine following a 4-week treatment period with donepezil.[79] 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.[84] 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 5-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.[71]

Impact on Physician Visits
Fillenbaum et al. evaluated the frequency of outpatient visits for patients with Alzheimer's disease.[73] 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.[74] 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.[75] 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.[76] 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
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 8. 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®*	$$$$-$$$$$	$$$-$$$$$
Galantamine	extended-release capsule, solution, tablet	Razadyne®*, Razadyne ER®*	$$$$-$$$$$	$$$-$$$$
Rivastigmine	capsule, solution, transdermal patch	Exelon®*	$$$$-$$$$$	$$$$
Central Nervous System Agents, Miscellaneous				
Memantine	solution, tablet	Namenda®	$$$$	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 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. Donepezil, galantamine and rivastigmine are available in a generic formulation.

There are several guidelines which discuss the role of these agents in the management of Alzheimer's disease.[15-18] The primary goal of treatment is to delay the progression of symptoms and preserve functional ability.[18] 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.[15,17-18] 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.[17-18] Guidelines do not give preference to one agent over another. Clinicians should base the treatment decision on tolerability, adverse events and ease of use.[15]

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.[15,18] 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.

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 generics and OTC 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.

XII. References

1. Drug Facts and Comparisons. Drug Facts and Comparisons 4.0 [online]. 2012. Available from Wolters Kluwer Health, Inc. Accessed April 2012.
2. Lexi-Comp Online, Lexi-Drugs Online, Hudson, Ohio: Lexi-Comp, Inc.; April 2012.
3. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed April 2012.
4. Aricept® [package insert]. Woodcliff Lake, NJ: Eisai, Inc.; February 2012.
5. Razadyne® [package insert]. Titusville, NJ: Ortho-McNeil-Janssen Pharmaceuticals, Inc.; July 2011.
6. Exelon® [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; June 2006.
7. Exelon® Patch [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; August 2010.
8. Namenda® [package insert]. St. Louis, MO: Forest Pharmaceuticals, Inc.; January 2011.
9. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th ed., text revision (DSM-IV-TR). Washington, DC: American Psychiatric Association; 2000.
10. Grabowski T. Clinical manifestations and diagnosis of Alzheimer disease. In: UpToDate, Wilterdink JL (Ed), UpToDate, Waltham, MA, 2012.
11. Press D, Alexander M. Treatment of dementia. In: UpToDate, Wilterdink JL (Ed), UpToDate, Waltham, MA, 2012.
12. Rodnitzky R. Parkinson disease dementia. In: UpToDate, Wilterdink JL (Ed), UpToDate, Waltham, MA, 2012.
13. 13Press D, Alexander M. Treatment of behavioral symptoms related to dementia. In: UpToDate, Wilterdink JL (Ed), UpToDate, Waltham, MA, 2012.
14. Press D, Alexander M. Cholinesterase inhibitors in the treatment of dementia. In: UpToDate, Wilterdink JL (Ed), UpToDate, Waltham, MA, 2012.
15. Qaseem A, Snow V, Cross J, et al. American College of Physicians/American Academy of Family Physicians Panel on Dementia. Current pharmacologic treatment of dementia: a clinical practice guideline from the American College of Physicians and the American Academy of Family Physicians. Ann Intern Med 2008;148:370-8.
16. Doody RS, Stevens JC, Beck C, Dubinsky RM, Kaye JA, Gwyther L, et al. Practice parameter: management of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2001 May 8;56(9):1154-66 [reaffirmed October 2003].
17. Waldemar G, Dubois B, Emre M, et al. Recommendations for the diagnosis and management of Alzheimer's disease and other disorders associated with dementia: EFNS guideline. Eur J Neurol 2007;14:e1-26.
18. American Psychiatric Association (APA). Practice guideline for the treatment of patients with Alzheimer's disease and other dementias. Arlington (VA): American Psychiatric Association (APA); 2007. Available at: http://psychiatryonline.org/data/Books/prac/AlzPG101007.pdf. Accessed May 2012.
19. Geldmacher DS, Provenzano G, McRae T, Mastey V, Ieni JR. Donepezil is associated with delayed nursing home placement in patients with Alzheimer's disease. J Am Geriatr Soc. 2003 Jul;51(7):937-44.
20. Courtney C, Farrell D, Gray R, Hills R, Lynch L, Sellwood E, Edwards S, Hardyman W, Raftery J, Crome P, Lendon C, Shaw H, Bentham P; AD2000 Collaborative Group. Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomised double-blind trial. Lancet. 2004 Jun 26;363(9427):2105-15.
21. Birks J, Harvey RD. Donepezil for dementia due to Alzheimer's disease. Cochrane Database Syst Rev. 2006 Jan 25;(1):CD001190. doi: doi: 10.1002/14651858.CD001190.pub2.
22. Black SE, Doody R, Li H, McRae T, Jambor KM, et al. Donepezil preserves cognition and global function in patients with severe Alzheimer disease. Neurology. 2007;69:459-69.
23. Winblad B, Kilander L, Eriksson S, Minthon L, Batsman S, Wetterholm AL Jansson-Blixt C, et al; Severe Alzheimer's Disease Study Group. Donepezil in patients with severe Alzheimer's disease: double-blind, parallel-group, placebo-controlled study. Lancet. 2006 Apr 1;367(9516):1057-65.
24. Winblad B, Wimo A, Engedal K, Soininen H, Verhey F, Waldemar G, et al. 3-year study of donepezil therapy in Alzheimer's disease: effects of early and continuous therapy. Dement Geriatr Cogn Disord. 2006;21(5-6):353-63.
25. Wallin A et al. Donepezil in Alzheimer's disease: what to expect after 3 years of treatment in a routine clinical setting. Dementia and Geriatric Cognitive Disorders. 2007;23:150-60.
26. Tariot PN, Farlow MR, Grossberg GT, Graham SM, McDonald S, Gergel I; Memantine Study Group. Memantine treatment in patients with moderate-to-severe Alzheimer disease already receiving donepezil: a randomized controlled trial. JAMA. 2004 Jan 21;291(3):317-24.

27. Cumming JL, Schneider E, Tariot P, et al. Behavioral effects of memantine in Alzheimer disease patients receiving donepezil treatment. Neurology. 2006;67:57-63.
28. Rogers SL, Farlow MR, Doody RS, Mohs R, Friedhoff LT. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. Donepezil Study Group. Neurology 1998 Jan;50(1):136-45.
29. Raskind MA, Peskind ER, Truyen L, Kershaw P, Damaraju CV. The cognitive benefits of galantamine are sustained for at least 36 months: a long-term extension trial. Arch Neurol. 2004 Feb;61(2):252-6.
30. Cummings JL, Schneider L, Tariot PN, Kershaw PR, Yuan W. Reduction of behavioral disturbances and caregiver distress by galantamine in patients with Alzheimer's disease. Am J Psychiatry. 2004 Mar;161(3):532-8.
31. Loy C, Schneider L. Galantamine for Alzheimer's disease and mild cognitive impairment. Cochrane Database Syst Rev. 2006, Issue 1.Art.No.:CD001747. DOI: 10.1002/14651858.CD001747.pub3.
32. Wilcock GK, Lilienfeld S, Gaens E. Efficacy and safety of galantamine in patients with mild-to-moderate Alzheimer's disease: multicentre randomised controlled trial. Galantamine International-1 Study Group. BMJ. 2000 Dec 9;321(7274):1445-9.
33. Dunbar F, Zhu Y, Brashear H. Post hoc comparison of daily rates of nausea and vomiting with once- and twice-daily galantamine from a double-blind, placebo-controlled, parallel-group, 6-month study. Clin Ther. 2006 Mar;28(3):365-72.
34. Brodaty H, Corey-Bloom J, Potocnik F, Truyen L, Gold M, et al. Galantamine prolonged-release formulation in the treatment of mild-to-moderate Alzheimer's disease. Dementia and Geriatric Cognitive Disorders. 2005;20:120-32.
35. Reisberg B, Doody R, Stoffler A, Schmitt F, Ferris S, Mobius HJ; Memantine Study Group. Memantine in moderate-to-severe Alzheimer's disease. N Engl J Med. 2003 Apr 3;348(14):1333-41.
36. Winblad B, Poritis N. Memantine in severe dementia: results of the 9M-Best Study (benefit and efficacy in severely demented patients during treatment with memantine). Int J Geriatr Psychiatry 1999;14(2):135-46.
37. Winblad B, Jones RW, Wirth Y, Stoffler A, Mobius HJ. Memantine in moderate-to-severe Alzheimer's disease: a meta-analysis of randomised clinical trials. Dement Geriatr Cogn Disord. 2007;24(1):20-7.
38. Wilkinson D and Andersen HF. Analysis of the effect of memantine in reducing the worsening of clinical symptoms in patients with moderate-to-severe Alzheimer's disease. Dementia and Geriatric Cognitive Disorders. 2007;24:138-45.
39. Miyasaki JM, Shannon K, Voon V, et al. Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter: evaluation and treatment of depression, psychosis, and dementia in Parkinson disease (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2006;66:996-1002.
40. Burns A, Spiegel R, Quarg P. Efficacy of rivastigmine in subjects with moderately severe Alzheimer's disease. Int J Geriatr Psychiatry. 2004 Mar;19(3):243-9.
41. Rockwood K, Dai D, Mitnitski A, et al. Patterns of decline and evidence of subgroups in patients with Alzheimer's disease taking galantamine for up to 48 months. Int J Geriatr Psychiatry 2008;23:207-14.
42. Rosler M, Anand R, Cicin-Sain A, Gauthier S, et al. Efficacy and safety of rivastigmine in patients with Alzheimer's disease: international randomized controlled trial. BMJ 1999;318:633-40.
43. Winblad B, Cummings J, Andreasen N, Grossberg G, et al. A six-month double-blind, randomized, placebo-controlled study of a transdermal patch in Alzheimer's disease-rivastigmine patch versus capsule. International Journal of Geriatric Psychiatry. 2007;22:456-67.
44. Winblad B, Grossberg G, Frolich L, Farlow M, et al. IDEAL: a 6 month, double-blind, placebo-controlled study of the first skin patch for Alzheimer disease. Neurology. 2007;69(Suppl1):S14-S22.
45. Blesa R, et al. Caregiver preference for rivastigmine patches versus capsules for the treatment of Alzheimer disease. Neurology. 2007;69(Suppl 1):S23-S28.
46. Winblad B, Kawata AK, Beusterien KM, Thomas SK, Wimo A, Lane R, et al. Caregiver preference for rivastigmine patch relative to capsules for treatment of probable Alzheimer's disease. Int J Geriatr Psychiatry. 2007 May;22(5):485-91.
47. Dantoine T, Auriacombe S, Sarazin M, et al. Rivastigmine monotherapy and combination therapy with memantine in patients with moderately severe Alzheimer's disease who failed to benefit from previous cholinesterase inhibitor treatment. International Journal of Clinical Practice. 2006;60(1):110-8.
48. Scarpini E, Bruno G, Zappalà G, et al. Cessation versus continuation of galantamine treatment after 12 months of therapy in patients with Alzheimer's disease: a randomized, double blind, placebo controlled withdrawal trial. J Alzheimers Dis 2011;26:211-20.
49. Harry RD, Zakzanis KK. A comparison of donepezil and galantamine in the treatment of cognitive symptoms of Alzheimer's disease: a meta-analysis. Hum Psychopharmacol. 2005 Apr;20(3):183-7.

50. Burns A, Gauthier S, Perdomo C, et al. Efficacy and safety of donepezil over 3 years: an open-label, multicentre study in patients with Alzheimer's disease. Int J Geriatr Psychiatry 2007;22:806-12.
51. Wilcock G, Howe I, Coles H, Lilienfeld S, Truyen L, Zhu Y, Bullock R, Kershaw P; GAL-GBR-2 Study Group. A long-term comparison of galantamine and donepezil in the treatment of Alzheimer's disease. Drugs Aging. 2003;20(10):777-89.
52. Jones RW, Soininen H, Hager K, Aarsland D, Passmore P, Murthy A, Zhang R, Bahra R. A multinational, randomised, 12-week study comparing the effects of donepezil and galantamine in patients with mild-to-moderate Alzheimer's disease. Int J Geriatr Psychiatry. 2004 Jan;19(1):58-67.
53. Wilkinson DG, Passmore AP, Bullock R, Hopker SW, Smith R, Potocnik FC, Maud CM, Engelbrecht I, Hock C, Ieni JR, Bahra RS. A multinational, randomised, 12-week, comparative study of donepezil and rivastigmine in patients with mild-to-moderate Alzheimer's disease. Int J Clin Pract 2002;56(6):441-6.
54. Mossello E, Tonon E, Caleri V, Tilli S, Cantini C, Cavallini MC, Bencini F, Mecacci R, Marini M, Bardelli F, Sarcone E, Razzi E, Biagini CA, Masotti G. Effectiveness and safety of cholinesterase inhibitors in elderly subjects with Alzheimer's disease: a "real world" study. Arch Gerontol Geriatr Suppl. 2004;(9):297-307.
55. Aguglia E, Onor ML, Saina M, Maso E. An open-label, comparative study of rivastigmine, donepezil and galantamine in a real-world setting. Curr Med Res Opin. 2004 Nov;20(11):1747-52.
56. Lopez-Pousa S, Turon-Estrada A, Garre-Olmo J, Pericot-Nierga I, Lozano-Gallego M, Vilalta-Franch M, Hernandez-Ferrandiz M, Morante-Munoz V, Isern-Vila A, Gelada-Batlle E, Majo-Llopart J. Differential efficacy of treatment with acetylcholinesterase inhibitors in patients with mild and moderate Alzheimer's disease over a 6-month period. Dement Geriatr Cogn Disord. 2005;19(4):189-95.
57. Trinh NH, Hoblyn J, Mohanty S, Yaffe K. Efficacy of cholinesterase inhibitors in the treatment of neuropsychiatric symptoms and functional impairment in Alzheimer disease: a meta-analysis. JAMA. 2003 Jan 8;289(2):210-6.
58. Lanctôt K, Herrmann N, Yau K, Khan L, Liu B et al. Efficacy and safety of cholinesterase inhibitors in Alzheimer's disease: a meta-analysis. CMAJ. 2003 Sept 16;(6) 2003;169.
59. Birks J. Cholinesterase inhibitors for Alzheimer's disease. Cochrane Database Syst Rev. 2006, Issue1.Art.No.:CD005593.DOI: 10.1002/14651858.CD005593.
60. Brodaty H et al. A Naturalistic Study of Galantamine for Alzheimer's disease. CNS Drugs. 2006;20(11):935-46.
61. Homma A, Imai Y, Tago H, et al. Donepezil treatment of patients with severe Alzheimer's disease in a Japanese population: results from a 24-week, double-blind, placebo-controlled, randomized trial. Dement Geriatr Cogn Disord 2008;25:399-407.
62. McShane R, Areosa Sastre A, Minakaran N. Memantine for dementia. Cochrane Database of Systematic Reviews 2006, Issue 2.Art.No.:CD003154. DOI: 10.1002/14651858.CD003154.pub5.
63. Emre M, Aarsland D, Albanese A, et al. Rivastigmine for dementia associated with Parkinson's disease. NEJM. 2004;351(24):2509-18.
64. Wesnes KA, McKeith I, Edgar C, Emre M, Lane R. Benefits of rivastigmine on attention in dementia associated with Parkinson disease. Neurology. 2005;65:1654-6.
65. Maidment I, Fox C, Boustani M. Cholinesterase inhibitors for Parkinson's disease dementia. Cochrane Database Syst Rev. 2006, Issue 1.Art. No.: CD004747. DOI: 10.1002/14651858.CD004747.pub2.
66. Roe CM, Anderson MJ, Spivack B. How many patients complete an adequate trial of donepezil? Alzheimer Dis Assoc Disord. 2002 Jan-Mar;16(1):49-51.
67. Scarpini E, Scheltens P, Feldman H. Treatment of Alzheimer's disease: current status and new perspectives. Lancet Neurol. 2003 Sep;2(9):539-47.
68. Gauthier S, Emre M, Farlow MR, Bullock R, Grossberg GT, Potkin SG. Strategies for continued successful treatment of Alzheimer's disease: switching cholinesterase inhibitors. Curr Med Res Opin 2003;19(8):707-14.
69. Wilkinson DG, Howe I. Switching from donepezil to galantamine: a double-blind study of two wash-out periods. Int J Geriatr Psychiatry. 2005 May;20(5):489-91.
70. Burns A, Bernabei R, Bullock R, et al. Safety and efficacy of galantamine (Reminyl) in severe Alzheimer's disease (the SERAD study): a randomised, placebo-controlled, double-blind trial. Lancet Neurol 2009;8:39-47.
71. Emre M. Switching cholinesterase inhibitors in patients with Alzheimer's disease. Int J Clin Pract Suppl. 2002 Jun;(127):64-72.
72. Grossberg G, Sadowsky C, Fröstl H, et al. Safety and tolerability of the rivastigmine patch: results of a 28-week open-label extension. Alzheimer Dis Assoc Disord 2009;23:158-64.
73. Fillenbaum G, Heyman A, Peterson BL, Pieper CF, Weiman AL. Use and cost of outpatient visits of AD patients: CERAD XXII. Neurology. 2001 Jun 26;56(12):1706-11.

74. Leibson C, Owens T, O'Brien P, Waring S, Tangalos E, Hanson V, Plevak M, Kokmen E. Use of physician and acute care services by persons with and without Alzheimer's disease: a population-based comparison. J Am Geriatr Soc. 1999 Jul;47(7):864-9.
75. Clark PA, Bass DM, Looman WJ, McCarthy CA, Eckert S. Outcomes for patients with dementia from the Cleveland Alzheimer's Managed Care Demonstration. Aging Ment Health. 2004 Jan;8(1):40-51.
76. Wimo A, Winblad B, Stoffler A, Wirth Y, Mobius HJ. Resource utilization and cost analysis of memantine in patients with moderate-to-severe Alzheimer's disease. Pharmacoeconomics. 2003;21(5):327-40.
77. Liepelt I, Maetzler W, Blaicher HP, et al. Treatment of dementia in Parkinsonian syndromes with cholinesterase inhibitors. Dement Geriatr Cogn Disord. 2007;23:351–67.
78. Miyasaki JM, Shannon K, Voon V, et al. Practice Parameter: Evaluation and treatment of depression, psychosis, and dementia in Parkinson disease (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2006;66:996-1002.
79. Sadowsky CH, Dengiz A, Olin JT, et al. Switching from donepezil tablets to rivastigmine transdermal patch in Alzheimer's disease. Am J Alzheimers Dis Other Demen 2009;24:267-75.
80. Homma A, Imai Y, Tago H, et al. Long-term safety and efficacy of donepezil in patients with severe Alzheimer's disease: results from a 52-week, open-label, multicenter, extension study in Japan. Dement Geriatr Cogn Disord 2009;27:232-9.
81. Bakchine S, Loft H. Memantine treatment in patients with mild to moderate Alzheimer's disease: results of a randomised, double-blind, placebo-controlled 6-month study. J Alzheimers Dis 2007;11:471-9.
82. Hansen RA, Gartlehner G, Webb AP, et al. Efficacy and safety of donepezil, galantamine, and rivastigmine for the treatment of Alzheimer's disease: a systematic review and meta-analysis. Clin Interv Aging 2008;3:211-25.
83. Porsteinsson AP, Grossberg GT, Mintzer J, et al. Memantine treatment in patients with mild to moderate Alzheimer's disease already receiving a cholinesterase inhibitor: a randomized, double-blind, placebo-controlled trial. Curr Alzheimer Res 2008;5:83-9.
84. Sakka P, Tsolaki M, Hort J, et al. Effectiveness of open-label donepezil treatment in patients with Alzheimer's disease discontinuing memantine monotherapy. Curr Med Res Opin 2007;23:3153-65.
85. Birks J, Grimley Evans J, Iakovidou V, et al. Rivastigmine for Alzheimer's disease. Cochrane Database Syst Rev 2009; (2); Cochrane AN: CD001191.
86. Bullock R, Touchon J, Bergman H, et al. Rivastigmine and donepezil treatment in moderate to moderately-severe Alzheimer's disease over a 2-year period. Curr Med Res Opin 2005;21:1317-1327.
87. Farlow MR, Alva G, Meng X, Olin JT. A 25-week, open-label trial investigating rivastigmine transdermal patches with concomitant memantine in mild-to-moderate Alzheimer's disease: a post hoc analysis. Curr Med Res Opin 2010;26:263-9.
88. Rodda J, Morgan S, Walker Z. Are cholinesterase inhibitors effective in the management of the behavioral and psychological symptoms of dementia in Alzheimer's disease? A systematic review of randomized, placebo-controlled trials of donepezil, rivastigmine and galantamine. Int Psychogeriatr 2009;21:813-24.
89. Howard R, McShane R, Lindesay J, et al. Donepezil and memantine for moderate-to-severe Alzheimer's disease. N Engl J Med 2012;366:893-903.
90. Wilkinson D, Schindler R, Schwam E, et al. Effectiveness of donepezil in reducing clinical worsening in patients with mild-to-moderate alzheimer's disease. Dement Geriatr Cogn Disord 2009;28:244-51.
91. Hashimoto M, Yatabe Y, Kaneda K, et al. Impact of donepezil hydrochloride on the care burden of family caregivers of patients with Alzheimer's disease. Psychogeriatrics 2009;9:196-203.
92. Modrego PJ, Fayed N, Errea JM, et al. Memantine versus donepezil in mild to moderate Alzheimer's disease: a randomized trial with magnetic resonance spectroscopy. Eur J Neurol 2010;17:405-12.
93. Van Puyvelde K, Mets T; RODOS Study Group. Galantamine (Reminyl) once daily outcome and satisfaction survey (RODOS) in mild to moderate Alzheimer's disease: a study in a real life population. Geriatr Gerontol Int 2011;11:256-61.
94. Kavanagh S, Howe I, Brashear HR, et al. Long-term response to galantamine in relation to short-term efficacy data: pooled analysis in patients with mild to moderate Alzheimer's disease. Curr Alzheimer Res 2011;8:175-86.
95. Feldman HH, Pirttila T, Dartigues JF, et al. Treatment with galantamine and time to nursing home placement in Alzheimer's disease patients with and without cerebrovascular disease. Int J Geriatr Psychiatry 2009;24:479-88.
96. Articus K, Baier M, Tracik F, et al. A 24-week, multicentre, open evaluation of the clinical effectiveness of the rivastigmine patch in patients with probable Alzheimer's disease. Int J Clin Pract 2011;65:790-6.

97. Gauthier S, Juby A, Dalziel W, Réhel B, Schecter R; EXPLORE investigators. Effects of rivastigmine on common symptomatology of Alzheimer's disease (EXPLORE). Curr Med Res Opin 2010;26:1149-60.
98. Schmitt FA, Farlow MR, Meng X, et al. Efficacy of rivastigmine on executive function in patients with Parkinson's disease dementia. CNS Neurosci Ther 2010;16:330-6.
99. Molinuevo JL, Arranz FJ. Impact of transdermal drug delivery on treatment adherence in patients with Alzheimer's disease. Expert Rev Neurother 2012;12:31-7.
100. Olin JT, Aarsland D, Meng X. Rivastigmine in the treatment of dementia associated with Parkinson's disease: effects on activities of daily living. Dement Geriatr Cogn Disord. 2010;29(6):510-5.
101. Farlow MR, Grossberg GT, Meng X, et al. Rivastigmine transdermal patch and capsule in Alzheimer's disease: influence of disease stage on response to therapy. Int J Geriatr Psychiatry. 2011 Dec;26(12):1236-43.
102. Cummings JL, Farlow MR, Meng X, et al. Rivastigmine transdermal patch skin tolerability: results of a 1-year clinical trial in patients with mild-to-moderate Alzheimer's disease. Clin Drug Investig 2010;30:41-9.
103. Olin JT, Bhatnagar V, Reyes P, et al. Safety and tolerability of rivastigmine capsule with memantine in patients with probable Alzheimer's disease: a 26-week, open-label, prospective trial (Study ENA713B US32). Int J Geriatr Psychiatry 2010;25:419-26.
104. Sadowsky CH, Farlow MR, Meng X, Olin JT. Safety and tolerability of rivastigmine transdermal patch compared with rivastigmine capsules in patients switched from donepezil: data from three clinical trials. Int J Clin Pract 2010;64:188-93.
105. Choi SH, Park KW, Na DL, et al.; Expect Study Group. Tolerability and efficacy of memantine add-on therapy to rivastigmine transdermal patches in mild to moderate Alzheimer's disease: a multicenter, randomized, open-label, parallel-group study. Curr Med Res Opin 2011;27:1375-83.
106. Herrmann N, Cappell J, Eryavec GM, Lanctôt KL. Changes in nursing burden following memantine for agitation and aggression in long-term care residents with moderate to severe Alzheimer's disease: an open-label pilot study. CNS Drugs 2011;25:425-33.
107. Farlow MR, Salloway S, Tariot PN, et al. Effectiveness and tolerability of high-dose (23 mg/d) versus standard-dose (10 mg/d) donepezil in moderate to severe Alzheimer's disease: A 24-week, randomized, double-blind study. Clin Ther 2010;32:1234-51.
108. Ferris SH, Schmitt FA, Saxton J, et al. Analyzing the impact of 23 mg/day donepezil on language dysfunction in moderate to severe Alzheimer's disease. Alzheimers Res Ther 2011;3:22.
109. Farlow M, Veloso F, Moline M, et al. Safety and tolerability of donepezil 23 mg in moderate to severe Alzheimer's disease. BMC Neurol 2011;11:57.
110. Wallin AK, Wattmo C, Minthon L. Galantamine treatment in Alzheimer's disease: response and long-term outcome in a routine clinical setting. Neuropsychiatr Dis Treat 2011;7:565-76.
111. Kim DH, Brown RT, Ding EL, et al. Dementia medications and risk of falls, syncope, and related adverse events: meta-analysis of randomized controlled trials. J Am Geriatr Soc. 2011 Jun;59(6):1019-31.
112. Blesa González R, Boada Rovira M, Martínez Parra C, et al. Evaluation of the convenience of changing the rivastigmine administration route in patients with Alzheimer disease. Neurologia 2011;26:262-71.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Antidepressants
AHFS Class 281604
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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.[1-32] Anxiety disorders include generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder and social phobia.[33] Some of the antidepressants are also approved to treat nonpsychiatric conditions, such as chronic musculoskeletal pain, diabetic peripheral neuropathy, fibromyalgia, insomnia, nocturnal enuresis and tobacco abuse.[1-32]

The antidepressants are categorized into 6 different 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 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).[1-3] 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.[4-7] The SNRIs are potent inhibitors of neuronal norepinephrine and serotonin reuptake.[8-10] The SSRIs inhibit the neuronal uptake of serotonin and have minimal effects on norepinephrine or dopamine neuronal uptake.[11-19] The clinical efficacy of the SNRIs and SSRIs is thought to be related to the potentiation of neurotransmitter activity in the central nervous system (CNS). 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. It also blocks $alpha_1$-adrenergic receptors, which may be associated with postural hypotension.[1-3] Trazodone is thought to selectively inhibit serotonin uptake at the presynaptic neuronal membrane.[1-3] Vilazodone is a selective serotonin reuptake inhibitor and partial serotonin $5\text{-}HT_{1A}$ receptor agonist.[21] The TCAs interact with a wide variety of CNS 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.[1-3,22-26] 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.[27-30] 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.[31-32] 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 February 2010.

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			

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Desvenlafaxine	extended-release tablet	Pristiq®	none
Duloxetine	delayed-release capsule	Cymbalta®	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, Lexapro®*
Fluoxetine	capsule, delayed-release capsule, solution, tablet	Prozac®*, Prozac Weekly®*, Sarafem®*	fluoxetine
Fluvoxamine	extended-release capsule, tablet	Luvox CR®	fluvoxamine
Paroxetine	extended-release tablet, suspension, tablet	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
Tricyclics and Other Norepinephrine-reuptake Inhibitors			
Amitriptyline	tablet	N/A	amitriptyline
Amitriptyline and chlordiazepoxide	tablet	N/A	amitriptyline and chlordiazepoxide
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	Vivactil®*	protriptyline
Trimipramine	capsule	Surmontil®*	trimipramine
Antidepressants, Miscellaneous			
Bupropion	extended-release tablet, sustained-release tablet, tablet	Aplenzin®, 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 (APA): **Practice Guideline for the Treatment of**	Choice of an Initial Treatment Modality • An antidepressant medication is recommended as an initial treatment choice for patients with mild to moderate major depressive disorder

Clinical Guideline	Recommendation(s)
Patients with Major Depressive Disorder, Third Edition[35] (2010)	and definitely should be provided for those with severe major depressive disorder unless electroconvulsive therapy is planned. • Because 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 for the individual patient, pharmacological properties of the medication (e.g., half-life, actions on cytochrome P450 enzymes, other drug interactions), and additional factors such as medication response in prior episodes, and patient preference. • For most patients, a selective serotonin reuptake inhibitor (SSRI), serotonin norepinephrine reuptake inhibitor (SNRI), mirtazapine, or bupropion is optimal. • In general, the use of nonselective monoamine oxidase inhibitors (e.g., phenelzine, tranylcypromine, isocarboxazid) should be restricted to patients who do not respond to other treatments. • In patients who prefer complementary and alternative therapies, S-adenosyl methionine (SAMe) or St. John's wort might be considered, although evidence for their efficacy is modest at best, and careful attention to drug-drug interactions is needed with St. John's wort.

National Institute for Health and Clinical Excellence (NICE): **Treatment and Management of Depression in Adults (Update)[38] (2009)**	<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 2 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 those 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 and provide:
	  o An antidepressant (normally a selective serotonin reuptake inhibitor [SSRI]) OR
	  o A high-intensity psychological intervention,
	• For those with moderate or severe depression, provide a combination of antidepressant medication and a high-intensity psychological intervention.
	• When an antidepressant is to be prescribed, it should normally be an SSRI in a generic form because SSRIs are equally effective as other antidepressants and have a favorable risk–benefit ratio.
	• When prescribing antidepressants, the following should be taken into account:
	  o SSRIs are associated with an increased risk of bleeding, especially in older people or in people taking other drugs that have the potential to damage the gastrointestinal mucosa or interfere with clotting.
	  o Fluoxetine, fluvoxamine and paroxetine are associated with a higher propensity for drug interactions than other SSRIs.
	  o Paroxetine is associated with a higher incidence of

Clinical Guideline	Recommendation(s)
	discontinuation symptoms than other SSRIs. o There is an increased likelihood of stopping treatment because of side effects with venlafaxine, duloxetine and TCAs. o Higher doses of venlafaxine have the potential to exacerbate cardiac arrhythmias. o There is an increased risk of possible exacerbation of hypertension with venlafaxine and duloxetine. o There is an increased risk for postural hypotension and arrhythmias with TCAs. o Non-reversible monoamine oxidase inhibitors (MAOIs) should normally be prescribed only by specialist mental health professionals. • Take into account toxicity in overdose when choosing an antidepressant for people at significant risk of suicide. o Compared with other equally effective antidepressants recommended for routine use in primary care, venlafaxine is associated with a greater risk of death from overdose. o Tricyclic antidepressants (TCAs) are associated with the greatest risk in overdose. • The evidence for the relative advantage of switching within or between classes is weak. When switching therapy, consider switching to: o Initially, a different SSRI or a better tolerated newer-generation antidepressant o An antidepressant from a different pharmacological class that may be less well tolerated (venlafaxine, TCA, MAOI). <u>Complex and Severe Depression</u> • Referral to specialist mental health services should normally be for people with depression who are at significant risk of self-harm, have psychotic symptoms, require complex multidisciplinary care, or where an expert opinion on treatment and management is needed.
American College of Physicians (ACP): **Clinical Practice Guideline: Using Second-Generation Antidepressants to Treat Depressive Disorders[36] (2008)**	<u>Treatment of Major Depressive Disorder (MDD)</u> • When treating acute-phase MDD, the second-generation antidepressants did not significantly differ in efficacy, effectiveness, or quality of life among the selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), selective serotonin norepinephrine reuptake inhibitors (SSNRIs), or other second-generation antidepressants. • Mirtazapine had a significantly faster onset of action; however, after 4 weeks, most response rates were similar. • Second-generation antidepressants did not differ in the rate of achieving remission. • First-generation antidepressants (tricyclic antidepressants and monoamine oxidase inhibitors) are less commonly used than second-generation antidepressants, which have similar efficacy to and lower toxicity in overdose than first-generation antidepressants. <u>Treatment of Depression in Patients with Accompanying Symptom Clusters</u> • When treating symptom clusters in patients with accompanying depression, second-generation antidepressants did not differ in efficacy in treating accompanying anxiety, pain, and somatization. • Limited evidence suggests that some agents may be more effective in treating insomnia. <u>Treatment of Depression in Selected Patient Populations</u> • Second-generation antidepressants did not differ in efficacy among subgroups and special populations categorized according to age, sex,

Clinical Guideline	Recommendation(s)
	race or ethnicity, or comorbid conditions. Risk for Harms and Adverse Events • Most of the second-generation antidepressants had similar adverse effects. • The most commonly reported adverse events were constipation, diarrhea, dizziness, headache, insomnia, nausea, sexual adverse events, and somnolence. Nausea and vomiting were the most common reasons for discontinuation in efficacy studies. • Paroxetine was associated with an increased risk for sexual dysfunction. • Selective serotonin reuptake inhibitors resulted in an increased risk for nonfatal suicide attempts. Recommendations • Clinicians should select second-generation antidepressants on the basis of adverse effect profiles and patient preferences. • Clinicians should assess patient status, therapeutic response, and adverse effects of antidepressant therapy on a regular basis beginning within 1 to 2 weeks of initiation of therapy. • Clinicians should modify treatment if the patient does not have an adequate response to pharmacotherapy within 6 to 8 weeks of the initiation of therapy for major depressive disorder. • Clinicians should continue treatment for 4 to 9 months after a satisfactory response in patients with a first episode of major depressive disorder. For patients who have had 2 or more episodes of depression, an even longer duration of therapy may be beneficial.
American Academy of Child and Adolescent Psychiatry (AACAP): **Practice Parameter for the Assessment and Treatment of Children and Adolescents with Depressive Disorders**[37] **(2007)**	All Types of Childhood/Adolescent Depression • All patients with depression should receive therapy in the acute (6-12 weeks) and continuation phases (6-12 months); some will require maintenance treatment (longer than 12 months). During each phase, treatment should be accompanied by psychotherapy, education, as well as family and school involvement. • Treatment should encompass the management of comorbid conditions. • Medication regimen may be optimized or augmented in partial responders; while switching to another regimen may be appropriate in non-responders. Uncomplicated Depression/Brief Depression/Mild Psychosocial Impairment • Initial management: education, support, and case management. Reevaluate if no response after 4-6 weeks. Moderate-to-Severe Depression • A trial of cognitive-behavioral therapy or interpersonal psychotherapy with and/or antidepressant therapy is indicated. • Antidepressant therapy may be initiated alone or with psychotherapy. Non-responders to monotherapy may benefit from combined psychotherapy and antidepressant therapy. • Fluoxetine is the only SSRI that is FDA-approved for the treatment of child/adolescent depression. Other SSRIs failed to demonstrate significant advantage over placebo. • In clinical trials, venlafaxine was not more effective in treating children and adolescents with depression than either mirtazapine or placebo. Secondary analysis suggests that venlafaxine may be more effective in treating adolescents than children. • Limited evidence suggests that bupropion may be used to treat child and adolescent depression with or without comorbid attention hyperactivity deficit disorder (ADHD).

Clinical Guideline	Recommendation(s)
	• Tricyclic antidepressants (TCAs) should not be used as 1st line therapy for child/adolescent depression due to poor efficacy (not statistically different from placebo) and unfavorable side-effect profile. Psychotic Depression • SSRIs combined with atypical antipsychotics are the treatment of choice. Seasonal Affective Disorder (SAD) • Bright light therapy is recommended as treatment of SAD in youths. Bipolar Disorder • A mood stabilizer such as lithium, valproate, or lamotrigine may be used.

National Institute for Clinical Excellence (NICE): **Generalized Anxiety Disorder and Panic Disorder (With or Without Agoraphobia) in Adults[39] (2011)**	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)
	  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.
	Panic Disorder General Considerations
	• 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 selective serotonin-reuptake inhibitors (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

Clinical Guideline	Recommendation(s)
	considered. • If the patient is showing improvement, the medication should be continued for at least 6 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 (APA): **Practice Guideline for the Treatment of Patients with Panic Disorder, Second Edition**[47] **(2009)**	• Selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (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 MAOIs. They are rarely lethal in overdose and have few serious effects on cardiovascular function. • Venlafaxine ER 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. • Selective serotonin reuptake inhibitors, 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. • Monoamine oxidase inhibitors 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.

Clinical Guideline	Recommendation(s)
	• 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 (AACAP): **Practice Parameter for the Assessment and Treatment of Children and Adolescents with Anxiety Disorders**[49] **(2007)**	• A multimodal treatment approach for children and adolescents with anxiety disorders should consider education of the parents and the child about the anxiety disorder, consultation with school personnel and primary care physicians, cognitive-behavioral interventions, psychodynamic psychotherapy, family therapy, and pharmacotherapy.
	• Treatment of childhood anxiety disorders of mild severity should begin with psychotherapy.
	• Valid reasons for combining medication and treatment with psychotherapy include the following:
	  o Need for acute symptom reduction in a moderately to severely anxious child
	  o A comorbid disorder that requires concurrent treatment
	  o Partial response to psychotherapy and potential for improved outcome with combined treatment.
	• Selective serotonin-reuptake inhibitors (SSRIs) have emerged as the medication of choice in the treatment of childhood anxiety disorders.
	• When anxiety disorder symptoms are moderate or severe or impairment makes participation in psychotherapy difficult, or psychotherapy results in a partial response, treatment with medication is recommended.
	• No controlled studies are available for medication treatment of childhood-onset panic disorder. The use of a SSRI in adolescents with panic disorder has shown significant improvement in panic symptoms.
	• Controlled trials have established the safety and efficacy of short-term treatment with SSRIs for childhood anxiety disorders; however, the benefits and risks of long-term use of SSRIs have not been studied. It is recommended that clinicians consider a medication-free trial for children who have a significant reduction in anxiety or depressive symptoms on an SSRI and maintain stability in these symptoms for 1 year.
	• There is no empirical evidence that a particular SSRI is more effective than another for treatment of childhood anxiety disorders. The choice is often based on side effects, duration of action, or positive response to a particular SSRI in a first-degree relative with anxiety.
	• The risk-benefit ratio for a medication trial needs to be carefully assessed because cognitive-behavioral therapy (CBT) has been shown to be effective and long-term side effects of medications have not been studied in youths.
	• The safety and efficacy of medications other than SSRIs for the treatment of childhood anxiety disorders have not been established.
	• Noradrenergic antidepressants (venlafaxine and tricyclic antidepressants [TCAs]), buspirone, and benzodiazepines have been suggested as alternatives to be used alone or in combination with the SSRIs.
	• Data are limited in childhood anxiety disorders to guide treatment with combinations of medications when a single medication is not effective in managing anxiety symptoms. Comorbid diagnoses are strongly considered in selection of medication.
	• Preliminary findings from controlled trials of extended-release venlafaxine in the treatment of youths with generalized anxiety disorder (GAD) and social phobia suggest it may be well tolerated and

Clinical Guideline	Recommendation(s)
	effective relative to placebo. • Controlled trials with tricyclic antidepressants (TCAs) for pediatric anxiety disorders have shown conflicting results and have not established efficacy for this use. • Buspirone may be an alternative to SSRIs for GAD in youths, but there are no published controlled trials. • Benzodiazepines have not shown efficacy in controlled trials in childhood anxiety disorders despite established benefit in adult trials. They are used as an adjunct short-term treatment with SSRIs to achieve rapid reduction in severe anxiety symptoms that may permit initiation of the exposure phase of CBT. Clinicians should use benzodiazepines cautiously because of the possibility of developing dependency.
American Psychiatric Association (APA): **Practice Guideline for the Treatment of Patients with Obsessive-Compulsive Disorder[40] (2007)**	General Considerations • Obsessive-compulsive disorder (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 (CBT), serotonin-reuptake inhibitors (SRIs), or a combination of the two. The choice depends on past treatment history, comorbid psychiatric conditions, severity of symptoms, and functional limitations. • CBT 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. • Clomipramine, fluoxetine, fluvoxamine, paroxetine, and sertraline are Food and Drug Administration (FDA)-approved for the treatment of OCD. • Meta-analyses and placebo-controlled trials suggest better efficacy for clomipramine compared to fluoxetine, fluvoxamine, and sertraline though head-to-head trials do not support this claim. • 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 4-6 after treatment initiation, and some may ultimately respond after as many as 10-12 weeks. • Patients not responding after 10-12 weeks may respond to a higher dose of the same medication.
National Institute for Health and Clinical Excellence (NICE): **Core Interventions in the Treatment of Obsessive-compulsive Disorder and Body**	• Initial pharmacological treatment of OCD in adults should be an SSRI (fluoxetine, fluvoxamine, paroxetine, sertraline, or citalopram). • The dose of SSRI may be increased after 4-6 weeks in adults not fully responding to treatment. • Other drugs including tricyclic antidepressants (other than

Clinical Guideline	Recommendation(s)
Dysmorphic Disorder[41] (2005)	clomipramine), serotonin and noradrenaline re-uptake inhibitors, monoamine oxidase inhibitors, anxiolytics, and antipsychotics should not be routinely used in patients without comorbidities. • Patients not responding to an SSRI or a combination of and SSRI and CBT (or in patients who cannot engage in CBT), another SSRI or clomipramine may be offered. • Clomipramine may also be used as a first-line agent in patients who have had a previous good response to it.
American Psychiatric Association (APA): **Guideline Watch: Practice Guideline for the Treatment of Patients with Acute Stress Disorder and Posttraumatic Stress Disorder[43] (2009)**	• Meta-analyses and several randomized controlled trials published since 2004 support the greater efficacy of selective serotonin-reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (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 with 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 with placebo; other agents have been studied against "treatment as usual" or as augmentation agents in patients with refractory illness.
American Psychiatric Association (APA): **Practice Guideline for the Treatment of Patients with Acute Stress Disorder and Posttraumatic Stress Disorder (PTSD)[42] (2004)**	• 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

Clinical Guideline	Recommendation(s)
	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 College of Obstetricians and Gynecologists (ACOG): **Practice Bulletin: Premenstrual Syndrome**[44] **(2000)**	• 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 (GnRH) 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.
American Psychiatric Association (APA): **Practice Guideline for the Treatment of Patients with Eating Disorders**[46] **(2006)**	• 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, tricyclic antidepressants, and monoamine oxidase inhibitors 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.
National Institute for Clinical Excellence (NICE): **Low Back Pain: Early Management of Persistent Non-Specific Low Back Pain**[164] **(2009)**	• The initial pharmacological treatment should be acetaminophen. • When acetaminophen alone provides insufficient pain relief, consider non-steroidal anti-inflammatory drugs and/or weak opioids. • Consider tricyclic antidepressants if other medicines provide insufficient pain relief. • Consider short-term use of strong opioids for patients in severe pain. • Skeletal muscle relaxants are not included among the pharmacological treatment options in this guideline.
American College of Physicians (ACP)/American Pain Society (APS): **Diagnosis and Treatment of Low Back Pain**[165] **(2007)**	• For most patients, first-line medication options are acetaminophen or nonsteroidal anti-inflammatory drugs. • Skeletal muscle relaxants are an option for short-term relief of acute low back pain, but all are associated with central nervous system adverse effects (primarily sedation). • There is no compelling evidence that skeletal muscle relaxants differ in efficacy or safety.
American College of Occupational and Environmental Medicine (ACOEM): **Low Back Disorders**[166] **(2007)**	Recommendations for the Treatment of Acute Low Back Pain include: • Nonsteroidal anti-inflammatory drugs (NSAIDs). • Cytoprotective agents for patients with contraindications for NSAIDs. • Acetaminophen if contraindications for NSAIDs. • Acetaminophen or aspirin as 1st-line therapy for patients with known or multiple risk factors for cardiovascular disease. • Skeletal muscle relaxants as 2nd-line treatment in select cases of moderate to severe acute low back pain (LBP). • Skeletal muscle relaxants are not recommended for mild to moderate acute LBP or chronic use in subacute or chronic LBP (other than acute exacerbations).
European League Against Rheumatism (EULAR): **Evidence-based Recommendations for the**	• 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.

Clinical Guideline	Recommendation(s)
Management of Fibromyalgia Syndrome[163] (2008)	• Corticosteroids and strong opioids are not recommended. • Amitriptyline, fluoxetine, duloxetine, milnacipran, moclobemide and pirlindole, 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 Pain Society (APS): **Guideline for the Management of Fibromyalgia Syndrome Pain in Adults and Children[48] (2005)**	Pharmacologic Therapies • Use multiple strategies and include both pharmacologic and nonpharmacologic therapies in the management of fibromyalgia syndrome (FMS). • For initial treatment of FMS, prescribe a tricyclic antidepressant for sleep, in particular 10 to 30 mg amitriptyline or cyclobenzaprine at bedtime. • Use selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, alone or in combination with tricyclics, for pain relief. • Do not use non-steroidal anti-inflammatory drugs (NSAIDs) as the primary pain medication for people with FMS. There is no evidence that NSAIDs are effective when used alone to treat FMS patients. NSAIDs, including COX-2 selective agents and acetaminophen, may provide some analgesia when used with other medications. • Use tramadol (50 to 100 mg two or three times daily) for pain relief in people with FMS. Tramadol can be used alone or in combination with acetaminophen. • Use opioids for management of FMS pain only after all other pharmacologic and nonpharmacologic therapies have been exhausted. • Use sleep and anti-anxiety medications such as trazodone, benzodiazepines, nonbenzodiazepine sedatives, or L-dopa and carbidopa in FMS, especially if sleep disturbances such as restless leg syndrome are prominent. • Do not use corticosteroids in the treatment of FMS unless there is concurrent joint, bursa, or tendon inflammation. Fibromyalgia Syndrome in Children and Adolescents • Utilize pharmacologic and nonpharmacologic strategies in the management of juvenile FMS (JFMS). • Use cognitive-behavioral training (CBT) to reduce pain and psychological disability by enhancing self-efficacy, self-management, and skills for coping with pain. • Use aerobic exercise to minimize pain, improve sleep quality, enhance self-efficacy and increase positive mood. • Emphasize sleep hygiene as part of the treatment plan, using both pharmacologic and nonpharmacologic techniques. • Treat anxiety and depression aggressively with both pharmacologic and nonpharmacologic approaches. • Fluoxetine should be the first antidepressant agent used to treat depression in children and adolescents; however, all of these medications should be used only with extreme caution and extensive parental education.
American Academy of Neurology (AAN)/American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM)/American Academy of Physical Medicine and Rehabilitation (AAPMR): **Evidence-based Guideline:**	Anticonvulsants • If clinically appropriate, pregabalin should be offered for the treatment of painful diabetic neuropathy (PDN). • Gabapentin and sodium valproate should be considered for the treatment of PDN. • There is insufficient evidence to support or refute the use of topiramate for the treatment of PDN. • Oxcarbazepine, lamotrigine, and lacosamide should probably not be

Clinical Guideline	Recommendation(s)
Treatment of Painful Diabetic Neuropathy[34] (2011)	considered for the treatment of PDN. Antidepressants • Amitriptyline, venlafaxine, and duloxetine should be considered for the treatment of PDN. Data are insufficient to recommend one of these agents over the others. • 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 PDN. Opioids • Dextromethorphan, morphine sulfate, tramadol, and oxycodone should be considered for the treatment of PDN. Data are insufficient to recommend one agent over the other. Other Pharmacologic Agents • Capsaicin and isosorbide dinitrate spray should be considered for the treatment of PDN. • Clonidine, pentoxifylline, and mexiletine should probably not be considered for the treatment of PDN. • The Lidoderm patch may be considered for the treatment of PDN. • There is insufficient evidence to support or refute the usefulness of vitamins and α-lipoic acid in the treatment of PDN.
European Federation of Neurological Societies (EFNS): **Guidelines on the Pharmacological Treatment of Neuropathic Pain: 2010 Revision[45] (2010)**	Painful Polyneuropathy (PPN) • TCA, gabapentin, pregabalin and SNRI (duloxetine, venlafaxine) are recommended as first-line treatments in PPN. • Tramadol is recommended second-line except for patients with exacerbations of pain (for the tramadol/acetaminophen combination) or those with predominant coexisting non-neuropathic pain. • Third-line therapy includes strong opioids because of concerns regarding their long-term safety including addiction potential and misuse. Central Neuropathic Pain (CP) • Pregabalin, amitriptyline or gabapentin are recommended as first-line therapy in CP. • Tramadol may be considered second-line. • Strong opioids are recommended second- or third-line if chronic treatment is not an issue. • Lamotrigine may be considered in CPSP or SCI pain with incomplete cord lesion and brush-induced allodynia and cannabinoids in MS only if all other treatments fail.

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[1-32]

Generic Name(s)	Depression	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; diabetic peripheral neuropathic pain; fibromyalgia
Venlafaxine	✔	✔ †			✔ †				✔ †	
Selective Serotonin-reuptake Inhibitors										
Citalopram	✔									
Escitalopram	✔	✔								
Fluoxetine	✔			✔	✔		✔			Bulimia nervosa
Fluvoxamine				✔						
Paroxetine	✔	✔ §		✔ §	✔	✔ §	✔ †		✔	
Serotonin Modulators										
Nefazodone	✔									
Trazodone	✔									
Vilazodone	✔									
Tricyclics and Other Norepinephrine-reuptake Inhibitors										
Amitriptyline	✔									
Amitriptyline and chlordiazepoxide			✔							
Amoxapine	✔		✔							
Clomipramine				✔						
Desipramine	✔									

Generic Name(s)	Depression	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
Doxepin	✔		✔							Insomnia
Imipramine	✔									Pediatric nocturnal enuresis
Maprotiline	✔									
Nortriptyline	✔									
Protriptyline	✔									
Trimipramine	✔									
Antidepressants, Miscellaneous										
Bupropion	✔							✔ †		
Mirtazapine	✔									

†Extended-release formulation only.
§Immediate-release formulation only.

IV. Pharmacokinetics

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

Table 4. Pharmacokinetic Parameters of the Antidepressants[1-32]

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	25-30	90	Liver	Renal (10) Feces (2)	18-25
Tranylcypromine	Not reported	Not reported	Not reported	Renal	1.5-3.5
Selective Serotonin- and Norepinephrine-reuptake Inhibitors					
Desvenlafaxine	80	30	Liver	Renal (45)	10-11
Duloxetine	30-80	>90	Liver	Renal (70) Feces (20)	8-17
Venlafaxine	12.6-45	27-30	Liver	Renal (87) Feces (2)	5
Selective Serotonin-reuptake Inhibitors					
Citalopram	80	80	Liver	Renal (20) Feces	24-48
Escitalopram	80	56	Liver	Renal (8)	22-32
Fluoxetine	100	95	Liver	Renal (60) Feces (12)	96-144
Fluvoxamine	53	80	Liver	Renal (94)	15-16
Paroxetine	Completely absorbed	95	Liver	Renal (65-67) Feces (36-37)	15-22
Sertraline	Not reported	99	Liver	Renal (40-45) Feces (40-45)	24
Serotonin Modulators					
Nefazodone	20	>99	Liver	Renal (55) Feces (20-30)	1.9-5.3
Trazodone	65	89-95	Liver	Renal (70-75) Feces (21)	7-8
Vilazodone	72	96-99	Liver	Renal (1) Feces (2)	25
Tricyclics and Other Norepinephrine-reuptake Inhibitors					
Amitriptyline	100	90-95	Liver	Renal (18)	9-27
Amitriptyline and chlordiazepoxide	100	90-98	Liver	Renal (18)	A: 9-27 C: 6.6-48
Amoxapine	18-54	90	Liver	Renal (69) Feces (18)	8
Clomipramine	20-78	97	Liver	Renal (51-60) Feces (24-32)	19-37
Desipramine	Not reported	Not reported	Liver	Renal (70)	14.3-24.7
Doxepin	Not reported	79-84	Liver	Bile	16.8
Imipramine	94-96	89	Liver	Renal	6-18
Maprotiline	100	88	Liver	Renal (70) Feces (30)	27-53
Nortriptyline	60	93-95	Liver	Renal Feces	28-31
Protriptyline	Not reported	Not reported	Liver	Renal Feces	54-198
Trimipramine	Not reported	95	Liver	Renal	23

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Antidepressants, Miscellaneous					
Bupropion	Not reported	84	Liver	Renal (87)	14-21
Mirtazapine	50	85	Liver	Renal (75) Feces (15)	20-40

V. Drug Interactions

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

Table 5. Significant Drug Interactions with the Antidepressants[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Monoamine Oxidase Inhibitors (MAOIs)			
MAOIs	1	Atomoxetine	Increased risk of serious or fatal reactions, including hyper-thermia, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes. Altered brain monoamine concentrations are possible.
MAOIs	1	Bupropion	Risk of acute bupropion toxicity may be increased, although the exact mechanism is unknown.
MAOIs	1	Buspirone	Possible increased risk of adverse effects, including severe hypertension. The mechanism is unknown.
MAOIs	1	Cyclobenzaprine	Concurrent use of cyclobenzaprine and MAOIs may increase the likelihood of hyperpyretic crisis, severe seizures and death. Though the mechanism of action is unknown, it is likely that adrenergic activity is enhanced with concurrent administration.
MAOIs	1	Dextromethorphan	Hyperpyrexia, abnormal muscle movement, hypotension, coma, and death have been associated with the coadministration of these agents.
MAOIs (isocarboxazid, phenelzine, tranylcypromine)	1	Levodopa	These MAOIs may increase pharmacologic and toxic effects of levodopa. Precipitation of a hypertensive crisis is possible. These MAOIs may decrease the enzymatic degradation of dopamine and norepinephrine formed from levodopa.
MAOIs	1	Linezolid	Adverse effects may be increased with concurrent administration of linezolid and

Generic Name(s)	Significance Level	Interaction	Mechanism
			MAOIs. The mechanism is unknown.
MAOIs	1	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.
MAOIs (selegiline)	1	Methadone	A severe reaction potentially involving the respiratory, cardiac and central nervous systems may occur shortly after administering methadone to patients receiving selegiline.
MAOIs	1	Methylphenidates	There is an increased risk of hypertensive crisis with the coadministration of MAOIs and methylphenidates. The precise mechanism of this interaction is unknown.
MAOIs	1	Nefazodone	The therapeutic effects of both drugs may be increased; however, additional toxicity may occur. The mechanism of this interaction is unknown.
MAOIs	1	Norepinephrine Reuptake Blockers	Toxic effects may be increased with concurrent administration of norepinephrine reuptake inhibitors and MAOIs. Serious and sometimes fatal reactions have occurred. Pharmacologic effects of these agents may be additive.
MAOIs	1	SNRIs and SSRIs	Additive adverse effects, including serious central nervous system reactions, have been reported in patients receiving the combination. Serotonin syndrome may result from concurrent administration.
MAOIs	1	Sympathomimetics	Coadministration of a MAOI and a sympathomimetic agent may cause a hypertensive crisis.
MAOIs	1	Tetrabenazine	The combination of MAOIs and tetrabenazine may produce severe unexpected toxicity. The mechanism of this interaction is unknown.
MAOIs	1	Tetracyclic antidepressants	Concomitant administration tetracyclic antidepressants and MAOIs may enhance the sympathomimetic effects of tetracyclic antidepressants. Nausea, dizziness, agitated

Generic Name(s)	Significance Level	Interaction	Mechanism
			delirium progressing to generalized hypertonicity, seizures, hyperpyrexia, dyspnea, and cardiovascular instability may occur. The mechanism of this interaction is unknown.
MAOIs	1	Tramadol	A severe reaction potentially involving the respiratory, cardiac, and central nervous system may occur shortly after administering tramadol to patients receiving MAOIs. The seizure threshold may also be reduced. The mechanism of this interaction is unknown.
MAOIs	1	Trazodone	The potential for the development of serotonin syndrome exists with concurrent use of MAOIs and trazodone. These agents may increase central nervous system serotonin activity, perhaps synergistically.
MAOIs	1	Tricyclic antidepressants	Hyperpyretic crises, convulsions, and death have occurred as a result of this interaction, although the exact mechanism is unclear.
MAOIs	1	Triptans	Prolonged vasospastic reaction is a possibility when triptans and MAOIs are coadministered. The potential for development of serotonin syndrome also exists. Inhibition of monoamine oxidase may decrease the metabolic elimination of triptans. Other mechanisms may exist.
MAOIs	2	Carbamazepine	On a theoretical basis, the administration of carbamazepine with MAOIs could cause a hypertensive or hyperpyretic crisis. The mechanism of this interaction is unknown.
MAOIs (isocarboxazid, phenelzine, tranylcypromine)	2	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.
MAOIs	2	Ginseng	Use of isocarboxazid with ginseng may produce unexpected toxic effects. The mechanism of this interaction is unknown.

Generic Name(s)	Significance Level	Interaction	Mechanism
MAOIs	2	Insulin	Coadministration of MAOIs may potentiate the hypoglycemic response to insulin and delayed recovery from hypoglycemia. This interaction may be the result of stimulation of insulin secretion and inhibition of gluconeogenesis.
MAOIs	2	Meglitinides	The hypoglycemic effects of meglitinides may be increased by MAOIs. Although the mechanism is unknown, both a direct effect of MAOIs on insulin release and interference with the sympathetic response to hypoglycemia have been suggested.
MAOIs (isocarboxazid, phenelzine, tranylcypromine)	2	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. The mechanism of this interaction is unknown.
MAOIs	2	Propoxyphene	A severe reaction potentially involving the respiratory, cardiac and central nervous systems may occur shortly after administering propoxyphene to patients receiving MAOIs. A clear causal relationship has not been established by the available literature; the mechanism is unknown.
MAOIs	2	Sibutramine	Use of sibutramine with MAOIs has been reported to increase the potential risk for serotonin syndrome. The mechanism of this interaction is unknown.
MAOIs	2	Sulfonylureas	MAOIs enhance the hypoglycemic action of sulfonylureas.
MAOIs	2	Tryptophan	The combination of MAOIs and tryptophan may produce severe unexpected toxicity. The mechanism is unknown.
Selective Serotonin- and Norepinephrine-reuptake Inhibitors			
SNRIs (desvenlafaxine, venlafaxine)	1	Linezolid	Serotonin syndrome may occur, possibly due to excessive accumulation of serotonin. Coadminister linezolid and SRIs with caution.
SNRIs	1	MAOIs	Use of MAOIs and SNRIs may increase the risk of adverse

Generic Name(s)	Significance Level	Interaction	Mechanism
			effects. Together, these agents may exert additive pharmacologic activity potentially leading to severe central nervous system toxicity.
SNRIs	1	Methylene blue	Coadministration of methylene blue and desvenlafaxine may increase the risk of central nervous system toxicity, including serotonin syndrome.
SNRIs (duloxetine)	1	Phenothiazines	Plasma concentrations and pharmacologic effects of phenothiazines may be increased by duloxetine. The possibility of serious ventricular dysrhythmias should be considered. Inhibition of CYP2D6 isoenzymes by duloxetine may decrease the metabolic elimination of phenothiazines; the combination should be avoided.
SNRIs (desvenlafaxine, venlafaxine)	1	Selegiline	The combination of these SNRIs and Selegiline may produce unexpected toxicity, characterized by manic-like behavior, shivering, diaphoresis, hypertension and ataxia. The mechanism of this interaction is unknown.
SNRIs (desvenlafaxine, venlafaxine)	1	Sibutramine	A serotonin syndrome may occur as the serotonergic effects of these agents may be additive.
SNRIs (duloxetine)	1	Tamoxifen	Pharmacologic effects of Tamoxifen may be decreased by Duloxetine. Coadministration of Duloxetine with Tamoxifen may increase the risk of breast cancer recurrence.
SNRIs	1	Tramadol	Increased risk of seizures is a possibility when tramadol and SNRIs are coadministered. Serotonin syndrome is also a risk with this combination. The mechanism of this interaction is unknown. Concomitant use is not recommended.
SNRIs (desvenlafaxine, venlafaxine)	2	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 (venlafaxine)	2	Bupropion	Unexpected adverse effects, including serotonin syndrome, may occur when Venlafaxine

Generic Name(s)	Significance Level	Interaction	Mechanism
			and Bupropion are coadministered. The mechanism of this interaction is unknown.
SNRIs (desvenlafaxine, venlafaxine)	2	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)	2	Fenfluramine & Derivatives	Use of fenfluramine and derivatives with these SNRIs may increase the risk of adverse effects, including the serotonin syndrome.
SNRIs (duloxetine)	2	Flecainide	Plasma concentrations of flecainide may be increased by duloxetine. Inhibition of CYP2D6 isoenzymes by duloxetine may decrease the metabolic elimination of flecainide.
SNRIs	2	Iobenguane	SNRIs may reduce uptake and diagnostic efficacy of Iobenguane. False-negative Iobenguane imaging tests may result. Inhibition of norepinephrine reuptake by SNRIs may result in decreased uptake of the structurally similar Iobenguane
SNRIs (desvenlafaxine, venlafaxine)	2	Ketorolac (nasal)	Toxic effects may be increased with concurrent administration of ketorolac (nasal) and these SNRIs. The risk of upper gastrointestinal bleeding may be increased. The mechanism of this interaction is unknown.
SNRIs	2	L-Tryptophan	Coadministration may lead to the development of serotonin syndrome. Both agents increase CNS serotonin activity.
SNRIs (desvenlafaxine, venlafaxine)	2	Lithium	Coadministration of lithium and desvenlafaxine or venlafaxine may cause CNS toxicity, including serotonin syndrome. Serum lithium concentrations may be increased due to increased serotonergic neurotransmission.
SNRIs (desvenlafaxine, venlafaxine)	2	Narcotic analgesics	The toxic effects of desvenlafaxine and venlafaxine with narcotic analgesics may be additive resulting in the development of serotonin syndrome.
SNRIs	2	NSAIDs	The toxic effects may be

Generic Name(s)	Significance Level	Interaction	Mechanism
(desvenlafaxine, venlafaxine)			increased with concurrent administration of NSAIDs and desvenlafaxine/venlafaxine. The risk of upper GI bleeding may be increased. The mechanism is unknown. Prolonged use of desvenlafaxine or venlafaxine may lead to depletion of serotonin in platelets, which is thought to play an important role in hemostasis.
SNRIs (duloxetine)	2	Propafenone	Plasma concentrations of propafenone may be increased by duloxetine due to inhibition of CYP2D6 isoenzymes.
SNRIs (duloxetine)	2	Quinolones	Plasma concentrations and pharmacologic effects of duloxetine may be increased when coadministered with quinolones. Inhibition of CYP1A2 by quinolones may decrease the metabolic elimination of duloxetine.
SNRIs (desvenlafaxine, venlafaxine)	2	Salicylates	The risk of upper Gl bleeding may 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	2	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 (desvenlafaxine, venlafaxine)	2	St. John’s wort	Unexpected toxicity may occur when St. John's wort and desvenlafaxine/venlafaxine are coadministered; the mechanism is unknown.
SNRIs (duloxetine)	2	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 (venlafaxine)	2	Terbinafine	Plasma concentrations and pharmacologic effects of venlafaxine may be increased

Generic Name(s)	Significance Level	Interaction	Mechanism
			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.
SNRIs (desvenlafaxine, venlafaxine)	2	Trazodone	Unexpected toxic effects may occur when trazodone is combined with desvenlafaxine or venlafaxine. The mechanism is unknown.
Selective Serotonin-reuptake Inhibitors (SSRIs)			
SSRIs (citalopram, escitalopram)	1	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, fluvoxamine, paroxetine, sertraline)	1	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	1	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 (citalopram)	1	Nilotinib	Prolongation of the QT interval with possible development of cardiac arrhythmias, including torsades de pointes, should be considered when Citalopram is coadministered with nilotinib. Pharmacologic effects of citalopram and nilotinib on electrical conduction tissue in the heart may be additive.
SSRIs (fluoxetine, fluvoxamine paroxetine)	1	Phenothiazines (chlorpromazine, thioridazine)	Pharmacologic effects and plasma concentrations of phenothiazines may be increased by SSRIs. Neurologic and cardiac toxicity may occur. Inhibition of CYP2D6 isoenzymes by SSRIs may decrease the elimination of phenothiazines.
SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine,	1	Pimozide	Plasma concentrations of pimozide may be increased by SSRIs. The risk of life-

Generic Name(s)	Significance Level	Interaction	Mechanism
sertraline)			threatening cardiac arrhythmias, including torsades de pointes, may be increased. The mechanism is unknown.
SSRIs (fluvoxamine)	1	Ramelteon	Plasma concentrations of ramelteon may be increased by coadministration of fluvoxamine. Inhibition of CYP1A2 by fluvoxamine may decrease the metabolic elimination of ramelteon.
SSRIs (fluoxetine, paroxetine)	1	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. The mechanism of this interaction is unknown.
SSRIs	1	Sibutramine	Serotonin syndrome may occur, since the serotonergic effects of these agents may be additive.
SSRIs (fluoxetine, paroxetine sertraline)	1	Tamoxifen	Pharmacologic effects of tamoxifen may be decreased by certain SSRIs. Coadministration may increase the risk of breast cancer recurrence. Inhibition of CYP2D6 isoenzymes by certain SSRIs may decrease the formation of endoxifen, an active metabolite of tamoxifen.
SSRIs (fluvoxamine)	1	Tizanidine	Tizanidine plasma concentrations may be elevated. Inhibition of tizanidine metabolism by fluvoxamine is suspected as a potential mechanism.
SSRIs	1	Tramadol	Serotonin syndrome may occur as the serotonergic effects of these agents may be additive.
SSRIs (citalopram)	1	Vandetanib	Additive QT prolongation may occur during coadministration of vandetanib and citalopram. The mechanism of this interaction is unknown.
SSRIs (paroxetine)	2	Abiraterone	Plasma concentrations and pharmacologic effects of paroxetine may be increased by abiraterone, due to the inhibition of CYP2D6 by abiraterone.
SSRIs	2	Anticoagulants	The risk of bleeding with anticoagulants may be potentiated with concomitant use

Generic Name(s)	Significance Level	Interaction	Mechanism
			of SSRIs and patients are at an increased risk of bleeding. The mechanism of this interaction is unknown.
SSRIs (citalopram, escitalopram, fluoxetine, paroxetine, sertraline)	2	Beta-Blockers	Coadministration of SSRIs and beta-blockers may increase risk of cardiac and central nervous system toxicity, due to the inhibition of CYP2D6 isoenzymes.
SSRIs (fluoxetine, sertraline)	2	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)	2	Carbamazepine	Plasma concentrations and pharmacologic effects of carbamazepine may be increased by these SSRIs. Toxicity may occur. Toxic serotonin syndrome may also occur.
SSRIs (fluvoxamine)	2	Cisapride	Fluvoxamine may decrease the hepatic metabolism and increase serum concentrations of cisapride. Cardiac arrhythmias, including torsades de pointes, may occur.
SSRIs	2	Cyproheptadine	Decreased pharmacologic effects of SSRIs may result. Since cyproheptadine is a serotonin antagonist, the interaction may occur at the receptor level.
SSRIs (fluoxetine)	2	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. This interaction may be because both agents inhibit CYP3A4 and 2D6.
SSRIs (fluoxetine)	2	Hydantoins	Serum hydantoin concentrations may be elevated. Close monitoring of hydantoin levels and observing patients for toxicity or loss of therapeutic activity if fluoxetine is started or stopped is advised.
SSRIs (fluoxetine, paroxetine)	2	Iloperidone	Plasma concentrations and pharmacologic effects of iloperidone may be increased by these SSRIs, due to their inhibition of CYP 2D6.
SSRIs	2	Ketorolac (nasal)	Toxic effects may be increased

Generic Name(s)	Significance Level	Interaction	Mechanism
			with concurrent administration of ketorolac and SSRIs. The risk of upper gastrointestinal bleeding may be increased. The mechanism of this interaction is unknown
SSRIs	2	L-tryptophan	Administration of SSRIs with L-tryptophan may produce the serotonin syndrome, possibly because both agents exhibit serotonergic activity.
SSRIs	2	Narcotic analgesics	Toxic effects of SSRIs and narcotic analgesics may be additive, resulting in the development of serotonin syndrome.
SSRIs	2	NSAIDs	Toxic effects may be increased with concurrent administration of NSAIDs and SSRIs. The risk of upper GI bleeding may be increased. The mechanism is unknown. Prolonged use of SSRIs may lead to depletion of serotonin in platelets, which is thought to play an important role in hemostasis.
SSRIs	2	Salicylates	The risk of upper Gl bleeding may be increased with concurrent administration of salicylates SSRIs. The mechanism is unknown. Prolonged use of SSRIs may lead to depletion of serotonin, which is thought to play an important role in hemostasis.
SSRIs	2	SNRIs	The development of serotonin syndrome is possible when SNRIs and SSRIs are coadministered. Plasma concentrations of SNRIS may be increased by SSRIs. The potential exists for the occurrence of additive serotonergic activity. Inhibition of CYP2D6 isoenzymes by citalopram may decrease the metabolic elimination of SNRIs.
SSRIs	2	St. John’s wort	Unexpected toxicity may occur when St. John's wort and SSRIs are coadministered. The mechanism is unknown.
SSRIs (fluvoxamine)	2	Tacrine	Plasma tacrine concentrations may be elevated, possibly due to the CYP1A2 inhibition of tacrine metabolism by fluvoxamine.

Generic Name(s)	Significance Level	Interaction	Mechanism
SSRIs (fluoxetine, paroxetine)	2	Tetrabenazine	Plasma concentrations and pharmacologic effects of tetrabenazine may be increased by these SSRIs, due to their inhibition of CYP 2D6.
SSRIs (fluvoxamine)	2	Theophyllines	Increased theophylline serum concentrations may occur. Fluvoxamine inhibits the hepatic metabolism (CYP1A2) of theophylline.
Serotonin Modulators			
Nefazodone	1	Aldosterone blockers	Nefazodone may increase plasma concentrations and pharmacologic or toxic effects of aldosterone blockers.
Nefazodone	1	Cisapride	Cisapride and nefazodone may, in theory, cause torsades de pointes and other types of ventricular arrhythmias.
Nefazodone	1	Colchicine	Plasma concentrations of colchicine may be increased by nefazodone and life-threatening and fatal colchicine toxicity may occur. Inhibition of CYP3A4 or P-glycoprotein transporter protein by nefazodone may increase the absorption and decrease the elimination of colchicine.
Nefazodone	1	Crizotinib	Plasma concentrations and toxic effects of crizotinib may be increased by nefazodone4.
Nefazodone	1	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.
Nefazodone	1	Dronedarone	Plasma concentrations and pharmacologic effects of dronedarone may be increased by nefazodone. Inhibition of CYP3A4 by nefazodone may decrease the metabolic elimination of dronedarone.
Nefazodone	1	H-1 antagonists	Coadministration of nefazodone and H-1 antagonists may cause severe cardiac abnormalities.
Nefazodone	1	Lurasidone	Plasma concentrations and pharmacologic effects of lurasidone may be increased by nefazodone due to the inhibition of CYP3A4 by nefazodone.
Nefazodone	1	Nilotinib	Plasma concentrations and pharmacologic effects of

Generic Name(s)	Significance Level	Interaction	Mechanism
			nilotinib may be increased by nefazodone. Inhibition of CYP3A4 isoenzymes by nefazodone may decrease the metabolic elimination of nilotinib.
Nefazodone	1	Pimozide	The risk of life-threatening cardiac arrhythmias may be increased, as nefazodone may inhibit the metabolism (CYP3A4) of pimozide.
Nefazodone	1	Ranolazine	Plasma concentrations and pharmacologic effects of ranolazine may be increased when coadministered with nefazodone. Inhibition of CYP3A4 by nefazodone may decrease the metabolic elimination of ranolazine.
Nefazodone	1	Statins	The risk of rhabdomyolysis and myositis may be increased with certain statins. Nefazodone inhibits the metabolism of statins.
Nefazodone	1	Sympathomimetics	The pharmacologic effects of sympathomimetics may be increased by nefazodone. Elevated sympathomimetic plasma concentrations with cardiovascular toxicity may occur. Inhibition of CYP3A4 isoenzymes by nefazodone may decrease the metabolic elimination of the sympathomimetic dose
Nefazodone	1	Ticagrelor	Plasma concentrations and pharmacologic effects of ticagrelor may be increased by nefazodone due to the inhibition of CYP3A4 by nefazodone.
Nefazodone	1	Toremifene	Plasma concentrations and pharmacologic effects of toremifene may be increased by nefazodone. Toxicity, including QT prolongation may occur.
Nefazodone	1	Vasopressin receptor agonists	Plasma concentrations and pharmacologic effects of vasopressin receptor antagonists may be increased by nefazodone. Inhibition of CYP3A4 by nefazodone may decrease the metabolic elimination of vasopressin receptor antagonists.
Trazodone	1	Sodium oxybate	Concurrent use of sodium oxybate and trazodone may

Generic Name(s)	Significance Level	Interaction	Mechanism
			result in an increase in sleep duration and CNS depression, due to additive effects.
Vilazodone	1	Linezolid	Coadministration of vilazodone and linezolid may cause central nervous system toxicity characterized by symptoms of serotonin syndrome.
Vilazodone	1	Methylene blue	Coadministration of vilazodone and methylene blue may increase the risk of central nervous system toxicity, including serotonin syndrome. This may be the result in increased serotonin concentrations in the central nervous system and produce serotonin-related toxicity.
Vilazodone	1	Selegiline	The combination of vilazodone and selegiline may produce unexpected toxicity, characterized by manic-like behavior, shivering, diaphoresis, hypertension and ataxia. The mechanism of this interaction is unknown.
Vilazodone	1	Sibutramine	Use of sibutramine with vilazodone has been reported by the manufacturer of sibutramine to increase the potential risk for serotonin syndrome. The mechanism of this interaction is unknown.
Vilazodone	1	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. The mechanism of this interaction is unknown.
Nefazodone	2	Axitinib	Plasma concentrations and pharmacologic effects of axitinib may be increased by nefazodone.
Nefazodone	2	Benzodiazepines	Nefazodone may increase the pharmacologic effects of certain benzodiazepines. Impaired psychomotor performance and increased sedation may result from elevated benzodiazepine plasma concentrations. Inhibition of CYP3A4 isoenzymes by nefazodone may decrease the metabolic

Generic Name(s)	Significance Level	Interaction	Mechanism
			elimination of certain benzodiazepines.
Nefazodone	2	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 (MMAE), the microtubule disrupting agent in brentuximab.
Nefazodone	2	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	2	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	2	Cabazitaxel	Plasma concentrations and pharmacologic effects cabazitaxel may be increased by nefazodone due to the inhibition of CYP3A4 by nefazodone.
Nefazodone	2	Cilostazol	Plasma concentration and pharmacologic effects of cilostazol may be increased by nefazodone due to the inhibition of CYP3A4 by nefazodone.
Nefazodone	2	Cyclosporine	Cyclosporine concentration may be increased as nefazodone may inhibit the metabolism (CYP3A4) of cyclosporine.
Nefazodone	2	Epothilones	The pharmacologic effects of epothilones may be increased by nefazodone due to a decrease in the metabolic elimination of epothilones through the inhibition of CYP3A4 by nefazodone.
Nefazodone	2	Erlotinib	Plasma concentrations of erlotinib may be increased by coadministration of nefazodone. The potential for increased adverse effects due to erlotinib exists. Inhibition of CYP3A4 isoenzymes by nefazodone may

Generic Name(s)	Significance Level	Interaction	Mechanism
			decrease the metabolic elimination of erlotinib.
Nefazodone	2	Eszopiclone	Plasma concentrations and the pharmacologic effects of eszopiclone may be increased by nefazodone. Inhibition of CYP3A4 by nefazodone may decrease the metabolic elimination of eszopiclone.
Nefazodone	2	Histone deacetylase inhibitors	Plasma concentrations and pharmacologic effects of histone deacetylase inhibitors may be increased by nefazodone. The potential for histone deacetylase inhibitors-related adverse effects, including QT prolongation, should be considered.
Nefazodone and Trazodone	2	HIV protease inhibitors	HIV protease inhibitors may increase the plasma concentration of nefazodone, which may be due to the inhibition of CYP3A4 by HIV protease inhibitors, which may decrease the metabolic elimination of nefazodone.
Nefazodone	2	Iloperidone	Plasma concentrations and pharmacologic effects of iloperidone may be increased by nefazodone.
Nefazodone	2	Ivacaftor	Plasma concentrations and pharmacologic effects of ivacaftor may be increased by nefazodone.
Nefazodone	2	Maraviroc	The pharmacologic effects of maraviroc may be increased by nefazodone. Inhibition of CYP3A4 isoenzymes by nefazodone may decrease the metabolic elimination of maraviroc.
Nefazodone	2	Mifepristone	Plasma concentrations and pharmacologic effects of mifepristone may be increased by nefazodone due to the inhibition of CYP3A4 by nefazodone.
Nefazodone	2	MTOR inhibitors	Pharmacologic effects of MTOR inhibitors may be increased by nefazodone. Inhibition of CYP34A isoenzymes by nefazodone may decrease the metabolic elimination of MTOR inhibitors.
Nefazodone	2	Muscarinic receptor antagonists	Plasma concentrations and pharmacologic effects of

Generic Name(s)	Significance Level	Interaction	Mechanism
			muscarinic receptor antagonists may be increased by nefazodone. Inhibition of CYP3A4 by nefazodone may decrease the metabolic elimination of muscarinic receptor antagonists.
Nefazodone and Vilazodone	2	Narcotic analgesics	Plasma concentrations and pharmacologic effects of narcotic analgesics may be increased by these serotonin modulators. Inhibition of CYP3A4 metabolism by these serotonin modulators may decrease the metabolic elimination of narcotic analgesics.
Nefazodone	2	Oxycodone	Plasma concentrations and pharmacologic effects of oxycodone may be increased by nefazodone due to the inhibition of CYP3A4 by nefazodone.
Nefazodone	2	Ruxolitinib	Plasma concentrations and pharmacologic effects of ruxolitinib may be increased by nefazodone.
Nefazodone	2	Saxagliptin	Plasma concentrations and pharmacologic effects of saxagliptin may be increased by nefazodone due to the inhibition of CYP3A4 by nefazodone.
Nefazodone	2	Triptans	Plasma concentrations and pharmacologic effects of triptans may be increased by nefazodone due to the inhibition of CYP3A4 by nefazodone.
Nefazodone	2	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	2	Vilazodone	Plasma concentrations and pharmacologic effects of vilazodone may be increased by nefazodone due to the inhibition of CYP3A4 by nefazodone.
Trazodone	2	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.
Trazodone	2	SSRIs	Unexpected toxic effects may

Generic Name(s)	Significance Level	Interaction	Mechanism
			occur when trazodone and certain SSRIs are coadministered. The mechanism of this interaction is unknown.
Vilazodone	2	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	2	Fenfluramine & derivatives	Use of fenfluramine and derivatives with vilazodone may increase the risk of adverse effects, including serotonin syndrome due to both of the agents' ability to increase the activity of serotonin.
Vilazodone	2	Ketorolac (nasal)	Toxic effects may be increased with concurrent administration of nasal ketorolac and vilazodone. The risk of upper gastrointestinal bleeding may be increased. The mechanism of this interaction is unknown.
Vilazodone	2	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	2	L-tryptophan	Both agents acutely increase CNS serotonin activity. Coadministration of these two agents could result in serotonin syndrome.
Vilazodone	2	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	2	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	2	SNRIs	The potential exists for the occurrence of additive serotonergic activity. Inhibition of cytochrome P450 2D6 isoenzymes by vilazodone may

Generic Name(s)	Significance Level	Interaction	Mechanism
			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	2	St. john's wort	Unexpected toxicity may occur when St. john's wort and vilazodone are coadministered. The mechanism of this is unknown.
Vilazodone	2	Strong CYP3A4 inhibitors	Strong CYP3A4 inhibitors may decrease the metabolic elimination of vilazodone, increasing the plasma concentrations and pharmacological effects of vilazodone.
Tricyclics and Other Norepinephrine-reuptake Inhibitors			
Tricyclic antidepressants (doxepin, maprotiline, nortriptyline)	1	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.
Tricyclic antidepressants (amitriptyline/ chlordiazepoxide)	1	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.
Tricyclic antidepressants (maprotiline)	1	Class III antiarrhythmics	Additive QT prolongation may occur when class III antiarrhythmics and maprotiline are coadministered. Use of class III antiarrhythmics and maprotiline is not recommended.
Tricyclic antidepressants (amitriptyline/ chlordiazepoxide)	1	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

Generic Name(s)	Significance Level	Interaction	Mechanism
			interaction is unknown. Clozapine and amitriptyline-chlordiazepoxide should not be started simultaneously.
Tricyclic antidepressants (amitriptyline, desipramine, imipramine, maprotiline)	1	Droperidol	Arrhythmias resulting from the potential for additive QT prolongation should be considered as a possibility when droperidol and certain tricyclic antidepressants are coadministered.
Tricyclic antidepressants (maprotiline)	1	Furazolidone	Concomitant administration of maprotiline and furazolidone may enhance the sympathomimetic effects of maprotiline. The mechanism is unknown.
Tricyclic antidepressants (maprotiline)	1	Halofantrine	Prolonged QT interval and cardiac arrhythmias are a potential when halofantrine and maprotiline are used concomitantly.
Tricyclic antidepressants	1	MAOIs	Although the combination of MAOIs and TCAs may be useful for treating depression, severe, sometimes lethal, toxicity may occur. Mechanism of this interaction is unknown.
Tricyclic antidepressants (clomipramine)	1	Methylene Blue	Coadministration of clomipramine and methylene blue may increase the risk of central nervous system toxicity, including serotonin syndrome.
Tricyclic antidepressants (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)	1	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.
Tricyclic antidepressants (maprotiline)	1	Nilotinib	Additive QT prolongation may occur during coadministration of nilotinib and maprotiline.
Tricyclic antidepressants (amitriptyline, desipramine, imipramine)	1	Pimozide	Certain TCAs and pimozide may cause additive adverse effects when coadministered. Cardiovascular toxicity may occur due to additive QT-interval prolongation.
Tricyclic antidepressants (maprotiline)	1	Quinolones	The risk of life-threatening cardiac arrhythmias may be increased. The exact mechanism is unknown. Levofloxacin should be avoided, while

Generic Name(s)	Significance Level	Interaction	Mechanism
			gatifloxacin and moxifloxacin should be used with caution.
Tricyclic antidepressants (nortriptyline)	1	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.
Tricyclic antidepressants (amitriptyline-chlordiazepoxide)	1	Sodium oxybate	Concurrent use of sodium oxybate and amitriptyline-chlordiazepoxide may result in an additive increase in sleep duration and CNS depression.
Tricyclic antidepressants (doxepin, maprotiline, nortriptyline)	1	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.
Tricyclic antidepressants (doxepin, maprotiline, nortriptyline)	1	Vandetanib	Additive QT prolongation may occur during coadministration of vandetanib and these TCAs.
Tricyclic antidepressants (amoxapine, clomipramine, desipramine, maprotiline, nortriptyline)	2	Abiraterone	Plasma concentrations and pharmacologic effects of these tricyclic antidepressants may be increased by abiraterone. Inhibition of CYP2D6 by abiraterone may decrease the metabolic elimination of these drugs.
Tricyclic antidepressants (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline)	2	Carbamazepine	Serum carbamazepine levels may be elevated, increasing pharmacologic and toxic effects, while TCA levels may be decreased. TCAs may compete with carbamazepine for hepatic microsomal enzyme metabolism, and carbamazepine may induce the hepatic metabolism of TCAs.
Tricyclic antidepressants (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline,	2	Cimetidine	Increased serum concentrations of the TCA may occur as a result of the interference with the metabolism of the TCA and decreased first-pass effects. The result of this interaction may lead to increased bioavailability

Generic Name(s)	Significance Level	Interaction	Mechanism
trimipramine)			and elevated serum concentrations.
Tricyclic antidepressants (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)	2	Clonidine	Loss of blood pressure control and possibly life-threatening elevations in blood pressure may result. This may be the result of inhibition of the central alpha$_2$-adrenergic receptors by TCAs.
Tricyclic antidepressants (amitriptyline-chlordiazepoxide)	2	Disulfiram	Pharmacologic effects of amitriptyline-chlordiazepoxide may be increased by disulfiram. Disulfiram may inhibit hepatic metabolism of amitriptyline-chlordiazepoxide and increase plasma concentrations.
Tricyclic antidepressants (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)	2	Fluconazole	Fluconazole may increase plasma concentrations and toxic effects of these TCAs. The mechanism of this interaction is unknown.
Tricyclic antidepressants (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)	2	Fluoxetine	The pharmacologic and toxic effects of TCAs may be increased, as fluoxetine may inhibit the hepatic metabolism of TCAs.
Tricyclic antidepressants (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)	2	Fluvoxamine	The pharmacologic and toxic effects of TCAs may be increased, as fluvoxamine may inhibit the oxidative metabolism (CYP2D6) of the TCA.
Tricyclic antidepressants (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)	2	Guanethidine	The antihypertensive effect of guanethidine may be decreased by TCAs. The mechanism is thought to be due to the inhibition of the uptake of guanethidine into the nerve terminal.
Tricyclic antidepressants (amitriptyline, amoxapine, clomipramine, desipramine,	2	Guanfacine	The antihypertensive effect of guanfacine may be decreased by TCAs. TCAs may antagonize the action of guanfacine at the CNS alpha-2 adrenergic

Generic Name(s)	Significance Level	Interaction	Mechanism
doxepin, imipramine, nortriptyline, protriptyline, trimipramine)			receptor.
Tricyclic antidepressants (amitriptyline-chlordiazepoxide)	2	Hydantoins	Pharmacologic effects of hydantoins may be increased by amitriptyline-chlordiazepoxide. Elevated hydantoin plasma concentrations may occur. Pharmacologic effects of amitriptyline-chlordiazepoxide may be decreased by hydantoins. Benzodiazepines may impair hepatic metabolism of hydantoins. Hydantoins may induce hepatic metabolism of benzodiazepines.
Tricyclic antidepressants (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)	2	Iobenguane	TCAs may reduce uptake and diagnostic efficacy of iobenguane. False-negative iobenguane imaging tests may result. Inhibition of norepinephrine reuptake by these TCAs may result in decreased uptake of the structurally similar iobenguane, possibly resulting in false-negative iobenguane imaging results.
Tricyclic antidepressants (amitriptyline-chlordiazepoxide)	2	Nefazodone	Nefazodone may increase the pharmacologic effects of benzodiazepines. Impaired psychomotor performance and increased sedation may result from elevated benzodiazepine plasma concentrations. Inhibition of CYP3A4 isoenzymes by nefazodone may decrease the metabolic elimination of benzodiazepines.
Tricyclic antidepressants (amitriptyline-chlordiazepoxide)	2	Omeprazole	Serum concentrations and pharmacologic effects of amitriptyline-chlordiazepoxide may be increased by omeprazole due to its effect on hepatic oxidative metabolism. Toxicity may occur.
Tricyclic antidepressants (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)	2	Paroxetine	The pharmacologic and toxic effects of TCAs may be increased. Paroxetine may inhibit the metabolism of TCAs in some patients.

Generic Name(s)	Significance Level	Interaction	Mechanism
Tricyclic antidepressants (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)	2	Phenothiazines	Plasma concentrations of phenothiazines and these TCAs may be increased when coadministered. Inhibition of CYP2D6 by phenothiazines may decrease the metabolic elimination of these TCAs.
Tricyclic antidepressants (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)	2	Rasagiline	The combination of rasagiline and these TCAs may precipitate symptoms of serotonin syndrome. Rasagiline and these TCAs increase CNS serotonin activity.
Tricyclic antidepressants (amitriptyline-chlordiazepoxide)	2	Rifamycins	Pharmacologic effects of chlordiazepoxide and amitriptyline may be decreased by rifamycins. Induction of cytochrome P450 3A4 isoenzymes by rifamycins may increase the metabolic elimination of chlordiazepoxide and amitriptyline.
Tricyclic antidepressants (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, protriptyline, trimipramine)	2	Sertraline	The pharmacologic and toxic effects of TCAs may be increased. Serotonin syndrome has been reported, which is likely due to the inhibition of TCA hepatic metabolism (CYP2D6).
Tricyclic antidepressants	2	SNRIs	Plasma concentrations of these TCAs may be increased. SNRIs may decrease the metabolic elimination of these TCAs.
Tricyclic antidepressants (amitriptyline, clomipramine, desipramine, imipramine, nortriptyline)	2	Terbinafine	The pharmacologic and toxic effects of TCAs may be increased due to the suspected inhibition of TCA metabolism (CYP2D6) by terbinafine.
Tricyclic antidepressants (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)	2	Tramadol	Increased risk of seizures may occur when tramadol and TCAs are coadministered. The mechanism of this interaction is unknown.
Tricyclic antidepressants (amitriptyline, clomipramine,	2	Valproic acid and derivatives	Plasma concentrations of TCAs may be increased due to decreased metabolism.

Generic Name(s)	Significance Level	Interaction	Mechanism
nortriptyline)			
Antidepressants, Miscellaneous			
Bupropion	1	MAOIs	The use of bupropion with MAOIs is contraindicated due to the potential for hypertensive crisis. The inhibitory effects of bupropion on norepinephrine and dopamine reuptake may be enhanced by concomitant use of MAOIs.
Bupropion	1	Pimozide	Plasma concentrations of pimozide may be increased by bupropion. The mechanism of this interaction is unknown.
Bupropion	1	Tamoxifen	Pharmacologic effects of tamoxifen may be decreased by bupropion. Coadministration of bupropion with tamoxifen may increase the risk of breast cancer recurrence. The inhibition of CYP2D6 by bupropion may decrease the formation of endoxifen, an active metabolite of tamoxifen.
Mirtazapine	1	Furazolidone	Concomitant administration of mirtazapine and furazolidone may enhance the sympathomimetic effects of mirtazapine. The mechanism is unknown.
Mirtazapine	1	MAOIs	The use of bupropion with MAOIs is contraindicated due to the potential for hypertensive crisis. The inhibitory effects of bupropion on norepinephrine and dopamine reuptake may be enhanced by concomitant use of MAOIs.
Bupropion	2	HIV protease inhibitors	Plasma concentrations and pharmacologic effects of bupropion may be decreased by HIV protease inhibitors. Induction of CYP2B6 by HIV protease inhibitors may increase the metabolic elimination of bupropion.
Bupropion	2	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 coadministered.
Bupropion	2	Serotonin reuptake blockers	Unexpected adverse effects, including serotonin syndrome,

Generic Name(s)	Significance Level	Interaction	Mechanism
			may occur when serotonin reuptake blockers and bupropion are coadministered. Serotonin reuptake blockers may inhibit cytochrome P450 2D6 leading to increased plasma concentrations of bupropion and its active metabolites.
Bupropion	2	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. The mechanism is unknown.
Mirtazapine	2	Hydantoins	Mirtazapine plasma concentrations may be reduced due to the induction of mirtazapine metabolism (CYP3A4) by hydantoins.

Significance Level 1 = major severity
Significance Level 2 = moderate severity

VI. Adverse Drug Events

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

Table 6a. Adverse Drug Events (%) Reported with the Monoamine Oxidase Inhibitors[1-32]

Adverse Events	Isocarboxazid	Phenelzine	Selegiline	Tranylcypromine
Cardiovascular				
Arrhythmia	-	-	<1	-
Atrial fibrillation	-	-	<1	-
Bradycardia	-	-	<1	-
Cardiovascular depression	-	✔	-	-
Chest pain	-	-	≥1	-
Hypertension	-	-	≥1	-
Hypotension	-	-	3-10	-
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	-

Adverse Events	Isocarboxazid	Phenelzine	Selegiline	Tranylcypromine
Anxiety	2	✔	-	✔
Ataxia	✔	✔	<1	✔
Behavior changes	-	-	>1	-
Bradykinesia	-	-	>1	-
Coma	✔	✔	-	-
Confusion	-	-	<1	✔
Convulsions	-	✔	-	-
Delirium	-	✔	-	-
Delusions	-	-	<1	-
Depersonalization	-	-	<1	-
Depression	-	-	<1	-
Disorientation	-	-	-	✔
Dizziness	15-29	✔	-	✔
Drowsiness	4	✔	-	✔
Emotional lability	-	-	<1	-
Euphoria	✔	✔	<1	-
Fatigue	-	✔	-	✔
Forgetfulness	2	-	-	-
Hallucinations	<1	-	-	-
Headache	15	✔	18	✔
Hostility	-	-	<1	-
Hyperactivity	2	-	-	-
Hyperesthesia	-	-	<1	-
Hyperkinesias	-	-	<1	-
Hyperreflexia	-	✔	-	✔
Hypersomnia	-	✔	-	-
Insomnia	4-6	✔	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	2-5	✔	-	✔
Tremor	4	✔	<1	✔
Twitching	-	✔	<1	✔
Vertigo	-	-	<1	-
Weakness	-	✔	-	✔
Dermatological				
Acne	-	-	≥1	-
Alopecia	-	-	<1	✔
Application site reaction	-	-	24	-
Bruising	-	-	≥1	-
Cystic acne flare-up	-	-	-	✔

Adverse Events	Isocarboxazid	Phenelzine	Selegiline	Tranylcypromine
Maculopapular rash	-	-	<1	-
Photosensitivity	✔	-	<1	-
Pruritus	-	✔	≥1	✔
Rash	-	✔	4	✔
Scleroderma	-	-	-	✔
Skin benign neoplasm	-	-	<1	-
Skin hypertrophy	-	-	<1	-
Urticaria	-	-	<1	✔
Vesiculobullous rash	-	-	<1	-
Gastrointestinal				
Abdominal pain	-	-	-	✔
Anorexia	-	-	≥1	✔
Appetite increased	-	-	<1	-
Black tongue	✔	-	-	-
Colitis	-	-	<1	-
Constipation	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	6	✔	-	✔
Rectal hemorrhage	<1	-	<1	-
Salivation increased	-	-	<1	-
Taste perversion	-	-	≥1	-
Tongue edema	-	-	<1	-
Vomiting	≥1	✔	≥1	-
Weight gain	-	✔	-	-
Weight loss	-	-	5	-
Xerostomia	6-9	✔	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	-

Adverse Events	Isocarboxazid	Phenelzine	Selegiline	Tranylcypromine
Urinary urgency	-	-	<1	-
Urination impaired	-	-	<1	-
Vaginal hemorrhage	-	-	<1	-
Vaginal moniliasis	-	-	<1	-
Hematologic				
Agranulocytosis	-	-	-	✔
Anemia	-	-	<1	✔
Hematologic changes	✔	-	-	-
Leukocytosis	-	-	<1	-
Leukopenia	-	✔	<1	✔
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	-

Adverse Events	Isocarboxazid	Phenelzine	Selegiline	Tranylcypromine
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	-
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	-
SIADH	✔	✔	-	✔
Suicide attempt	-	-	<1	-
Sweating	2	✔	>1	-
Toxic delirium	-	✔	-	-
Viral infection	-	-	<1	-

✔ Percent not specified
- Event not reported

Table 6b. Adverse Drug Events (%) Reported with the Selective Serotonin- and Norepinephrine-reuptake Inhibitors[1-32]

Adverse Events	Desvenlafaxine	Duloxetine	Venlafaxine
Cardiovascular			
Aneurysm	-	-	<1
Angina pectoris	-	-	<1
Arrhythmia	-	-	<1
Atrial fibrillation	-	<1	-
Atrioventricular block	-	-	<1
Bigeminy	-	-	<1
Bradycardia	-	-	<1
Bundle branch block	-	<1	<1
Cardiovascular disorder	-	-	<1
Cerebral ischemia	-	-	<1
Chest pain	-	-	2
Congestive heart failure	-	<1	<1
Coronary artery disease	-	-	<1
Edema	-	-	✔
EKG abnormalities	-	-	<1
Extrasystoles	-	-	<1
Heart arrest	-	-	<1

Adverse Events	Desvenlafaxine	Duloxetine	Venlafaxine
Hemorrhage	-	-	<1
Hypertension, dose related	<1	-	3-13
Hypertensive crisis	-	<1	-
Hypotension	-	-	<1
Myocardial infarct	<2	<1	<1
Myocardial ischemia	<1	-	-
Orthostatic hypotension	<2	<1	-
Palpitation	≤3	1-2	3
Peripheral edema	-	<1	-
Postural hypotension	-	-	1
Syncope	<2	<1	<1
Tachycardia	-	<1	2
Vasodilation	-	-	3-4
Central Nervous System			
Abnormal dreams	2-3	2-3	3-7
Abnormal thinking	-	-	2
Agitation	-	5-6	2-4
Aggression	-	<1	-
Amnesia	-	-	✔
Anxiety	3-5	3	5-6
Ataxia	-	<1	<1
Blurred vision	-	4	4-6
Bradykinesia	-	-	<1
Chills	-	-	3
Concentration decreased	≤1	-	-
Confusion	-	-	2
Deafness	-	-	<1
Delusions	-	-	<1
Dementia	-	-	<1
Depersonalization	<2	-	1
Depression	-	-	1-3
Diplopia	-	<1	-
Disorientation	-	<1	-
Dizziness	10-13	6-17	11-20
Dystonia	-	-	<1
Extrapyramidal symptoms	<2	-	-
Fatigue	7	2-15	-
Fever	-	1-3	✔
Guillain-Barre syndrome	-	-	<1
Hostility	-	-	<1
Hypoesthesia	-	1	-
Headache	-	13	25-38
Hypoesthesia	-	1	✔
Hypomania	<2	-	-
Insomnia	9-12	8-16	15-23
Irritability	2	1	-
Lethargy	-	1	-
Loss of consciousness	-	-	<1
Mania	-	<1	-
Migraine	-	-	✔
Mood swings	-	<1	-
Nervousness	-	1	6-21
Neuropathy	-	-	<1
Neutropenia	-	-	<1

Adverse Events	Desvenlafaxine	Duloxetine	Venlafaxine
Nightmares	-	1	-
Paresthesia	≤2	1	2-3
Parkinsonism	<1	-	-
Photopsia	-	<1	-
Photosensitivity	-	<1	-
Restlessness	-	1	-
Seizure	-	<1	<1
Sleep disorder	-	1	-
Somnolence	≤9	13-20	12-23
Trismus	-	-	✔
Vertigo	-	1	✔
Yawning	-	1	3-5
Dermatological			
Acne	-	<1	-
Alopecia	-	<1	-
Bruising	-	-	✔
Ecchymosis	-	<1	-
Eczema	-	<1	-
Erythema	-	<1	-
Erythema multiforme	-	-	<1
Exfoliative dermatitis	-	-	<1
Hyperhidrosis	-	6-8	-
Maculopapular rash	-	-	<1
Miliaria	-	-	<1
Pruritus	-	3	1
Rash	1	4	3
Skin atrophy	-	-	<1
Stevens-Johnson syndrome	-	<1	<1
Toxic epidermal necrolysis	-	-	<1
Urticaria	-	<1	-
Endocrine and Metabolic			
Bilirubin increased	-	<1	<1
Blood urea nitrogen increased	-	-	<1
Cholesterol increased	3-4	<1	-
Creatinine increased	-	-	<1
Diabetes mellitus	-	-	<1
Dyslipidemia	-	<1	-
Electrolyte abnormalities	-	-	<1
Hepatic steatosis	-	<1	-
Hepatitis	-	<1	<1
Hot flushes	-	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
Hypokalemia	-	-	<1

Adverse Events	Desvenlafaxine	Duloxetine	Venlafaxine
Hyponatremia	-	<1	<1
Hypophosphatemia	-	-	<1
Hypothyroidism	-	-	<1
Jaundice	-	<1	<1
Kidney function abnormal	-	-	<1
LDL increased	≤1	-	-
Liver enzymes increased	≤2	-1	<1
SIADH	-	<1	<1
Transaminase elevation	-	1	-
Triglycerides increased	-	-	✔
Weight gain	-	<1	✔
Weight loss	≤2	1-2	1-4
Gastrointestinal			
Abdominal pain	-	<1	6
Abnormal taste	-	-	2
Anorexia	5-8	3-5	8-20
Aphthous stomatitis	-	<1	-
Appetite decreased	-	3-11	-
Appetite increased	-	-	✔
Bloody stools	-	<1	-
Cholelithiasis	-	-	<1
Colitis	-	<1	-
Constipation	9-11	5-15	8-15
Diarrhea	9-11	7-13	6-8
Diverticulitis	-	<1	-
Dyspepsia	-	4-5	7
Dysphagia	-	<1	-
Eructation	-	<1	-
Esophageal stenosis	-	<1	-
Flatulence	-	-	3-4
Gastric emptying impaired	-	<1	-
Gastric irritation	-	<1	-
Gastric ulcer	-	<1	<1
Gastritis	-	1	-
Hematemesis	-	-	<1
Intestinal obstruction	-	-	<1
Irritable bowel syndrome	-	<1	-
Loose stools	-	2-3	-
Melena	-	<1	-
Nausea	22-26	14-30	21-58
Vomiting	≤4	1-6	3-6
Xerostomia	11-17	5-18	12-22
Genitourinary			
Crystalluria	-	-	<1
Dysuria	-	1	-
Ejaculation abnormality	≤1	1-4	2-19
Erectile dysfunction	3-6	1-5	-
Impotence	-	-	4-10
Libido decreased	4-5	2-4	3-9
Menstrual abnormalities	-	-	<1
Micturition urgency	-	<1	-
Nocturia	-	<1	-
Pollakiuria	-	1-5	-
Prostatic disorder	-	-	✔

Adverse Events	Desvenlafaxine	Duloxetine	Venlafaxine
Proteinuria	6-8	-	-
Pyelonephritis	-	-	<1
Pyuria	-	-	<1
Urinary frequency	-	-	3
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	-	-	<1
Hypertonia	-	-	3
Malaise	-	<1	-
Muscle cramp	-	4-5	-
Muscle pain	-	1-5	-
Muscle tightness	-	1	1-2
Muscle twitching	-	4	<1
Myalgia	-	1-3	-
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	3-4	4-10
Weakness	≤2	2-8	8-19
Respiratory			
Asthma	-	-	<1
Atelectasis	-	-	<1
Cough	-	3-6	✔
Dyspnea	-	-	✔
Epistaxis	<2	-	-
Nasopharyngitis	-	7-9	-
Pharyngitis	-	-	7
Pharyngolaryngeal pain	-	1-6	-

Adverse Events	Desvenlafaxine	Duloxetine	Venlafaxine
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	-	1-3	4-6
Bruxism	-	<1	-
Cataract	-	-	<1
Catatonia	-	-	<1
Cellulites	-	-	<1
Cyanosis	-	-	<1
Deep vein thrombosis	-	-	<1
Dehydration	-	<1	<1
Diaphoresis increased	10-14	6	10-14
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	-	2-3	-
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
Stomatitis	-	<1	-
Suicidal ideation/attempt	-	<1	<1-2
Thirst	-	<1	-
Tinnitus	2	-	2
Trauma	-	-	2
Trismus	-	-	✔
Visual disturbance	-	<1	-
Withdrawal syndrome	-	<1	<1

✔ Percent not specified
- Event not reported

Table 6c. Adverse Drug Events (%) Reported with the Selective Serotonin-reuptake Inhibitors[1-32]

Adverse Events	Citalopram	Escitalopram	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline
Cardiovascular						
Angina	-	-	<1	<1	<1	-
Arrhythmia	-	-	<1	-	-	-
Atrial arrhythmia	-	-	-	-	<1	<1
Atrial fibrillation	-	<1	<1	-	-	-
AV block	-	-	-	<1	-	<1
Bradycardia	1-10	<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	-	-
ECG abnormal	-	<1	-	<1	-	-
Edema	<1	<1	<1	≤1	-	<1
Hemorrhage	-	-	✔	<1	-	-
Hypertension	<1	<1	>1	1-2	≥1	<1
Myocardial infarct	-	-	<1	<1	<1	-
Orthostatic hypotension	-	<1	-	≤1	<1	-
Palpitation	-	<1	>1	-	2-3	>1
Pericarditis	-	-	-	<1	-	-
Peripheral edema	-	-	<1	-	-	<1
Postural hypotension	1-10	-	<1	-	<1	<1
Pulmonary hypertension	-	-	<1	-	-	<1
QT_c prolongation	<1	<1	<1	-	-	<1
Supraventricular extrasystoles	-	-	-	<1	-	-
Syncope	-	<1	<1	≤1	<1	<1
Tachycardia	1-10	<1	<1	≤1	≥1	-
Vasculitis	-	<1	<1	<1	<1	<1
Vasodilation	-	-	1-5	2	2-4	-
Ventricular arrhythmia	<1	<1	-	-	<1	-
Ventricular tachycardia	<1	<1	<1	<1	<1	<1
Central Nervous System						
Abnormal dreams	-	3	1-5	3	3-4	<1
Abnormal gait	-	<1	<1	-	-	<1
Abnormal thinking	-	-	2	3	<1	-

Adverse Events	Citalopram	Escitalopram	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline
Aggression	-	<1	-	-	-	<1
Agitation	3-10	<1	>1	2-3	3-5	5
Akathisia	-	<1	<1	-	-	-
Akinesia	-	-	-	<1	<1	-
Amnesia	>1	<1	>1	✔	2	<1
Anxiety	4	<1	6-15	5-8	5	4
Apathy	>1	<1	<1	1-3	-	<1
Aphasia	-	-	-	-	<1	-
Asthenia	-	-	-	14	-	>1
Ataxia	-	-	<1	<1	<1	<1
Auditory hallucination	-	<1	-	-	-	-
Blindness	-	-	-	-	-	<1
Blurred vision	-	1-10	-	-	-	-
Chills	-	-	>1	2	<1	-
CNS stimulation	-	-	<1	2	-	-
Concentration impaired	✔	1-10	-	-	3-4	<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	11-15	6-14	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	5-8	-	-	-	12
Fever	2	<1	2	-	-	-
Guillain-Barre syndrome	-	-	-	-	<1	-
Hallucinations	-	<1	<1	<1	<1	<1
Headache	-	24	21	22-35	17-18	25
Hiccup	-	-	<1	-	-	-
Hyperkinesia	-	-	<1	✔	-	<1
Hyperreflexia	-	<1	-	-	-	-
Hypertonia	-	-	<1	2	<1	>1

Adverse Events	Citalopram	Escitalopram	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline
Hypoesthesia	-	<1	-	-	-	1-10
Hypokinesia	-	-	-	✔	-	<1
Hypomania	-	-	-	<1	-	-
Insomnia	>10	9-12	10-33	21-35	11-24	21
Irritability	-	<1	-	-	-	-
Lethargy	-	3	-	-	-	-
Lightheadedness	-	<1	-	-	-	-
Malaise	-	<1	<1	✔	-	1-10
Mania	-	-	-	✔	-	-
Meningitis	-	-	-	-	<1	-
Migraine	>1	<1	<1	-	<1	<1
Nervousness	-	-	8-14	10-12	4-9	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	6-13	5-17	22-27	15-24	13
Tardive dyskinesia	-	<1	-	<1	-	-
Tetany	-	-	-	-	<1	-
Tremors	-	-	-	4	-	8
Vertigo	-	<1	<1	-	>1	<1
Yawning	<10	2	<11	2-5	2-4	>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	2-6	-	2-3	>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
BUN 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
SIADH	<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	1-2	<1	-
Gastrointestinal						
Abdominal cramps	-	1-10	-	-	-	-
Abdominal pain	3	2	-	5	4	<1
Abnormal taste	✔	<1	✔	2-3	2	-
Anorexia	4	-	4-17	6-14	5-9	6
Aphthous stomatitis	-	-	<1	-	<1	<1
Appetite decreased	-	3	-	4	5-9	-
Appetite increased	>1	1-10	✔	-	2-4	>1
Carbohydrate craving	-	<1	-	-	-	-
Cholelithiasis	-	-	<1	-	-	-
Colitis	-	-	<1	<1	<1	-
Constipation	-	3-5	5	4-10	5-16	6
Diarrhea	8	8	8-18	11-18	9-12	20
Dyspepsia	5	-	6-10	8-10	2-5	8
Dysphagia	-	<1	<1	2	<1	<1
Esophagitis	-	-	<1	-	-	<1
Flatulence	>1	2	3	4	4	1-10
Gastritis	-	-	<1	-	<1	-
Gastroenteritis	-	<1	<1	-	<1	<1
Gastroesophageal reflux	-	<1	-	-	-	-
GI bleeding	-	-	-	<1	-	-
GI 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	12-29	34-40	19-26	25
Pancreatitis	<1	<1	<1	<1	<1	<1
Vomiting	4	1-10	3	4-6	2-3	4
Xerostomia	>10	6-9	4-12	10-14	9-18	>10
Genitourinary						

Adverse Events	Citalopram	Escitalopram	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline
Acute renal failure	<1	<1	<1	<1	<1	<1
Anorgasmia	-	2-6	2	2-5	2-9	-
Anuria	-	-	-	<1	-	-
Ejaculation disorder	6	9-14	<7	7-11	13-28	7-19
Hematuria	-	-	<1	<1	<1	<1
Impotence	3	2-3	<7	2	2-9	>1
Libido decreased	1-4	3-7	1-11	2-10	3-15	6
Menstrual cramps	-	1-10	-	-	-	-
Menstrual disorder	3	<1	<1- 2	3	5	<1
Micturition disorders	✔	-	-	-	-	<1
Priapism	<1	<1	<1	-	-	<1
Sexual dysfunction	✔	-	-	2-4	-	>1
Urinary frequency	-	<1	✔	2-3	2-3	<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	1-2	<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						

Adverse Events	Citalopram	Escitalopram	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline
Arthralgia	2	<1	-	-	>1	<1
Arthritis	-	-	<1	-	<1	-
Back pain	-	-	-	-	3	>1
Bursitis	-	-	<1	-	-	-
Choreoathetosis	-	<1	-	-	-	-
Limb pain	-	1-10	-	-	-	-
Muscle contractions	-	<1	-	2	-	-
Muscle cramp	-	<1	<1	-	-	<1
Myalgia	2	<1	-	5-8	2-4	>1
Myoclonus	<1	-	-	-	2-3	-
Neck/shoulder pain	-	1-10	-	-	<1	-
Neuroleptic malignant syndrome	<1	<1	<1	<1	<1	<1
Osteoporosis	-	-	-	-	<1	-
Rhabdomyolysis	<1	<1	-	-	-	-
Rigors	<1	-	-	-	-	-
Tics	-	<1	-	-	-	-
Tremor	8	1-10	3-13	5-8	4-11	-
Weakness	-	<1	7-21	14-26	12-22	<1
Respiratory						
Asthma	-	-	<1	<1	<1	-
Bronchitis	-	<1	-	2	<1	<1
Cough	>1	1-10	-	✔	-	<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	-	1-10	-	-	-	-
Pharyngitis	-	-	3-11	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

Adverse Events	Citalopram	Escitalopram	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline
Sinus headache	-	<1	-	-	-	-
Sinusitis	3	3	1-6	✔	4	<1
Other						
Allergic reaction	-	<1	-	<1	>1	<1
Allergy	-	<1	<1	-	<1	-
Amblyopia	-	-	-	2-3	-	-
Anaphylaxis	<1	<1	<1	<1	<1	<1
Angioedema	<1	<1	-	-	-	-
Blindness	-	-	-	-	-	<1
Blurred/abnormal vision	-	<1	✔	<1	2-4	3
Cataract	-	-	<1	-	<1	<1
Dehydration	-	-	<1	-	<1	-
Diaphoresis	>10	4-5	2-8	6-7	5-14	4-6
Ear ache	-	<1	✔	-	-	-
Flu-like syndrome	-	5	3-10	3	-	-
Gout	-	-	<1	-	-	-
Gum hyperplasia	-	-	-	-	-	<1
Infection	-	-	-	-	5-6	-
Lupus-like syndrome	-	-	<1	-	-	<1
Oculogyric crisis	-	-	-	-	-	<1
Pain	-	-	<1	10	-	1-10
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	-	2-3	-	-
Vasculitis	-	-	<1	-	-	-
Visual difficulty	-	<1	2	-	2-4	<1
Withdrawal syndrome	<1	<1	-	-	-	<1

✔ Percent not specified
- Event not reported

Table 6d. Adverse Drug Events (%) Reported with the Serotonin Modulators[1-32]

Adverse Events	Nefazodone	Trazodone	Vilazodone
Cardiovascular			
Atrioventricular block	<1	-	-
Bradycardia	1-10	<1	-
Edema	-	1-10	-
Hypertension	-	1-10	-
Hypotension	1-10	1-10	-
Palpitation	-	-	2
Peripheral edema	1-10	-	-
Postural hypotension	1-10	-	-
Syncope	-	1-10	-
Tachycardia	-	<1	-
Vasodilation	1-10	-	-
Ventricular extrasystoles	-	-	<1
Central Nervous System			
Abnormal dreams	1-10	-	4
Agitation	>10	<1	-
Anxiety	-	<1	-
Ataxia	1-10	-	-
Chills	1-10	-	-
Concentration decreased	1-10	1-10	-
Confusion	1-10	1-10	-
Dizziness	>10	>10	9
Drowsiness	>10	-	-
Fatigue	-	1-10	4
Fever	1-10	-	-
Hallucinations	<1	-	-
Headache	>10	>10	1-10
Incoordination	1-10	1-10	-
Insomnia	>10	-	6
Lightheadedness	1-10	-	-
Mania	-	-	<1
Memory impairment	1-10	-	-
Panic attacks	-	-	<1
Paresthesia	1-10	-	3
Psychomotor retardation	1-10	-	-
Restlessness	-	-	3
Sedation	-	>10	1-10
Seizure	<1	<1	-
Speech impairment	-	<1	-
Dermatological			
Alopecia	-	<1	-
Hyperhidrosis	-	-	1-10
Photosensitivity	<1	-	-
Pruritus	1-10	-	-
Rash	1-10	<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
Liver function tests abnormal	<1	-	-
Prolactin increased	<1	-	-
Weight gain	-	1-10	-
Weight loss	-	1-10	-
Gastrointestinal			
Abnormal taste	1-10	-	-
Appetite decreased	-	-	1-10
Appetite increased	1-10	-	2
Constipation	>10	1-10	-
Diarrhea	1-10	1-10	28
Dyspepsia	1-10	-	3
Flatulence	-	-	3
Gastroenteritis	1-10	-	3
Nausea	>10	>10	23
Vomiting	1-10	-	5
Xerostomia	>10	>10	8
Genitourinary			
Ejaculation delayed	-	-	2
Erectile dysfunction	-	-	2
Impotence	1-10	-	-
Libido decreased	1-10	-	3-5
Orgasm abnormal	-	-	2-4
Priapism	<1	<1	-
Sexual dysfunction	-	-	<2
Urinary frequency	1-10	-	-
Urinary retention	1-10	<1	-
Hematologic			
Hematocrit decreased	1-10	-	-
Leukopenia	<1	-	-
Thrombocytopenia	<1	-	-
Musculoskeletal			
Arthralgia	1-10	-	3
Extrapyramidal symptoms	-	<1	-
Hypertonia	1-10	-	-
Jittery	-	-	2
Myalgia	-	1-10	-
Neck rigidity	1-10	-	-
Rhabdomyolysis	<1	-	-
Tremor	1-10	1-10	2
Weakness	>10	-	-
Respiratory			
Bronchitis	1-10	-	-
Cough	1-10	-	-
Dyspnea	1-10	-	-
Nasal congestion	-	1-10	-
Pharyngitis	1-10	-	-
Other			
Abnormal feeling	-	-	<1
Abnormal taste	-	-	<1
Allergic reaction	<1	<1	-
Angioedema	<1	-	-
Blurred/abnormal vision	7-9	>10	1-10
Breast pain	1-10	-	-
Cataracts	-	-	<1

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

- Event not reported

Table 6e. Adverse Drug Events (%) Reported with the Tricyclics and Other Norepinephrine-reuptake Inhibitors[1-32]

Adverse Events	Amitrip-tyline	Amitriptyline/ Chlordiazepoxide	Amox-apine	Clomip-ramine	Desip-ramine	Dox-epin	Imip-ramine	Mapro-tiline	Nortrip-tyline	Protrip-tyline	Trimip-ramine
Cardiovascular											
Aneurysm	-	-	-	<1	-	-	-	-	-	-	-
Arrhythmia	✔	✔	✔	<1	✔	-	✔	✔	✔	✔	✔
Atrial flutter	-	-	-	<1	-	-	-	-	-	-	-
AV 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	-	-	-	-	-	-	-
ECG changes	✔	✔	-	<1	-	-	✔	-	-	-	-
Edema	✔	-	>1	3	✔	-	-	-	✔	-	-
Encephalopathy	-	-	-	<1	-	-	-	-	-	-	-
Extrasystole	-	-	-	<1	-	-	-	-	-	-	-
Heart block	✔	✔	✔	<1	-	-	✔	✔	✔	✔	✔
Hypertension	✔	✔	<1	-	✔	✔	✔	✔	✔	✔	✔
Hypotension	✔	✔	<1	1-10	✔	✔	-	✔	✔	✔	✔
Myocardial infarction	✔	✔	✔	<1	✔	-	✔	-	✔	✔	✔
Myocardial ischemia	-	-	-	<1	-	-	-	-	-	-	-
Orthostatic hypotension	✔	✔	-	6	-	-	✔	-	✔	-	-
Palpitations	✔	✔	>1	4	✔	-	✔	-	✔	✔	✔
Peripheral ischemia	-	-	-	<1	-	-	-	-	-	-	-
Stroke	✔	✔	✔	-	✔	-	✔	-	✔	✔	✔
Syncope	✔	✔	<1	>1	-	-	-	✔	✔	-	-
Tachycardia	✔	✔	<1	4	✔	✔	✔	-	✔	✔	✔
Vasospasm	-	-	-	<1	-	-	-	-	-	-	-
Central Nervous System											
Abnormal dreaming	-	-	-	3	-	-	-	-	-	-	-
Aggressiveness	-	-	-	2	-	-	-	-	-	-	-
Agitation	-	-	-	3	✔	-	✔	1-10	✔	✔	✔
Akathisia	-	1-10	-	-	-	-	-	<1	-	-	-
Anxiety	✔	✔	1-10	9	✔	-	✔	1-10	✔	✔	✔

Adverse Events	Amitrip-tyline	Amitriptyline/ Chlordiazepoxide	Amox-apine	Clomip-ramine	Desip-ramine	Dox-epin	Imip-ramine	Mapro-tiline	Nortrip-tyline	Protrip-tyline	Trimip-ramine
Aphasia	-	-	-	<1	-	-	-	-	-	-	-
Apraxia	-	-	-	<1	-	-	-	-	-	-	-
Ataxia	✔	>10	1-10	<1	✔	✔	-	<1	✔	✔	-
Catalepsy	-	-	-	<1	-	-	-	-	-	-	-
Confusion	-	1-10	-	3	-	-	-	-	✔	✔	-
Cognitive function (impaired)	✔	✔	-	-	-	-	-	-	-	-	-
Coma	✔	✔	-	<1	-	-	-	-	-	-	-
Confusion	✔	✔	>1	3	✔	✔	✔	✔	✔	-	✔
Coordination impairment	✔	✔	<1	5	✔	-	✔	-	✔	✔	✔
Deafness	-	-	-	<1	-	-	-	-	-	-	-
Delirium	-	-	-	<1	✔	-	-	-	✔	✔	✔
Delusions	✔	✔	✔	<1	-	-	✔	✔	✔	✔	✔
Depersonalization	-	-	-	2	-	-	-	-	-	-	-
Depression	-	-	-	5	-	<1	-	-	✔	-	-
Disinhibition	-	1-10	-	-	-	-	-	-	-	-	-
Disorientation	✔	✔	<1	-	✔	✔	✔	✔	✔	-	✔
Dizziness	✔	✔	>1	54	✔	>1	✔	-	✔	✔	✔
Drowsiness	✔	✔	>14	>10	✔	✔	✔	-	✔	✔	✔
Dysarthria	✔	>10	-	-	-	-	-	✔	-	-	-
Dyskinesia	-	-	-	<1	-	-	-	-	-	-	-
Dysphagia	-	-	-	-	-	-	-	<1	-	-	-
Dysphonia	-	-	-	<1	-	-	-	-	-	-	-
Dystonia	-	-	-	<1	-	-	-	-	-	-	-
Emotional lability	-	-	-	2	-	-	-	-	-	-	-
Euphoria	✔	✔	-	-	-	-	-	-	-	-	-
Excitement	✔	✔	>1	-	-	-	-	-	-	-	-
Extrapyramidal symptoms	✔	✔	<1	<1	✔	✔	✔	✔	✔	✔	✔
Fatigue	✔	✔	-	39	✔	<1	✔	4	✔	✔	✔
Fever	✔	✔	<1	4	✔	-	-	-	✔	-	-
Flushing	-	-	-	8	✔	<1	-	-	✔	-	✔
Hallucinations	✔	✔	-	<1	✔	✔	✔	✔	✔	✔	✔
Hangover effect	-	-	-	-	-	-	-	-	-	✔	-
Headache	✔	✔	>1	52	✔	✔	✔	4	✔	-	✔
Hemiparesis	-	-	-	<1	-	-	-	-	-	-	-
Hostility	-	-	-	<1	-	-	-	-	-	-	-
Hyperesthesia	-	-	-	<1	-	-	-	-	-	-	-
Hyperkinesia	-	-	-	<1	-	-	-	-	-	-	-

Adverse Events	Amitrip-tyline	Amitriptyline/ Chlordiazepoxide	Amox-apine	Clomip-ramine	Desip-ramine	Dox-epin	Imip-ramine	Mapro-tiline	Nortrip-tyline	Protrip-tyline	Trimip-ramine
Hyperreflexia	-	-	-	<1	-	-	-	-	-	-	-
Hypertonia	-	-	-	4	-	-	-	-	-	-	-
Hypoesthesia	-	-	-	<1	-	-	-	-	-	-	-
Hypokinesia	-	-	-	<1	-	-	-	-	-	-	-
Hypomania	-	-	-	-	✔	-	-	-	✔	✔	-
Ideation	-	-	-	<1	-	-	-	-	-	-	-
Insomnia	✔	✔	>1	25	✔	-	✔	2	✔	✔	✔
Irritability	-	-	-	2	-	-	-	-	-	-	-
Malaise	✔	✔	-	>1	-	-	-	-	✔	-	✔
Mania	-	-	-	<1	-	-	-	✔	-	-	-
Memory impairment	-	-	-	9	-	-	-	✔	-	-	-
Migraine	-	-	-	3	-	-	-	-	-	-	-
Nervousness	-	-	>1	18	✔	-	-	6	-	-	✔
Neuralgia	-	-	-	<1	-	-	-	-	-	-	-
Neuropathy	-	-	-	<1	-	-	-	-	-	-	-
Nightmares	✔	✔	>1	-	-	-	✔	✔	✔	✔	✔
Oculogyric crisis	-	-	-	<1	-	-	-	-	-	-	-
Oculomotor nerve paralysis	-	-	-	<1	-	-	-	-	-	-	-
Panic	-	-	-	1	-	-	-	-	✔	✔	-
Paranoia	-	-	-	<1	-	-	-	-	-	-	-
Paresis	-	-	-	9	-	-	-	-	-	-	-
Paresthesia	-	-	-	2	-	-	-	-	-	-	-
Parkinsonian syndrome	-	-	-	-	✔	-	-	-	-	-	-
Psychosis exacerbation	-	-	-	<1	✔	-	✔	-	✔	✔	✔
Psychosomatic disorder	-	-	-	3	-	-	-	-	-	-	-
Restlessness	✔	✔	1-10	-	✔	-	✔	-	✔	✔	✔
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											

Adverse Events	Amitrip-tyline	Amitriptyline/ Chlordiazepoxide	Amox-apine	Clomip-ramine	Desip-ramine	Dox-epin	Imip-ramine	Mapro-tiline	Nortrip-tyline	Protrip-tyline	Trimip-ramine
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	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	-	-	✔	-	✔	✔	-
Hyperglycemia	✔	✔	-	<1	✔	✔	✔	-	✔	-	✔
Hypoglycemia	✔	✔	-	-	✔	✔	✔	-	-	-	✔
Lactation	-	-	-	4	-	-	-	-	-	-	-
Prolactin levels increased	-	-	>1	-	-	-	-	-	-	-	-
SIADH	✔	✔	<1	<1	✔	✔	✔	-	✔	✔	✔
Thirst	-	-	-	2	-	-	-	-	-	-	-
Gastrointestinal											
Abdominal pain/cramps	-	-	<1	11	✔	<1	✔	-	✔	-	✔
Anorexia	✔	✔	-	12	✔	✔	✔	-	✔	✔	✔
Appetite decreased	-	✔	-	11	-	<1	-	-	✔	-	-
Appetite increased	-	✔	>1	11	-	<1	-	-	✔	✔	✔
Black tongue	✔	✔	✔	-	✔	-	✔	-	✔	-	✔
Blood in stool	-	-	-	<1	-	-	-	-	-	-	-
Chronic enteritis	-	-	-	<1	-	-	-	-	-	-	-
Constipation	✔	✔	12	47	✔	<1	✔	6	✔	✔	✔
Diarrhea	✔	✔	<1	13	✔	✔	✔	-	✔	✔	✔

Adverse Events	Amitrip-tyline	Amitriptyline/ Chlordiazepoxide	Amox-apine	Clomip-ramine	Desip-ramine	Dox-epin	Imip-ramine	Mapro-tiline	Nortrip-tyline	Protrip-tyline	Trimip-ramine
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	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	✔	✔	>10	84	✔	✔	✔	>10	✔	✔	✔
Genitourinary											
Albuminuria	-	-	-	<1	-	-	-	-	-	-	-
Cervical dysplasia	-	-	-	<1	-	-	-	-	-	-	-
Cystitis	-	-	-	2	-	-	-	-	-	-	-
Dysmenorrhea	-	-	-	12	-	-	-	-	-	-	-
Dysuria	-	-	-	2	-	-	-	-	-	-	-
Ejaculation failure	-	-	-	42	-	-	-	-	-	-	-
Epididymitis	-	-	-	<1	-	-	-	-	-	-	-
Hematuria	-	-	-	<1	-	-	-	-	-	-	-
Impotence	✔	✔	<1	20	✔	-	✔	<1	✔	✔	✔
Incontinence	-	✔	-	<1	-	-	-	-	-	-	-
Leucorrhea	-	-	-	2	-	-	-	-	-	-	-
Menstrual Disorder	-	-	-	4	-	-	-	-	-	-	-
Micturition disorder/difficulty	-	>10	-	4-14	-	-	-	<1	✔	✔	-
Micturition frequency	-	-	-	5	-	-	-	-	-	-	-

Adverse Events	Amitrip-tyline	Amitriptyline/ Chlordiazepoxide	Amox-apine	Clomip-ramine	Desip-ramine	Dox-epin	Imip-ramine	Mapro-tiline	Nortrip-tyline	Protrip-tyline	Trimip-ramine
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	-	-	-	-	-	-	-
Myositis	-	-	-	<1	-	-	-	-	-	-	-
Neuroleptic malignant syndrome	✔	✔	<1	-	-	-	-	-	-	-	-
Numbness	✔	✔	<1	-	✔	✔	✔	✔	✔	✔	✔

Adverse Events	Amitrip-tyline	Amitriptyline/ Chlordiazepoxide	Amox-apine	Clomip-ramine	Desip-ramine	Dox-epin	Imip-ramine	Mapro-tiline	Nortrip-tyline	Protrip-tyline	Trimip-ramine
Paresthesia	✔	✔	<1	1-10	✔	✔	✔	-	✔	-	✔
Peripheral neuropathy	✔	✔	-	-	✔	-	✔	-	✔	-	✔
Tardive dyskinesia	✔	✔	<1	-	-	✔	-	-	-	-	-
Tingling	✔	✔	<1	-	✔	-	✔	✔	✔	✔	✔
Torticollis	-	-	-	<1	-	-	-	-	-	-	-
Tremor	✔	✔	1-10	54	✔	✔	✔	3	✔	✔	✔
Weakness	✔	✔	>1	1	✔	✔	✔	1-10	-	✔	✔
Ocular											
Abnormal Vision	-	-	-	18	-	-	-	-	-	-	-
Accommodation disturbances	✔	✔	<1	<1	✔	-	✔	<1	✔	-	✔
Anisocoria	-	-	-	>1	-	-	-	-	-	-	-
Blepharitis	-	-	-	<1	-	-	-	-	-	-	-
Blepharospasm	-	-	-	>1	-	-	-	-	-	-	-
Blurred vision	✔	✔	7	1-10	✔	<1	✔	4	✔	✔	✔
Conjunctival hemorrhage	-	-	-	<1	-	-	-	-	-	-	-
Conjunctivitis	-	-	-	1	-	-	-	-	-	-	-
Exophthalmos	-	-	-	<1	-	-	-	-	-	-	-
Eye pain	-	-	-	1-10	-	-	-	-	✔	✔	✔
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	✔	1-10	<1	6	✔	✔	✔	<1	✔	✔	✔
Respiratory											
Bronchitis	-	-	-	<1	-	-	-	-	-	-	-
Bronchospasm	-	-	-	2	-	-	-	-	-	-	-
Cough	-	-	-	6	-	-	-	-	✔	-	-
Dyspnea	-	-	-	>1	-	-	-	-	-	-	-
Hypo/hyperventilation	-	-	-	<1	-	-	-	-	-	-	-
Epistaxis	-	-	-	2	-	-	-	-	-	-	-
Laryngitis	-	-	-	>1	-	-	-	-	-	-	-

Adverse Events	Amitrip-tyline	Amitriptyline/ Chlordiazepoxide	Amox-apine	Clomip-ramine	Desip-ramine	Dox-epin	Imip-ramine	Mapro-tiline	Nortrip-tyline	Protrip-tyline	Trimip-ramine
Nasal congestion	-	✔	<1	-	-	-	-	-	✔	-	-
Pharyngitis	-	-	-	14	-	-	-	-	-	-	-
Pneumonia	-	-	-	<1	-	-	-	-	-	-	-
Rhinitis	-	-	-	12	-	-	-	-	-	-	-
Sinusitis	-	-	-	6	-	-	-	-	✔	-	-
Other											
Allergic reactions	-	-	<1	3	✔	✔	-	-	✔	✔	✔
Dehydration	-	-	-	<1	-	-	-	-	-	-	-
Diaphoresis	✔	✔	>1	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

Table 6f. Adverse Drug Events (%) Reported with the Antidepressants, Miscellaneous[1-32]

Adverse Events	Bupropion	Mirtazapine
Cardiovascular		
Abnormal dreams	3	4
Abnormal thinking	-	3
Aggression	✔	-
Agitation	2-9	>
Akathisia	2	-
Akinesia	✔	-
Amnesia	✔	>1
Anxiety	5-7	>1
Aphasia	✔	-
Arrhythmias	5	-
Ataxia	✔	<1
Atrioventricular block	✔	-
Blurred vision	2-3	-
Central Nervous System		
Central nervous system stimulation	1-2	-
Chest pain	3-4	-
Chills	<1	<1
Coma	✔	-
Confusion	8	2
Delirium	✔	<1
Delusions	✔	<1
Depersonalization	✔	<1
Depression	✔	-
Derealization	✔	-
Diplopia	✔	<1
Dizziness	6-11	7
Dyskinesia	✔	-
Dysphoria	✔	-
Dystonia	✔	<1
EEG abnormality	✔	-
Emotional lability	✔	<1
Euphoria	✔	-
Extrasystoles	✔	-
Fever	1-2	<1
Hallucinations	✔	<1
Headache	25-34	-
Hostility	6	<1
Hyperkinesia	✔	<1
Hypertension	2-4	2
Hypertonia	✔	-
Hypoesthesia	✔	-
Hypokinesia	✔	<1
Hypomania	✔	-
Hypotension	3	-
Incoordination	✔	-
Insomnia	11-20	-
Irritability	2-3	-
Malaise	✔	✔
Manic reaction	✔	<1
Memory decreased	<3	-
Migraine	1-4	<1
Myocardial infarct	✔	<1

Adverse Events	Bupropion	Mirtazapine
Nervousness	3-5	-
Neuropathy	✔	-
Orthostatic hypotension	-	<1
Pain	2-3	-
Palpitation	2-6	-
Paranoia	✔	<1
Paresthesia	1-2	<1
Peripheral edema	<1	2
Postural hypotension	✔	-
Restlessness	✔	-
Seizure	✔	-
Sensory disturbance	4	-
Sleep disturbance	4	-
Somnolence	2-3	54
Stroke	✔	-
Syncope	✔	<1
Tachycardia	11	-
Vasodilation	✔	2
Vertigo	✔	-
Dermatological		
Maculopapular rash	✔	-
Photosensitivity	<1	<1
Pruritus	2-4	>1
Rash	1-5	>1
Urticaria	1-2	<1
Endocrine and Metabolic		
Appetite increased	4	17
Glycosuria	✔	-
Gynecomastia	✔	-
Hepatic damage	✔	-
Hepatitis	✔	-
Hypercholesterolemia	-	✔
Hyperglycemia	✔	-
Hypertriglyceridemia	-	✔
Hypoglycemia	✔	-
Hot flashes	1-3	-
Jaundice	<1	-
Liver function abnormal	<1	<1
SIADH	✔	-
Weight gain	-	12
Weight loss	14-23	<1
Gastrointestinal		
Abdominal pain	2-9	>1
Abnormal taste	2-4	-
Anorexia	3-5	>1
Colitis	✔	<1
Constipation	5-10	13
Diarrhea	5-7	-
Dysphagia	<2	-
Dyspepsia	3	-
Flatulence	6	-
Gastric reflux	<1	-
Gastrointestinal hemorrhage	✔	-
Intestinal perforation	✔	-

Adverse Events	Bupropion	Mirtazapine
Nausea	1-18	<1
Pancreatitis	✔	-
Stomach ulcer	✔	<1
Vomiting	2-4	>1
Xerostomia	17-26	25
Genitourinary		
Cystitis	✔	-
Dyspareunia	✔	-
Ejaculation abnormality	✔	-
Impotence	<1	<1
Libido decreased	3	-
Libido increased	✔	-
Menopause	✔	-
Menstrual complaints	2-5	<1
Painful erection	✔	-
Prostate disorder	✔	-
Salpingitis	✔	-
Urinary frequency	2-5	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	1-4	2
Arthritis	2	-
Back pain	-	2
Dysarthria	✔	-
Extrapyramidal syndrome	✔	-
Musculoskeletal chest pain	✔	-
Myalgia	2-6	2
Neck pain	✔	<1
Rhabdomyolysis	✔	-
Rigidity	✔	-
Tardive dyskinesia	✔	-
Tremor	3-6	2
Twitching	1-2	<1
Weakness	2-4	8
Respiratory		
Bronchospasm	✔	-
Cough	1-4	-
Dyspnea	-	1
Pharyngitis	3-13	-
Pneumonia	✔	-
Pulmonary embolism	✔	-

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

✔ Percent not specified
- Event not reported

Table 7. Boxed Warning for the Antidepressants[1]

WARNING
Suicidality and antidepressant drugs: Antidepressants increased the risk compared with placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) 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 with placebo in adults older than 24 years of age; there was a reduction in risk with antidepressants compared with 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 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, maprotiline, mirtazapine, nortriptyline, paroxetine, phenelzine, protriptyline, tranylcypromine, trazodone, trimipramine, venlafaxine, and vilazodone 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 (OCD). Escitalopram is not approved for use in children younger than 12 years of age. Fluoxetine (except Sarafem®) is approved for use in children with MDD and obsessive-compulsive disorder (OCD). 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: Wellbutrin®, Wellbutrin SR®, and Wellbutrin XL® are not approved for smoking cessation treatment, but bupropion under the name Zyban® is 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 ZYBAN in the postmarketing experience. When symptoms were reported, most were during treatment with ZYBAN, but some were following discontinuation of treatment with ZYBAN. 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 ZYBAN. 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 ZYBAN 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. ZYBAN has been demonstrated to increase the likelihood of abstinence from smoking for as long as 6 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 US is approximately 1 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, 1 patient-year is equal to 2 patients each treated for 6 months, 3 patients each treated for 4 months, etc. This represents a rate of about 3 to 4 times the estimated background rate of liver failure. This rate is an underestimate because of underreporting, and the true risk could be considerably greater than this. A large cohort study of antidepressant users found no cases of liver failure leading to death or transplant among nefazodone users in approximately 30,000 patient-years of exposure. The spontaneous report data and the cohort study results provide estimates of the upper and lower limits of the risk of liver failure in nefazodone-treated patients, but are not capable of providing a precise risk estimate. 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, GI 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 AST or serum ALT levels greater than or equal to 3 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[1-32]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Monoamine Oxidase Inhibitors			
Isocarboxazid	Depression: 10 mg 2 to 3 times per day; maximum, 60 mg/day; reduce dose to 10-20 mg/day when condition improves	Safety and efficacy in children have not been established.	Tablet: 10 mg
Phenelzine	Depression: 15 mg 3 times per day; may increase to 60-90 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: 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: 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	Depression: 50 mg once daily	Safety and efficacy in children have not been established.	Tablet (ER): 50 mg 100 mg
Duloxetine	Chronic Musculoskeletal Pain: 60 mg once daily; maximum, 60 mg/day Depression: Initial, 40 mg/day (20 mg twice daily) to 60 mg/day (once daily or as 30 mg twice daily); maintenance, 60 mg/day; maximum, 120	Safety and efficacy in children have not been established.	Capsule (DR): 20 mg 30 mg 60 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	mg/day Diabetic Peripheral Neuropathic Pain: 60 mg once daily; maximum, 60 mg/day Fibromyalgia: Initial, 30 mg once daily for 1 week, then 60 mg once daily; maximum, 60 mg/day Generalized Anxiety Disorder: 60 mg once daily; maximum, 120 mg/day		
Venlafaxine	Depression: Tablet (IR): 75 mg/day administered in two or three divided doses, taken with food; dose may be increased in 75 mg/day increments at intervals of at least four days; maximum, 225-375 mg/day Capsule/tablet (ER): 75 mg once daily with food; may start at 37.5 mg/day for four to seven days before increasing to 75 mg once daily; dose may be increased by up to 75 mg/day increments every four days as tolerated; maximum, 225 mg/day Generalized Anxiety Disorder: Capsule (ER): 75 mg once daily taken with food; may start at 37.5 mg/day for four to seven days before increasing to 75 mg once daily; dose may be increased by up to 75 mg/day increments every four days as tolerated; maximum, 225 mg/day Panic Disorder: Capsule (ER): 37.5 mg once daily for 1 week; may increase to 75 mg daily, with subsequent weekly increases of 75 mg/day Social Anxiety Disorder: Capsule (ER): 75 mg once daily with food; may start at 37.5 mg/day for four to seven	Safety and efficacy in children have not been established.	Capsule (ER): 37.5 mg 75 mg 150 mg Tablet (ER): 37.5 mg 75 mg 150 mg 225 mg Tablet (IR): 25 mg 37.5 mg 50 mg 75 mg 100 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	days before increasing to 75 mg once daily; dose may be increased by up to 75 mg/day increments every 4 days as tolerated; maximum, 225 mg/day Tablet (ER): 75 mg once daily with food; there is no evidence that doses >75 mg/day offer any additional benefit		
Selective Serotonin-reuptake Inhibitors			
Citalopram	Depression: Initial, 20 mg/day, generally with an increase to 40 mg/day; doses of more than 40 mg are not usually necessary; should a dose increase be necessary, it should occur in 20 mg increments at intervals of no less than one week; maximum dose: 60 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: Initial, 10 mg/day; dose may be increased to 20 mg/day after at least one week Generalized Anxiety Disorder: Initial, 10 mg/day; dose may be increased to 20 mg/day after at least one week	Depression: ≥12 years of age: Initial, 10 mg/day; dose may be increased to 20 mg/day after at least 3 weeks	Solution: 5 mg/5 ml Tablet: 5 mg 10 mg 20 mg
Fluoxetine	Bulimia Nervosa: Capsule/tablet/solution (IR): 20 mg once daily; usual dose: 60 mg/day; maximum, 80 mg/day; doses >20 mg may be given once daily or divided twice daily Depression: Capsule/tablet/solution (IR): 20 mg once daily; usual dose: 20-40 mg/day; maximum, 80 mg/day; doses >20 mg may be given once daily or divided twice daily Capsule (DR): patients maintained on fluoxetine IR 20 mg/day may be changed to fluoxetine DR capsule 90 mg/week, starting dose seven days after the last 20 mg/day dose Depressive Episodes	Depression: 8 to 18 years of age: 10-20 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: 7-18 years of age: 10 mg/day; in adolescents and higher-weight children, dose may be increased to 20 mg/day after two weeks; range: 10-60 mg/day	Capsule (DR): 90 mg Capsule (IR): 10 mg 20 mg 40 mg Solution (IR): 20 mg/5 ml Tablet (IR): 10 mg 20 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Associated with Bipolar I Disorder and Treatment Resistant Depression: Fluoxetine 20 mg and olanzapine 5 mg once daily in the evening Obsessive-Compulsive Disorder: Capsule/tablet/solution (IR): 20 mg once daily; usual dose: 40-80 mg/day; maximum, 80 mg/day; doses >20 mg may be given once daily or divided twice daily Panic Disorder: Capsule/tablet/solution (IR): Initial, 10 mg/day; after 1 week, increase to 20 mg/day; may increase after several weeks; doses >60 mg/day have not been evaluated Premenstrual Dysphoric Disorder: Capsule/tablet/solution (IR): 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)		
Fluvoxamine	Obsessive-Compulsive Disorder: Tablet: Initial, 50 mg at bedtime; adjust dose in 50 mg increments every 4 to 7 days; usual dose: 100-300 mg/day; divide total daily dose into 2 doses; administer larger portion at bedtime; when total daily dose exceeds 100 mg, the dose should be given in 2 divided doses Capsule (ER): Initial, 100 mg at bedtime; may be increased in 50 mg increments at intervals of at least one week; usual dose range: 100-300 mg/day Social Anxiety Disorder: Capsule (ER): Initial, 100 mg at bedtime; may be increased in 50 mg increments at	Obsessive-Compulsive Disorder: 8 to 17 years of age: Initial, 25 mg at bedtime; adjust in 25 mg increments at 4 to 7 day intervals; range: 50-200 mg/day	Capsule (ER): 100 mg 150 mg Tablet: 25 mg 50 mg 100 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	intervals of at least one week; usual dose range: 100-300 mg/day		
Paroxetine	Depression: Tablet/suspension (IR): Initial, 20 mg once daily; increase by 10 mg/day increments at intervals of at least one week; maximum dose: 50 mg/day Tablet (ER): 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: Tablet/suspension (IR): Initial, 20 mg once daily; increase if needed by 10 mg/day increments at intervals of at least one week; doses of 20-50 mg/day were used in clinical trials; however, no greater benefit was seen with doses >20 mg Obsessive-Compulsive Disorder: Tablet/suspension (IR): 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: 20-60 mg/day Panic Disorder: Tablet/suspension (IR): 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: 10-60 mg/day Tablet (SR): 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: Tablet (SR): Initial, 12.5 mg	Safety and efficacy in children have not been established.	Suspension (IR): 10 mg/5 ml Tablet (IR): 10 mg 20 mg 30 mg 40 mg Tablet (ER): 12.5 mg 25 mg 37.5 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	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: Tablet/suspension (IR): Initial, 20 mg once daily; increase if needed by 10 mg/day increments at intervals of at least one week; range: 20-50 mg; limited data suggest doses of 40 mg/day were not more efficacious than 20 mg/day Social Anxiety Disorder: Tablet/suspension (IR): Initial, 20 mg once daily, preferably in the morning; recommended dose: 20 mg/day; range: 20-60 mg/day; doses >20 mg/day may not have additional benefit Tablet (SR): 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: 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: 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 Panic Disorder: Initial, 25 mg once daily; increased after one week to 50 mg once daily Posttraumatic Stress Disorder:	Obsessive-Compulsive Disorder: 6 to 12 years of age: Initial, 25 mg once daily 13 to 17 years of age: Initial, 50 mg once daily May increase daily dose, at intervals of not less than one week; maximum, 200 mg/day; if somnolence is noted, give at bedtime	Oral concentrate: 20 mg/ml Tablet: 25 mg 50 mg 100 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Initial, 25 mg once daily; increased after one week to 50 mg once daily Premenstrual Dysphoric Disorder: 50 mg/day 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: Initial, 25 mg once daily; increased after one week to 50 mg once daily		
Serotonin Modulators			
Nefazodone	Depression: 200 mg/day divided in 2 doses initially, with a range of 300-600 mg/day in 2 divided doses thereafter	Safety and efficacy in children have not been established.	Tablet: 50 mg 100 mg 150 mg 200 mg 250 mg
Trazodone	Depression: Tablet (ER): Initial, 150 mg once daily at bedtime; may increase by 75 mg/day every 3 days; maximum dose: 375 mg/day Tablet (IR): Initial, 150 mg/day in three divided doses; dose may be increased by 50 mg/day every three-seven days; maximum, 600 mg/day	Safety and efficacy in children have not been established.	Tablet (ER): 150 mg 300 mg Tablet (IR): 50 mg 100 mg 150 mg 300 mg
Vilazodone	Depression: Initial, 10 mg once daily for 7 days, then increase to 20 mg once daily for 7 days, then to recommended dose of 40 mg daily	Safety and efficacy in children have not been established.	Tablet: 10 mg 20 mg 40 mg
Tricyclics and Other Norepinephrine-reuptake Inhibitors			
Amitriptyline	Depression: 50-150 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: Initial, 25-50 mg/day; may administer in divided doses; increase gradually to 100 mg/day in divided doses	Tablet: 10 mg 25 mg 50 mg 75 mg 100 mg 150 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Amitriptyline and chlordiazepoxide	Depression and Anxiety: Initial, 3 to 4 tablets in divided doses; may be increased to 6 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
Amoxapine	Depression: Initial, 25 mg 2 to 3 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)	Depression: >16 years of age: Initial, 25-50 mg/day; increase gradually to 100 mg/day; may administer as divided doses or as a single dose at bedtime	Tablet: 25 mg 50 mg 100 mg 150 mg
Clomipramine	Obsessive-Compulsive Disorder: 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: 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: Initial, 75 mg/day in divided does; increase gradually to 150-200 mg/day in divided or single dose; maximum, 300 mg/day	Depression: >12 years of age: Initial, 25-50 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, 25-150 mg/day at bedtime or in 2 to 3 divided doses; may gradually increase up to 300 mg/day; single dose should not exceed 150 mg; select patients may respond to 25-50 mg/day Depression: Capsule/oral concentrate: Initial, 25-150 mg/day at bedtime or in 2 to 3 divided doses; may gradually increase up to 300 mg/day; single dose should not exceed 150 mg; select patients may respond to 25-50 mg/day Insomnia: Tablet: 6 mg once daily at bedtime; maximum 6 mg/day	Anxiety: >12 years of age: Capsule/oral concentrate: Initial, 25-50 mg/day in single or divided doses; gradually increase to 100 mg/day Depression: >12 years of age: Capsule/oral concentrate: Initial, 25-50 mg/day in single or divided doses; gradually increase to 100 mg/day	Capsule: 10 mg 25 mg 50 mg 75 mg 100 mg 150 mg Oral concentrate: 10 mg/ml Tablet: 3 mg 6 mg
Imipramine	Depression:	Depression:	Capsule:

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Capsule: Initial, 75 mg/day; dosage may be increased to 150-200 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	Adolescents: Tablet: Initial, 30-40 mg/day; increase gradually; maximum, 100 mg/day in single or divided doses Enuresis: ≥6 years of age: Tablet: Initial, 25 mg at 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 6-12 years of age) or 75 mg at bedtime (if ≥12 years of age)	75 mg 100 mg 125 mg 150 mg Tablet: 10 mg 25 mg 50 mg
Maprotiline	Depression: Mild to moderate: Initial, 75 mg/day for 2 weeks (lower doses may be considered in some patients); increase by 25 mg as tolerated up to 150 mg/day; given in divided doses or in a single daily dose Severe: Initial, 100-150 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: 25 mg 3 to 4 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: 10 mg/5 ml
Protriptyline	Depression: 15-60 mg/day in 3 to 4 divided doses	Depression: Adolescents: 15-20 mg/day in 3 divided doses	Tablet: 5 mg 10 mg
Trimipramine	Depression: 50-150 mg/day as a single bedtime dose; maximum, 200 mg/day for outpatients and 300 mg/day for inpatients	Depression: Adolescents: Initial, 50 mg/day, with gradual increments up to 100 mg/day	Capsule: 25 mg 50 mg 100 mg
Antidepressants, Miscellaneous			
Bupropion	Depression: Tablet, hydrochloride (ER): 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	Safety and efficacy in children have not been established.	Tablet (ER): 150 mg 174 mg 300 mg 348 mg 522 mg Tablet (IR):

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Tablet, hydrobromide (ER): Initial, 174 mg/day in the morning; may increase as early as day four to 348 mg/day; maximum dose: 522 mg/day Tablet (IR): Initial, 100 mg twice daily; maximum, 450 mg/day Tablet (SR): Initial, 150 mg/day; may increase to 150 mg twice daily by day 4 if tolerated; target dose: 150 mg twice daily; maximum dose: 400 mg/day Seasonal Affective Disorder: Tablet (SR): Initial, 150 mg/day in the morning; if tolerated, may increase after one week to 300 mg/day Smoking Cessation: Tablet (IR): Initial, 150 mg once daily for 3 days; increase to 150 mg twice daily; treatment should continue for seven to twelve weeks		75 mg 100 mg Tablet (SR): 100 mg 150 mg 200 mg
Mirtazapine	Depression: Initial, 15 mg at bedtime; titrate up to 15-45 mg/day with dose increases made no more frequently than every one to two weeks	Safety and efficacy in children have not been established.	Tablet: 7.5 mg 15 mg 30 mg 45 mg Tablet (ODT): 15 mg 30 mg 45 mg

DR=delayed-release, ER=extended-release, IR=immediate-release, ODT=orally disintegrating tablet, SR=sustained-release

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				
Clayton et al.[105] (2006) Bupropion ER 300-450 mg daily vs escitalopram 10-20 mg daily vs placebo	DB, PC, RCT Adult outpatients with moderate-to-severe major depressive disorder with normal sexual function	N=830 8 weeks	Primary: Orgasm dysfunction at 8 weeks and incidence of worsened sexual functioning; CSFQ, HAM-D_{17}	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 8 were 15% with bupropion ER, 30% with escitalopram, and 15% with placebo. The mean change in CSFQ sores for all domains at week 8 was statistically significantly worse for escitalopram compared with 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.
Hewett et al.[60] (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	RCT, MC, DB, PC Patients 18–64 years of age with major depressive disorder	N=576 8 weeks	Primary: Mean change from baseline at week 8 in the MADRS total score (LOCF) Secondary: MADRS total score (observed cases - OC), MADRS subscore, percentage of MADRS responders and remitters at week	Primary: The mean changes from baseline at week 8 (LOCF) in MADRS total score were greater for patients receiving bupropion ER and venlafaxine ER compared to 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 8 (OC) in MADRS total scores were significantly greater for bupropion ER and venlafaxine ER patients compared with 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo			8; CGI-I score at week 8; CGI-S score and HAMA total score at weeks 1, 2, 4, 6 and 8	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 with placebo at week 8 (−1.7 and −1.4, respectively). Significant improvements in MADRS lassitude score were found for venlafaxine ER compared with 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 8 compared with 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 8 compared with 53% of placebo patients. The mean change from baseline in the MEI total score was 24.6 for bupropion ER (P<0.001), 25.9 for venlafaxine ER (P<0.001) and 17.4 for placebo. Mean changes from baseline in the Q-LES-Q-SF general activities and life satisfaction and contentment scores were significantly greater for bupropion ER (21.9, P<0.001 and 1.3, P<0.001, respectively) and venlafaxine ER (21.1, P=0.004 and 1.2, P<0.001, respectively) compared with placebo (16.1 and 0.9, respectively) at week 8. 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 with 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Weihs et al.[82] (2000) Bupropion SR 100-300 mg/day vs paroxetine 10-40 mg/day	DB, MC, RCT Patients ≥60 years of age with major depressive disorder	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.[83] (1997) Bupropion SR 100-300 mg/day vs sertraline 50-200 mg/day	DB, PG, RCT Outpatients with moderate-to-severe major depressive disorder	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 with bupropion SR-treated patients. Adverse events (nausea, diarrhea, somnolence, and sweating) were 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.[84] (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)	Primary: Both treatments induced notable improvement of depressive symptoms. No statistically significant differences were found between the 2 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 1 month, 3 month, and end follow-up periods, P=0.3466, 0.7570, and 0.2537, respectively.
Thase et al.[51] (2009) Desvenlafaxine	RCT, DB, PC (Pooled analysis) Patients ≥18 years	N=3,023 (9 trials) 8 weeks	Primary: HAM-D_{17} total score Secondary:	Primary: Decreases in HAM-D_{17} total scores (LOCF) were significantly greater compared with placebo for the overall nine-study desvenlafaxine group (-11.2 for desvenlafaxine vs -9.4 for placebo; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
50-400 mg/day vs placebo	of age with major depressive disorder		MADRS total score, HAM-D_6 total score, CGI-I and CGI-S scales, and rates of response and remission	Secondary: The overall desvenlafaxine group had a significantly greater change from baseline compared with placebo on the CGI-S (-1.63 for desvenlafaxine vs -1.32 for placebo; P<0.001), CGI-I (2.32 for desvenlafaxine vs 2.62 for placebo; P<0.001), MADRS total scores (-14.78 for desvenlafaxine vs -11.79 for placebo; P<0.001), and the HAM-D_6 total score (-6.28 for desvenlafaxine vs -4.89 for placebo; P<0.001). The overall desvenlafaxine group had significantly higher rates of response and remission compared to placebo (P<0.001 for all outcomes assessed compared to placebo).
Soares et al.[146] (2010) Desvenlafaxine 100 to 200 mg/day vs escitalopram 10 to 20 mg/day	RCT, DB, AC, MC Postmenopausal women 40 to 70 years of age with major depressive disorder	N=607 Acute phase: 8 weeks Continuation phase: 6 months	Primary: HAM-D_{17} total score, response and remission rates, anxiety scores, quality of life, menopause-related symptoms, safety and tolerability	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). 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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.
Acharya et al.[79] (2006) Duloxetine 40-120 mg daily vs placebo	MA Patients with major depressive disorder	N=2,996 (12 trials) Variable duration	Primary: Incidence of suicide-related events with duloxetine (MHID, MHRD, HAM-D Item-3)	Primary: There were no significant differences in the incidence of suicide-related events with duloxetine versus 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).
Gaynor et al.[142] (2011) Duloxetine 60 mg once daily vs placebo	RCT, DB, PC, MC Patients ≥18 years of age with a current episode of major depressive disorder (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, Sheehan Disability Scale (SDS) global functional impairment score,	Primary: Treatment with duloxetine resulted in a significantly greater improvement in MADRS total score compared to 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 2 and at all remaining visits (P≤0.001). There was a significantly greater reduction in average pain rating from baseline to week 8 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 1, 2, 4, and 8 with duloxetine compared to placebo (all P≤0.005).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			safety	Secondary: A significantly greater proportion of patients receiving duloxetine met the criteria for remission than 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 versus placebo (all P≤0.001). The LS 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 with the placebo group (35.2%; P≤0.001). Patients receiving duloxetine demonstrated significantly greater improvements in the SDS global functional impairment score compared to 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.[149] (2011) Duloxetine 60 mg once daily vs placebo	RCT, DB, PC, MC Patients ≥18 years of age with a current episode of major depressive disorder (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, Sheehan Disability	Primary: Treatment with duloxetine resulted in a significantly greater improvement in MADRS total score compared to 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 8 with duloxetine compared to placebo (-1.66 vs -1.17, respectively; 27.7% vs 18.9% reduction in pain, respectively; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Scale (SDS) global functional impairment score	Patients also had greater improvement in their average pain rating at weeks 2, 4, and 8 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 placebo (23.0%; P<0.001). 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 versus placebo. The LS 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 placebo (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.[144] (2012) Duloxetine 120 mg/day vs bupropion ER 300 mg/day	RCT, SB Patients ≥18 years of age with major depressive disorder who failed to respond to two consecutive antidepressant trials with SSRIs	N=49 6 weeks	Primary: Change in HAM-D_{17} Secondary: CGI-S, global assessment of functioning (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 compared to baseline (all P<0.001). The 6-item-HAM-D mean score decreased significantly by week 2 with duloxetine (from 11.84 to 6.04; P<0.001) and bupropion (from 12.05 to 5.52; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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.[108] (2007) Duloxetine 60 mg daily vs escitalopram 10 mg daily vs placebo	AC, DB, RCT, PC Patients ≥18 years of age with major depressive disorder	N=547 8 weeks	Primary: Percentage of patients achieving onset criteria at week 2 (defined as 20% decrease from baseline in Hamilton Rating Scale for Depression)	Primary: No significant difference was observed in the probability of patients meeting onset criteria at week 2 between the duloxetine group and the escitalopram group (P=0.097). Duloxetine and escitalopram both showed significant improvement compared to placebo on primary efficacy analysis at week 1 and week 8 (P<0.05).
Pigott et al.[56] (2007) Acute Phase Duloxetine 60 mg/day vs escitalopram 10 mg/day vs placebo Extension Phase Duloxetine 60-120 mg/day	RCT, DB, MC, PC Patients >18 years of age with major depressive disorder	N=684 Acute Phase 8 weeks Extension Phase 24 weeks	Primary: HAM-D_{17}, CGI-S, PGI-I, HAMA, remission rates	Primary: After 8 months of treatment, there were no significant differences in efficacy between duloxetine and escitalopram as assessed by mean changes from baseline in the HAM-D_{17} total score and the HAM-D_{17} Maier, anxiety/somatization, and retardation/ somatization subscales. The only HAM-D_{17} subscale with a significant drug difference was the HAM-D_{17} sleep subscale, which demonstrated that escitalopram was associated with a significantly greater improvement in insomnia than duloxetine at the 8-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 8 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 8 weeks (duloxetine 40%, escitalopram 33%; P=0.25) or at 8 months (duloxetine 70%,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs escitalopram 10-20 mg/day				escitalopram 75%; P=0.44).
Goldstein et al.[109] (2004) Duloxetine 20-40 mg twice daily 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-item total change by 3.62 points (95% CI: 1.38 to 5.86; P=0.002). Duloxetine at 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.[114] (2006) Duloxetine 40 mg twice daily vs duloxetine 60 mg twice daily vs paroxetine 20 mg daily	DB, MC, PC, RCT Patients ≥18 years of age with major depressive disorder	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 8 compared with 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
vs placebo				
Martinez et al.[141] (2012) Duloxetine 30 to 120 mg once daily 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 200 mg/day at the investigator's discretion)	RCT, MC, AC Adult outpatients with severe major depressive disorder	N=750 12 weeks	Primary: Remission at week 12 as measured by Quick Inventory of Depressive Symptomatology Self-Report (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 with 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}. 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 versus patients treated with SSRIs

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(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 TEAEs.
Van Baardewijk et al.[85] (2005) Duloxetine 40-120 mg daily for at least 8 weeks vs venlafaxine ER 75-225 mg daily for at least 8 weeks	MA Adults with moderate-to-severe major depressive disorder	N=not specified 6 months	Primary: Remission (an improvement in the HAM-D scale to a score of <7, or a score of ≤10 on the MADRS scale), symptom-free days (SFD)	Primary: Patients receiving duloxetine and venlafaxine ER experienced similar success rates after 6 months of treatment (53% and 57%, respectively). Patients receiving duloxetine and venlafaxine ER experienced similar number of SFDs after 6 months of treatment (52.72% and 57.03%, respectively). Duloxetine therapy was associated with a greater hospitalization rate compared to venlafaxine ER therapy (47% and 43%, respectively).
Vis et al.[110] (2005) Duloxetine 40-120 mg/day vs venlafaxine ER 75-225 mg/day vs placebo	MA Patients >18 years of age with major depressive disorder	N=1,791 (8 trials) 8 weeks	Primary: HAM-D, MADRS Secondary: Dropout rates and rates of adverse events	Primary: Both treatment groups demonstrated a statistically significant difference compared with placebo for both remission and response (P<0.001). Secondary: More patients receiving placebo dropped out due to lack of efficacy compared with the treatment arms (P<0.001 for both drugs). Dropout rates due to adverse reactions were also statistically significant when active drugs were compared with placebo. More patients in the active drug treatment groups than in the placebo groups dropped out due to adverse reactions (venlafaxine ER P<0.001; duloxetine P=0.008).
Perahia et al.[69] (2008) Duloxetine 60-120 mg/day vs	RCT, DB, MC (pooled analysis) Patients >18 years of age with major depressive disorder	N=667 (2 trials) 12 weeks	Primary: Global benefit–risk ([GBR] defined as remission at endpoint using the 17-item Hamilton Depression Rating	Primary: There were no significant differences in GBR with duloxetine and venlafaxine at the end of 6 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
venlafaxine ER 75-225 mg/day			Scale [HAM-D_{17}] ≤7) Secondary: Efficacy	not different between the duloxetine and venlafaxine 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, 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 at 6 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 2, 4, 8 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.[145] (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	RCT, SB, PC, MC Patients 18 to 75 years of age with major depressive disorder	N=665 7 months	Primary: Symptom remission (QIDS-SR), attrition, anxiety (IDS-C), functioning, quality of life, adverse events	Primary: At 12 weeks, the remission rates were 38.8% for escitalopram-placebo, 38.9% for bupropion-escitalopram, and 37.7% for venlafaxine-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 quality of life. At 7 months, the treatment groups were not different in terms of remission rate (range: 41.8%-46.6%), response rate (range: 57.4%-59.4%), or attrition rate. There was no difference in the percentage of change in QIDS-SR, quality of life, or work and social adjustment. The venlafaxine-mirtazapine group had greater side effect frequency and intensity at 12 weeks and greater side effect frequency, intensity, and burden at 7 months as compared to escitalopram-placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
to 45 mg/day				
Moore et al.[86] (2005) Escitalopram 20 mg daily vs citalopram 40 mg daily	DB, MC, RCT Outpatients with major depressive disorder 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	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 with the citalopram group (56.1% vs 43.6%, P<0.05). Tolerability was similar in both treatment groups.
Colonna et al.[88] (2005) Escitalopram 10 mg daily vs citalopram 20 mg daily	DB, RCT Patients with moderate-to-severe major depressive disorder	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.[107] (2002) Escitalopram 10 mg daily vs escitalopram 20 mg daily vs citalopram 40 mg daily	DB, MC, RCT Outpatients 18-65 years of age with major depressive disorder	N=491 8 weeks	Primary: Change from baseline in the MADRS total score at week 8 Secondary: Change from baseline in the MADRS total score at weeks 1,2,4, and 6, change from baseline in the HAM-D, CGI-S,	Primary: Mean changes from baseline for the MADRS score were significantly greater compared with 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 arm exhibited significantly greater improvement in the HAM-D score from baseline compared with placebo (P<0.01 and P<0.05, respectively). Response to treatment was observed in 50% of escitalopram 10 mg, 51.2%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo			CGI-I, HAMA, QOL, and CES-D	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 mg and 20 mg group exhibited significantly greater improvement in the HAMA score from baseline compared with placebo (P=0.04 and P<0.01, respectively). Mean changes from baseline for the QOL score were significantly greater compared with 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 with 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 significantly greater adverse event rates compared to placebo (85.6% vs 86.4%, P<0.01).
Yevtushenko et al.[58]	RCT, DB, MC, AC	N=330	Primary: MADRS total	Primary: The mean changes in MADRS total score were significantly greater in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2007) Escitalopram 10 mg/day vs citalopram 10 mg/day vs citalopram 20 mg/day	Patients 25-45 years of age with major depressive disorder	6 weeks	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	patients receiving escitalopram than citalopram 10 mg or 20 mg (-28.70 vs -20.11 and -25.19; both, P 0.001). The difference between the 2 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 mg and 20 mg groups were -9.46 and-3.99, respectively (both, P<0.001). The difference between the citalopram 20 mg 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 mg and 20 mg groups were -6.00 and -2.48, respectively (both, P<0.001). The difference between the citalopram 20 mg 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 mg and 20 mg groups were -0.99 and -0.55, respectively (both, P<0.001). The difference between the citalopram 20 mg 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 versus citalopram 10 mg and 20 mg groups, respectively (both, P<0.001). Remission rates were 89.8% vs 25.5% and 50.9% in the escitalopram versus citalopram 10 mg and 20 mg groups, respectively (both, P<0.001).
Lam et al.[87] (2006) Escitalopram 10-20 mg daily vs	MA Outpatients with major depressive disorder	N=1,321 (3 trials) 8 weeks	Primary: MADRS, response rate Secondary: CGI-I, CGI-S, HAM-D	Primary: No significant difference in response rate between the 2 treatment groups was seen at week 8. 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
citalopram 20-40 mg daily				the patient was at baseline. Secondary: Similar results were seen in the secondary outcomes.
Gorman et al.[89] (2002) Escitalopram 10-20 mg daily vs citalopram 20-40 mg daily	MA Outpatients with major depressive disorder	N=1,321 (3 trials) 8 weeks	Primary: MADRS, CGI-I	Primary: Mean change in MADRS score from baseline at week 8 was significantly improved in both treatment groups compared to baseline (P<0.05). Mean change in MADRS score from baseline at week 8 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 8 was significantly improved in both treatment groups compared to baseline (P<0.05). No significant difference in CGI-I scores between the 2 treatment groups was reported at week 8 (P>0.05).
Llorca et al.[106] (2005) Escitalopram 10-20 mg daily vs citalopram 20-40 mg daily vs placebo	MA Patient 18-80 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 with 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 with citalopram treatment (P=0.01 and P=0.001 for CGI-I and CGI-S, respectively).
Ou et al.[156] (2010) Escitalopram 10 to	RCT, DB, MC Patients 18 to 65 years of age with	N=240 6 weeks	Primary: Change in HAM-D_{17} total score	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
20 mg/day vs citalopram 20 to 40 mg/day	major depressive disorder (MDD)		Secondary: Response and remission rates	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 AEs. No serious AEs were observed.
Wade et al.[63] (2007) Escitalopram 20 mg/day vs duloxetine 60 mg/day	RCT, DB Patients 18-65 years of age with major depressive disorder	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 8, 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; P0.077), CGI-S (2.11 vs 2.28; P=0.214) at 24 weeks between escitalopram-treated patients and duloxetine-treated patients.
Khan et al.[91] (2007) Escitalopram 10-20 mg daily	DB, MC, PG, RCT Patients with major depressive disorder	N=278 8 weeks	Primary: Change from base-line to week 8 in MADRS scores using the last observation carried	Primary: At week 8, 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs duloxetine 60 mg daily			forward approach (LOCF)	groups in the observed case (OC) analysis (P=0.79).
Boulenger et al.[92] (2006) Escitalopram 20 mg daily vs paroxetine 40 mg daily	DB, MC, RCT Patients with major depressive disorder	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.[94] (2004) Escitalopram 10-20 mg daily vs venlafaxine ER 75-150 mg daily	DB, RCT Patients with major depressive disorder	N=293 8 weeks	Primary: Change from baseline in MADRS scores	Primary: No significant difference between groups was observed at week 8 in MADRS scores. Escitalopram-treated patients achieved remission significantly faster compared to venlafaxine patients in a post-hoc analysis.
Fava et al.[113] (2002)	DB, MC, RCT Patients ≥18 years	N=284 10-16 weeks	Primary: HAM-D_{17} scores	Primary: As indicated by baseline-to-endpoint improvement on the HAM-D_{17}, there were no statistically significant differences between fluoxetine, sertraline,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Fluoxetine 20 mg daily vs sertraline 50 mg daily vs paroxetine 20 mg daily	of age with depression		Secondary: Improvement in insomnia/sleep disturbances	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.[95] (2002) Imipramine (IMI) (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	Primary: The 2 groups were equal in response rates for completers, 63% and 55% for the sertraline and IMI 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 IMI experienced significant increases in 8 adverse events and significant reductions in 3 adverse events while those patients going from IMI to sertraline experienced a significant reduction in 7 adverse events and no increase in any adverse event.
Versiani et al.[96] (2005) Mirtazapine 15-60 mg daily vs fluoxetine 20-40 mg daily	DB, RCT Patients 18-65 years of age with major depressive disorder	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 7; 9.7% vs 3.4%, P=0.032).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				No significant between-group differences were observed for the majority of quality-of-life 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 with a mean decrease in weight of 0.4 ± 2.1 kg for fluoxetine-treated patients (P<0.001).
Wheatley et al.[97] (1998) Mirtazapine 15-60 mg/day vs fluoxetine 20-40 mg/day	DB, MC, RCT Patients with major depressive disorder aged 18 to 75 years	N=123 6 weeks	Primary: HAM-D	Primary: The mean HAM-D_{17} scores were not different at week 6 for the two groups; although at week 3 (the estimated treatment difference was -3.4 in favor of mirtazapine; 95% CI: –6.1 to –0.76; P=0.006) and week 4 (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 6.
Blier et al.[62] (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)	RCT, DB Patients with major depressive disorder	N=61 8 weeks	Primary: MADRS, HAM-D_{17}, CGI	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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. Non-responders on combination therapy had the dosage of both drugs increased by 50%.				at day 35 versus 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 7 and 5 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.
Behke et al.[98] (2003) Mirtazapine orally disintegrating tablets 30-45 mg/day vs sertraline 50-150 mg/day	DB, RCT Patients with major depressive disorder	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 2 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.[99] (2001) Mirtazapine 15-60 mg/day	DB, MC, RCT Hospitalized patients with severe depressive episode	N=157 8 weeks	Primary: HAM-D, MADRS Secondary:	Primary: Both drugs were effective in reducing overall symptoms of depression, showing substantial reductions in group mean MADRS scores (-20.1 for mirtazapine and -17.5 for venlafaxine) and HAM-D_{17} scores (-17.1 for mirtazapine and -14.6 for venlafaxine) at the end of the treatment (P=NS).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs venlafaxine 75-375 mg/day	with melancholic features		Adverse effects	There was no significant difference in responder rates (≥50% reduction) on the HAM-D (62% vs 52%) and MADRS (64% vs 58%) between the treatment groups at endpoint. A statistically significant difference favoring mirtazapine was found on the HAM-D Sleep Disturbance factor at all assessment points (P≤0.03). Secondary: A statistically 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.[80] (1998) Nefazodone 200 mg twice daily vs placebo	DB, PC, PG Patients that were hospitalized due to depression	N=120 6 weeks	Primary: HAM-D_{17}, CGI-I, MADRS	Primary: Nefazodone treatment resulted in a significant reduction (P<0.01) of the HAM-D_{17} total score compared with 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} 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 2 and through the end of the trial.
Dunner et al.[81] (2005) Paroxetine CR 12.5-62.5 mg	DB, PC, RCT (Pooled analysis) Adults with major depressive disorder	N=303 (4 trials) 8-12 weeks	Primary: Changes in depressive symptoms according to	Primary: Statistically significant improvements in depressive symptoms in favor of paroxetine CR compared with 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, -

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo			HAM-D_{17} and CGI-I, patients achieving remission	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.[100] (2004) Phenelzine 10 mg twice daily vs tranylcypromine 10 mg twice daily	DB, RCT Patients 18-65 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 versus 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 dizziness, agitation, and insomnia. The incidence was the same in both samples (21%).
Rossini et al.[101] (2005) Sertraline 150 mg daily vs fluvoxamine 200 mg daily	DB, RCT Patients >59 years of age with major depressive disorder	N=88 7 weeks	Primary: Response rate (HAM-D)	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).
Sheehan et al.[137] (2009) Trazodone ER 150 to 375 mg/day vs	RCT, DB, PC, MC Patients ≥18 years of age with major depressive disorder	N=412 8 weeks	Primary: Change in HAM-D_{17} total score Secondary: HAM-D_{17} responders and	Primary: The change in the HAM-D_{17} total score decreased by an average of 11.4 in the trazodone group versus 9.3 in the placebo group (49% vs 41%, respectively; P=0.012). Secondary: At the last study visit, the number of HAM-D_{17} remitters and percentages

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo			remitters, change in HAM-D_{17} depressed mood item, MADRS total score, CGI-I, PGI-I, sleep	of CGI-I and PGI-I responders in patients receiving trazodone were not significantly difference than placebo (LOCF). The mean percentages of HAM-D_{17} remitters in the modified ITT and PP populations were significantly higher for patients in the trazodone group than placebo during all other treatment period assessment days. The PGI-I with trazodone was significantly different from placebo for the PP population (P=0.033): 85.7% of patients receiving trazodone were "improved" compared to 75.0% of patients receiving placebo. At the end of the study, the patients from the modified ITT/LOCF dataset in the trazodone group had significant improvements in all quality of sleep parameters compared to placebo. The most frequent adverse events were the same for both the treatment and placebo groups: headache and somnolence. There were no serious adverse events that were considered related to treatment.
Lenox-Smith et al.[66] (2008) Venlafaxine ER 75-300 mg/day vs citalopram 20-60 mg/day	RCT, DB, MC, Patients 18-65 years of age with major depressive disorder who had not experienced a treatment response to 8 weeks of monotherapy with an adequate regimen of an SSRI	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). 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.[102] (2004) Venlafaxine ER 225 mg/day vs	DB, RCT Patients with major depressive disorder	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 $\leq$10) rates at endpoint were 41.2% for

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
escitalopram 20 mg/day				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% vs 4.1%; P<0.01).
Nemeroff et al.[111] (2007) Venlafaxine 75-225 mg/day vs fluoxetine 20-60 mg/day vs placebo	DB, MC, PC, RCT Outpatients ≥18 years of age with major depressive disorder	N=308 6 weeks	Primary: HAM-D	Primary: On the HAM-D, overall differences among treatment groups at week 6 did not reach statistical significance (P=0.051), though the difference between the venlafaxine and placebo groups was statistically significant (P=0.016). The differences between fluoxetine and placebo (P=0.358) and between venlafaxine and fluoxetine (P=0.130) were not statistically significant. The difference on the HAM-D depressed mood item was statistically significant among treatment groups at week 6 (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).
Rudolph et al.[112] (1999) Venlafaxine ER 75-225 mg/day vs fluoxetine 20-60 mg/day	DB, MC, PC, PG, RCT Outpatients ≥18 years of age with major depressive disorder	N=301 8 weeks	Primary: HAM-D, MADRS, CGI	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 statistically significant (P<0.05). Venlafaxine ER produced a statistically 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				investigational sites.
Benkert et al.[103] (1996) Venlafaxine 150-375 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	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.
Kok et al.[67] (2007) Venlafaxine ER 75-375 mg/day vs nortriptyline 25-200 mg/day	RCT, DB Inpatients ≥60 years of age with major depressive disorder	N=81 12 weeks	Primary: Remission (MADRS ≤10) Secondary: Remission on HAM-D and Geriatric Depression Scale (GDS), response rates	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 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).
Mazeh et al.[50] (2007) Venlafaxine 75-300 mg/day vs paroxetine 10-60 mg/day	RCT, SB Inpatients ≥65 years of age with major depressive disorder who did not respond to two adequate pharmacological treatments for depression during	N=30 6 weeks	Primary: CGI, HAM-D, Geriatric Depression Scale (GDS)	Primary: Nine patients treated with venlafaxine (60%) and 5 patients treated with paroxetine (33%) remitted after 8 weeks of treatment. Three patients from each group responded without achieving remission after 8 weeks of treatment (20%). Four patients treated with venlafaxine (26.7%) and 8 patients treated with paroxetine (53.3%) failed to respond.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	the current depressive episode			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 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).
Khan et al.[143] (2011) Vilazodone 40 mg once daily vs placebo	RCT, DB, MC, PC Patients 18 to 70 years of age with major depressive disorder (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, Changes in Sexual Functioning Questionnaire (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 8 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.[159] (2009)	RCT, DB, MC, PC Patients 18 to 65	N=410 8 weeks	Primary: Change in MADRS total	Primary: The mean change on the MADRS total score was significantly greater with vilazodone compared to placebo (-12.9 vs -9.6, respectively;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Vilazodone 40 mg once daily vs placebo	years of age with major depressive disorder (single episode or recurrent)		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)	P=0.001). The difference was evident by week 1 (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 1 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.
Robinson et al.[138] (2011) Vilazodone 40 mg once daily	OL, MC Patients 18 to 70 years of age with major depressive disorder	N=616 52 weeks	Primary: Safety, sexual function (CSFQ), effectiveness (MADRS, CGI-S and CGI-I scales)	Primary: A total of 93.8% of patients had ≥1 treatment-emergent adverse events (TEAEs). The most frequent TEAE were diarrhea (35.7%), nausea (31.6%), and headache (20.0%). The incidence of severe AEs was 14.9%. The incidence of severe gastrointestinal AEs was 3.5% and the incidence of severe headache was 1.2%. Mean weight increase was 1.7 kg at week 52. At 6 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 kg 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				scores improved and exceeded threshold values for sexual dysfunction at week 4 for men and week 8 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 8 patients who had AEs of either suicidal ideation or behavior. The mean MADRS scores improved from 29.9 at baseline to 11.4 at week 8 (change, -18.5), 8.2 at week 24 (change, -21.7), and 7.1 at 1 year (change, -22.8). The mean CGI-S improved from 4.3 at baseline to 2.5 at week 8 (change, -1.9) and 1.7 at 1 year (change, -2.6). The CGI-I mean score decreased from 3.5 at week 1 to 1.9 at week 8 and 1.4 at 1 year.
Cipriani et al.[53] (2009) New-generation antidepressants (bupropion, citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, milnacipran, mirtazapine, paroxetine, reboxetine, sertraline, venlafaxine)	MA Patients with major depressive disorder	N=25,928 (117 trials) 6-12 weeks (acute treatment)	Primary: Response (defined as the proportion of patients who had a reduction of ≥50% from the baseline score on the HDRS or MADRS, or who scored much improved or very much improved on the CGI at 8 weeks) and dropout rates	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 Meta-analyses 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 less well tolerated than citalopram, escitalopram, and sertraline; venlafaxine less well tolerated than escitalopram; reboxetine less well tolerated than many other antidepressants, such as bupropion, citalopram, escitalopram, fluoxetine, and sertraline; and escitalopram and sertraline were better tolerated than duloxetine,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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. 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%).
Moncrieff et al.[76] (2004) Antidepressants vs placebo	MA Patients with major depressive disorder	N=751 (9 trials) Variable duration	Primary: Efficacy	Primary: TCAs were statistically better than active placebo in the pooled analysis (0.39, 95% CI: 0.24 to 0.54).
Walsh et al.[77] (2002) Antidepressants vs placebo	MA Adult outpatients with major depressive disorder	N=not specified (75 trials) Variable duration	Primary: HAM-D, CGI	Primary: The mean proportion of patients in the placebo group who responded was 29.7% (range, 12.5%-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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				year of publication (for placebo P<0.001; for medication P=0.02). The association between year of publication and response rate was more statistically robust for placebo than medication.
Geddes et al.[78] (2003) Antidepressants vs placebo	MA Studies evaluating relapse prevention of depression	N=4,410 (31 trials) 6-36 months	Primary: Proportion of patients relapsing; withdrawal from the trial	Primary: Continuing treatment with antidepressants reduced the odds of relapse by 70% (95% CI: 62 to 78; P<0.00001) compared with treatment discontinuation. The average rate of relapse on placebo was 41% compared with 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).
Thase et al.[115] (1995) Phenelzine (PHZ) vs isocarboxazid (ISO) vs tranylcypromine (TRP) vs placebo	MA Patients with major depressive disorder	Review of Medline and Psychological abstracts from 1959-1992	Primary: Efficacy	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%).
Cipriani et al.[116] (2005)	MA Patients with major	N=9,311 (132 trials)	Primary: Number of patients who responded to	Primary: On a dichotomous outcome fluoxetine was less effective than sertraline (OR: 1.40, 95% CI: 1.11 to 1.76), mirtazapine (OR: 1.64, 95% CI: 1.01 to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Fluoxetine, sertraline, nortriptyline, amitriptyline, venlafaxine, imipramine, nefazodone, citalopram, desipramine, paroxetine, pramipexole, fluvoxamine, trazodone, bupropion, clomipramine, duloxetine, mirtazapine, doxepin	depressive disorder	Variable duration	treatment (HAM-D, MADRS) Secondary: Tolerability	2.65) and venlafaxine (OR: 1.40, 95% CI: 1.15 to 1.70). On a continuous outcome, fluoxetine was less effective than venlafaxine (SMD random effect: 0.11, 95% CI: 0.00 to 0.23). Secondary: Fluoxetine was better tolerated than tricyclic antidepressants considered as a group (OR: 0.78, 95% CI: 0.68 to 0.89), and was better tolerated in comparison with individual antidepressants, in particular than amitriptyline (OR: 0.64, 95% CI: 0.47 to 0.85) and imipramine (OR: 0.79, 95% CI: 0.63 to 0.99), and among newer antidepressants than pramipexole (OR: 0.20, 95% CI: 0.08 to 0.47).
Stahl et al.[104] (1997) Mirtazapine up to 35 mg daily vs amitriptyline up to 280 mg daily vs placebo up to 7 capsules daily	MA Patients with major depressive disorder	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), MADRS, CGI Secondary: Change from baseline in the "depressed mood" item on the HDRS	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). 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).

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			scale, anxiety/ somatization factor, sleep disturbance factor, melancholia factor, tolerability	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% 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%), constipation (31.1% vs 18%), 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.[117] (2002) Continuation of an SSRI vs discontinuation of	RETRO Adult patients diagnosed with a depressive disorder, taking an SSRI for at least 6 months were interviewed over the phone;	N=137,401 6 months	Primary: Patient-physician communication about therapy duration and adverse effects, therapy discontinuation or switching of	Primary: While 72% of physicians reported instructing their patients on taking 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;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
an SSRI vs switching of an SSRI	prescribing physicians were asked to complete a survey		medication within 3 months of SSRI use, BDI-FS, depression symptoms	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 3 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 6 times more likely to switch their medication (OR 6.15, 95% CI: 2.11 to 17.89).
Anderson et al.[118] (2000) Tricyclic antidepressants (TCAs) vs selective serotonin-reuptake inhibitors (SSRIs)	MA Patients with major depressive disorder	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). 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.[119] (2003) Tricyclic antidepressants	MA Patients with major depressive disorder	N=2,951 (11 trials) Variable duration	Primary: HAM-D; MADRS Secondary: Tolerability	Primary: Efficacy between selective serotonin-reuptake inhibitors 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:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(TCAs) vs selective serotonin-reuptake inhibitors (SSRIs)				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.[120] (1997) Tricyclic antidepressants (TCAs) vs selective serotonin-reuptake inhibitors (SSRIs)	MA Patients with major depressive disorder	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 intention-to-treat 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				
Kaur et al.[139] (2011) Duloxetine 20 to 60 mg once daily for 6 weeks vs amitriptyline 10 to 50 mg once daily at bedtime for 6 weeks	RCT, DB, AC, 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 by DNE score, DNS score, modified NSS, 24-point Hamilton Rating	Primary: There was a significant improvement in pain at 6 weeks with both treatments compared with 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% improvement was seen in 50% of patients receiving duloxetine and 55% of patients receiving placebo. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Scale for Depression, change in sleep pattern, and patient self-evaluation of change in PGI-C scale	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 mg, 40 mg, and 60 mg, respectively. A total of 5%, 22%, and 9% of patients preferred amitriptyline 10 mg, 25 mg, and 50 mg. The number of mild treatment-emergent adverse effects (TEAEs) was higher with duloxetine compared to amitriptyline (P<0.02). The number of moderate to severe TEAEs was higher with amitriptyline (P<0.01). Dry mouth was significantly more common with amitriptyline that duloxetine (55% vs 24%, respectively; P<0.01).
Tanenberg et al.[151] (2011) Duloxetine 60 mg/day vs pregabalin 300 mg/day vs duloxetine 60 mg/day and gabapentin ≥900 mg/day (existing therapy)	RCT, OL, MC Patients ≥18 years of age with type 1 or type 2 diabetes and diabetic peripheral neuropathic pain who had been treated with gabapentin (≥900 mg/day) and had an inadequate response	N=407 12 weeks	Primary: Weekly mean of the daily 24-hour pain (daily pain) Secondary: Worst pain and night pain, CGI-S, BPI, BDI-II, PGI-I, and SDS	Primary: Changes from baseline to week 12 in the weekly mean of the daily pain severity for duloxetine- and pregabalin-treated patients were -2.6 and - 2.1, respectively (treatment difference, 0.49; 95% Cl, -0.05 to 1.04; P=0.08). The non-inferiority comparison between duloxetine monotherapy and duloxetine plus gabapentin on the differences between end point mean changes in daily pain diary ratings in the ITT patient population was also met. Secondary: Reduction in BPI average pain and BPI worst pain severity ratings was significantly greater with duloxetine monotherapy vs pregabalin monotherapy, but differences between treatments were not significant for the other BPI pain measures. There was no significant difference among the treatment groups in CGI-S, depressive symptoms, or the SDS global measure. Significantly more patients discontinued therapy due to adverse events in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				the duloxetine monotherapy group (19.6%; P=0.04) vs the pregabalin monotherapy group (10.4%), but not vs the duloxetine plus gabapentin group (13.3%; P=0.19). Peripheral edema associated with pregabalin treatment (3.7%) was the only adverse event reported as a reason for discontinuation with significantly greater frequency than for the other treatments (duloxetine, 0%; P=0.03; duloxetine plus gabapentin, 0%; P=0.03). Rates of discontinuation for other reasons did not differ significantly among the treatment groups. Nausea, insomnia, hyperhidrosis, and decreased appetite occurred more frequently with duloxetine than pregabalin.
Fibromyalgia				
Arnold et al.[54] (2009) Duloxetine 60-120 mg/day vs placebo	RCT, MC, DB, PC (pooled analysis) Outpatients ≥18 years of age with fibromyalgia and a score of ≥4 on the average pain severity item of the Brief Pain Inventory (BPI)	N=1,332 (4 trials) 12-15 weeks	Primary: Pain severity (BPI) Secondary: BPI pain interference items, Fibromyalgia Impact Questionnaire (FIQ), CGI-S, Patient Global Impression of Improvement scale (PGI-I), HAM-D, Short-Form Health Survey (SF-36), Sheehan Disability Scale (SDS), Multidimensional Fatigue Inventory (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 (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 (P<0.001). The treatment-by-MDD status interaction was not significant (P=0.39). 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 with placebo (P<0.05). All treatment-by-MDD status interactions were not significant for these assessments (P=NS). 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,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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 with 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 ‘‘very much improved’’ compared with placebo-treated patients (P<0.001). The treatment-by-MDD status interaction was not significant (P=0.45).
Russell et al.[57] (2008) Duloxetine 20 mg/day vs duloxetine 60 mg/day vs	RCT, DB, MC, PC Patients ≥18 years of age with fibromyalgia	N=502 6 months	Primary: Pain severity (BPI) and Patient Global Impression of Improvement (PGI-I) scale Secondary: Fibromyalgia Impact Questionnaire (FIQ), Clinical Global	Primary: After 3 months of therapy, patients treated with duloxetine 60 mg/day and duloxetine 120 mg/day experienced significantly greater improvements in average pain severity score compared to placebo (-1.99, -2.31, -1.39, respectively; P≤0.05 and P≤0.001 compared to placebo, respectively). There was no significant difference in pain severity with duloxetine 20 mg/day. At the 6-month endpoint, patients treated with duloxetine experienced greater improvements in average pain severity score compared with placebo (duloxetine 26/60 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 3 months of therapy, the mean endpoint PGI-I score was

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
duloxetine 120 mg/day vs placebo			Impressions-Severity (CGI-S), tender-point pain assessments, Multidimensional Fatigue Inventory (MFI), HAM-D_{17}, Sheehan Disability Scale (SDS), Short-Form Health Survey (SF-36), EuroQoL Questionnaire-5 Dimensions (EQ-5D)	significantly lower in patients treated with duloxetine 20 mg/day and 120 mg/day compared to placebo (2.79, 2.93, 3.37, respectively; P≤0.01 and P≤0.05 compared to placebo, respectively). There was no significant difference in PGI-I scores with duloxetine 60 mg/day compared to placebo. After 6 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=NS) compared with the placebo group (3.37). Secondary: After 3 months of therapy, duloxetine-treated patients demonstrated greater improvements in the CGI-S score (60 mg 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 mg, 60 mg, 120 mg; P≤0.05, P≤0.01, and P≤0.001) compared with placebo. There were no differences between duloxetine and placebo on other secondary efficacy and health outcome measures. After 6 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 other efficacy and health outcome measures that achieved significance in the duloxetine treatment groups compared with 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 3-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 with placebo (23.7%). Response rates from baseline to the 6-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 with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				placebo (21.6%). In patients diagnosed with MDD at study entry, LS mean changes in HAM-D_{17} total score at 6 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 with placebo.
Mease et al.[160] (2010) Duloxetine 60 to 120 mg/day	ES Patients ≥18 years of age with fibromyalgia	N=278 6 months	Primary: Safety and efficacy	Primary: Overall study drug compliance during the 6-month extensions phases 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 (TEAEs) in Study 1 were nausea, dry mouth, and insomnia. The most common TEAEs 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 6-month period. The placebo/duloxetine groups in both studies showed significant improvement in the PGI-I, as well as improvement in nearly all 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.
Generalized Anxiety Disorder (GAD)				
Hartford et al.[55] (2007) Duloxetine 60-120 mg/day vs venlafaxine ER 75-225 mg/day	RCT, DB, MC, PC Outpatients ≥18 years of age with generalized anxiety disorder	N=487 10 weeks	Primary: HAMA total score Secondary: HAMA psychic anxiety factor score, somatic anxiety factor score, mood item, and tension item;	Primary: Patients receiving duloxetine or venlafaxine ER experienced greater improvements in anxiety symptom severity (as measured by HAMA) compared to placebo (duloxetine, P=0.007; 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 with 9.2 in the placebo group. Secondary: Patients treated duloxetine and venlafaxine ER demonstrated greater improvements in HAMA psychic anxiety factor score, HAMA anxious

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo			HADS anxiety and depression subscales scores; CGI-I, Patient Global Impression of Improvement (PGI-I) rating scales; Sheehan Disability Scale impairment scores (SDS)	mood, HAMA tension, and HADS anxiety and depression subscales compared to placebo (all comparisons, P<0.01). Patients treated with both duloxetine and venlafaxine ER had greater improvement ratings at endpoint on the CGI-I and PGI-I compared to placebo (all comparisons, P<0.01). 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 with 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=NS). 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.[61] (2009) Duloxetine 20 mg/day vs duloxetine 60–120 mg/day	RCT, DB, MC, PC Outpatients ≥18 years of age with generalized anxiety disorder	N=581 10 weeks	Primary: HAMA total score Secondary: HAMA psychic and somatic factor scores, Sheehan Disability Scale (SDS), HADS, CGI-I and Patient Global	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 60–120 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 60–120 mg/day, -8.7 [P≤0.001]; venlafaxine ER, -8.6 [P≤0.001]; placebo

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs venlafaxine ER 75–225 mg/day vs placebo			Impression Improvement (PGI-I)	-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 60–120 mg/day, -6.6 [P≤0.05]; venlafaxine ER, -7.0 [P≤0.01]; placebo -5.5). Response rates were 60% for duloxetine 20 mg/day (P<0.01), 65% for duloxetine 60–120 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 60–120 mg/day, 44% for venlafaxine ER, and 20% for placebo (P<0.001 for each comparisons versus placebo). Overall improvement ratings at endpoint were greater for duloxetine-treated patients (20 mg/day or 60–120 mg/day) and venlafaxine ER-treated patients compared with 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 60–120 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 60–120 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 60–120 mg/day, -8.9 [P<0.01]; venlafaxine ER, -9.1 [P<0.001]; placebo, -6.2).
Davidson et al.[121] (2005)	MC, OL	N=526	Primary: CGI-I, HAMA	Primary: Ninety two percent of the patients were considered responders.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Escitalopram 10-20 mg daily	Patients who completed an 8-week, DB, PC, lead-in and were diagnosed with GAD were eligible to enter extension trial	24 weeks	core ≤7 Secondary: Safety	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 1 completed suicide.
Goodman et al.[122] (2005) Escitalopram 10-20 mg daily vs placebo	DB, MC, PC Patients 18-80 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 8 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.[124] (2005) Escitalopram 10-20 mg/day vs paroxetine 20-50 mg/day	DB, RCT Patients with generalized anxiety disorder	N=121 24 weeks	Primary: Mean change from baseline in the Hamilton Anxiety Scale (HAMA) scores at week 24, treatment-emergent adverse effects	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%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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 more frequently with escitalopram than paroxetine (21.3% vs 8.1%, and 14.8% vs 4.8%, respectively).
Bose et al.[64] (2008) Escitalopram 10-20 mg/day vs venlafaxine ER 75-225 mg/day vs placebo	RCT, DB, PC Outpatients 18-65 years of age with generalized anxiety disorder	N=404 8 weeks	Primary: Change from baseline to week 8 in the HAMA total score Secondary: HAMA psychic anxiety subscale, CGI-I, CGI-S, VAS, Hospital Anxiety and Depression Scale (HAD), QoL, Sheehan Disability Scale (SDS)	Primary: The mean change in HAMA total score (LOCF) for escitalopram and venlafaxine ER versus placebo was -1.52 (P=0.09) and -2.27 (P=0.01), respectively at week 8. The mean change in HAMA total score (OC) for escitalopram and venlafaxine ER versus placebo was -1.92 (P=0.033) and -3.02 (P=0.001), respectively at week 8. 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 versus 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 HAD 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.[125] (2005) Paroxetine 10-40 mg daily	DB, FD, PG Patients with generalized anxiety disorder	N=55 8 weeks	Primary: HAMA scores as well as responder and remission rates based on the Clinical Global	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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs sertraline 25-100 mg daily			Impressions scale Secondary: Improvement in IU-GAM	The percent of treatment responders was 68% in the paroxetine group and 61% in the sertraline group. 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.[123] (2005) Sertraline 50-150 mg daily vs placebo	MC, RCT Outpatients with generalized anxiety disorder	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 4 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. Quality of life was significantly improved in the sertraline group compared with placebo with improvement seen in 51% of patients on sertraline compared with 35% on placebo (P<0.01).
Schmitt et al.[126] (2005) Venlafaxine, paroxetine, imipramine, trazodone,	MA Patients with generalized anxiety disorder	N=2,238 8-28 weeks	Primary: Absence of treatment response Secondary: Acceptability of the treatment as	Primary: Antidepressants (imipramine, venlafaxine and paroxetine) were found to be more effective when compared to placebo in treating GAD. The calculated number needed to treat (NNT) for antidepressants as a group in GAD was 5.15. Considering all trials, the pooled RR for non-treatment response was 0.70

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
diazepam, sertraline			measured by the number of people dropping out during the trial	(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). For venlafaxine the calculated RR for non-treatment response was 0.68 (95% CI: 0.46 to 0.99), and the calculated NNT was 5.0 (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: 3.9 to 24.7). 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.[162] (2007) Doxepin 1 mg vs	RCT, DB, PC, XO Patients 18 to 64 years of age with chronic primary insomnia	N=67 2 nights	Primary: Wake time during sleep (WTDS) Secondary: WASO, sleep efficiency (SE),	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
doxepin 3 mg vs doxepin 6 mg vs placebo			TST, LPS, number of awakenings after sleep onset (NAASO), wake time after sleep (WTAS), and sleep architecture	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. There was no significant difference in LPS with doxepin (all doses) compared to placebo. TST and overall SE 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. sWASO 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). sNAASO 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). sTST 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,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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 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 and SCT) 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.[157] (2008) Doxepin 1 mg vs doxepin 3 mg vs doxepin 6 mg vs placebo	RCT, DB, PC, XO Elderly patients with primary insomnia	N=76 2 nights	Primary: Wake time during sleep (WTDS) Secondary: Wake after sleep onset (WASO), total sleep time (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 mg 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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Krystal et al.[152] (2010) Doxepin 1 mg (DXP) vs doxepin 3 mg (DXP) vs placebo	RCT, DB, PC Patients ≥65 years of age with primary insomnia	N=240 12 weeks	Primary: Wake time after sleep onset (WASO) on N1 Secondary: WASO at other time points, LPS, number of awakenings after sleep onset (NAW), TST, SE, and wake time after sleep (WTAS), CGI-S, CGI-I	Primary: WASO was significantly improved on N1 for doxepin 3 mg (P<0.0001) and doxepin 1 mg (P=0.0053) compared to placebo. Secondary: WASO was significantly improved on N29 (P=0.0005) and N85 (P<0.0001) for doxepin 3 mg, and on N85 (P=0.0330) for doxepin 1 mg compared to placebo. Mean change from N1 to N85 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 SE were significantly improved on N1 (P<0.0001), N29 (P=0.0161), and N85 (P=0.0007) for doxepin 3 mg, and on N1 (P=0.0119) and N85 (P=0.0257) for doxepin 1 mg compared to placebo. There was a s significant improvement in sTST at weeks 1 (P=0.0043), 4 (P=0.0035), and 12 (P=0.0001) for doxepin 3 mg, and at weeks 4 (P=0.0343) and 12 (P=0.0027) for doxepin 1 mg compared to placebo. SE in the last quarter of the night was significantly increased on N1 (P<0.0001), N29 (P=0.0004), and N85 (P=0.0014) for doxepin 3 mg compared to placebo. For doxepin 1 mg, SE in the last quarter of the night was significantly increased on N1 (P=0.0011) compared to placebo. SE in hour 8 was significantly increased on N1 (P<0.0001) and N29 (P=0.0029) for doxepin 3 mg compared to placebo. For doxepin 1 mg, SE in hour 8 was significantly increased on N1 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. Patient-reported IVRS data revealed sleep onset improvements. LSO was significantly decreased at weeks 1 (P=0.0033), 4 (P=0.0397), and 12 (P=0.0464) for doxepin 3 mg, and at weeks 4 (P=0.0116) and 12 (P=0.0028) for doxepin 1 mg compared to placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Sleep quality was significantly increased at weeks 1 (P=0.0039), 4 (P=0.0049), and 12 (P=0.0100) for doxepin 3 mg, and at weeks 4 (P=0.0464) and 12 (P=0.0107) for doxepin 1 mg compared to placebo. There was significant improvement after 2 weeks (P=0.0047), after 4 weeks (P=0.0356), and after 12 weeks (P=0.0005) on the CGI-S scale score for doxepin 3 mg, and after 12 weeks (P=0.0101) for doxepin 1 mg compared to placebo. There was significant improvement after 2 weeks (P=0.0060), after 4 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. There was significant improvement on the ISI total score at N15 (P=0.0216), N29 (P=0.0068), and N85 (P=0.0056) for doxepin 3 mg compared to placebo. Daytime function ratings were significantly improved on N1 for doxepin 3 mg (P=0.0282) and 1 mg (P=0.0192) and on N85 for doxepin 3 mg (P=0.0028) and 1 mg (P=0.0102) compared to placebo. Sleep stages were preserved compared with 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 and SCT) or subjective next-day alertness (VAS) or drowsiness at any time point during the trial. Rates of treatment-emergent AEs were lower in patients treated with doxepin 1 mg (40%) and doxepin 3 mg (38%) compared with placebo (52%). The most common AEs were headache and somnolence.
Krystal et al.[153] (2011) Doxepin 3 mg vs	RCT, DB, PC Patients 18 to 64 years of age with primary insomnia	N=229 35 days	Primary: Wake time after sleep onset (WASO) on N1 Secondary:	Primary: WASO was significantly improved on N1 for doxepin 3 mg (P<0.0001) and doxepin 6 mg (P<0.0001) compared to placebo. Secondary: WASO was significantly improved on N15 (P=0.0053) and N29

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
doxepin 6 mg vs placebo			WASO at other time points, LPS, number of awakenings after sleep onset (NAASO), TST, SE, and wake time after sleep (WTAS)	(P=0.0299) for doxepin 3 mg, and on N15 (P=0.0023) and N29 (P=0.0012) for doxepin 6 mg compared to placebo. There were no significant differences between doxepin groups on WASO. TST and SE were significantly improved on N1 (P<0.0001) and N29 (P=0.0262) for doxepin 3 mg, and on N1 (P<0.0001), N15 (P=0.0157), and N29 (P=0.0003) for doxepin 6 mg compared to placebo. There were no significant differences in NAASO for any dose at any time point. SE in the last quarter of the night was significantly improved on N1 (P=0.0008) and N15 (P=0.0220) for doxepin 3 mg, and on N1 (P<0.0001), N15 (P=0.0239), and N29 (P=0.0029) for doxepin 6 mg compared to placebo. SE in hour 8 was significantly improved on N1 (P<0.0001) and N29 (P=0.0315) for doxepin 3 mg, and on N1 (P<0.0001), N15 (P=0.0162), and N29 (P=0.0020) for doxepin 6 mg compared placebo. WTAS was significantly improved on N1 (P=0.0001) for doxepin 3 mg, and also on N1 (P=0.0016) for doxepin 6 mg compared to placebo. LPS was significantly improved on N1 (P=0.0047) for doxepin 3 mg, and on N1 (P=0.0007) for doxepin 6 mg compared to placebo. There were significant improvements in patient-reported WASO for both doses of doxepin on N1 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 N1 compared to placebo (3 mg P=0.0088; 6 mg P=0.0135). Sleep quality was significantly improved for both doses of doxepin at N1 compared to placebo (3 mg P=0.0068; 6 mg P<0. 0001). Subjective LSO was significantly improved on N1 with doxepin 6 mg compared to placebo (P=0.0492). There was no evidence of tolerance to the sleep maintenance effects.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There is evidence to suggest the development of tolerance to the sleep onset effects. There were increases in the duration of stage 2 sleep for both doses of doxepin, which were significant at most time points. There were no significant differences between the 2 doxepin groups vs placebo in minutes of stage 1 sleep, stage 3/4 sleep, or REM sleep. Across 2 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.[154] (2010) Doxepin 6 mg vs placebo	RCT, DB, PC, MC Healthy adults 25 to 55 years of age with normal sleep habits	N=565 Single dose	Primary: Latency to persistent sleep (LPS) Secondary: Wake after sleep onset (WASO), total sleep time (TST), wake time during sleep (WTDS), wake time after sleep (WTAS), sleep efficiency (TST/8hX100), and number of awakenings after sleep onset (NASSO), sleep architecture measurements, digit symbol substitution test (DSST), symbol copying test (SCT), and visual	Primary: LPS was significantly lower for doxepin compared to placebo (21 minutes vs 34 minutes, respectively; P<0.0001). Secondary: WASO was significantly lower for doxepin compared to placebo (38 minutes 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 NAASO (P value not reported). TST was significantly higher for doxepin compared to placebo (425.2 minutes vs 374.1 minutes, respectively; P<0.0001). Overall SE was significantly higher for doxepin compared to placebo (P value not reported). WTAS, SE in the final quarter of the night, and SE at hours 7 and 8 were significantly improved for doxepin compared to placebo (all P<0.0001). Doxepin had significantly higher SE at each hour compared to placebo (P<0.0001). Subject- reported LSO was significantly lower for doxepin compared to placebo. sWASO and sNAASO were significantly lower for doxepin

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			analog scale (VAS)	compared to placebo. sTST was significantly higher for doxepin compared to placebo. Sleep quality was significantly improved for doxepin compared to placebo. There were significantly more minutes of Stage N2 (259.5 min for doxepin versus 218.8 for placebo; P<0.0001) and Stage N3 sleep (66.6 min for doxepin versus 58.4 for placebo; P=0.0284) with doxepin compared to placebo. There were no changes in the duration of Stage N1 and REM sleep. There was a significantly greater percentage of Stage N2 sleep (61.0% for doxepin versus 58.3% for placebo; P=0.0036), and significantly less percentage of REM sleep (13.5% for doxepin and 15.2% for placebo; P<0.0001). There were no changes in percentage of Stage N2 and Stage N3 sleep. There were no significant differences between doxepin and placebo in the mean change in DSST score from predose to postdose. There were no significant differences in sleepiness with doxepin compared to placebo (SCT P=0.0228; VAS P=0.0241). The incidence of adverse events with doxepin was comparable to placebo.
Musculoskeletal Pain				
Skljarevski et al.[148] (2010) Duloxetine 60 mg once daily vs placebo	RCT, DB, PC 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, Roland Morris Disability Questionnaire (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 placebo (P≤0.001). Secondary: Duloxetine-treated patients reported significantly greater improvements in PGI-I scores compared to placebo (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 4 domains of BPI-S (average pain, worst pain, least pain, and pain right now) pain scores was reported with duloxetine compared to placebo. All 7 domains of the BPI-I (general

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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 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 4 of 6 mood states on the POMS-Brief Form, along with the total mood disturbance score, between the 2 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-dejection and fatigue-inertia states were not significant. The change in EQ-5D was significantly different between duloxetine and placebo with the UK index (P≤0.001) and US index (P=0.002). In the SF-36 domains, the differences between duloxetine and placebo treatments were significant with regards 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 regards 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.[155] (2010) Duloxetine 60 to	RCT, DB, PC, MC Patients ≥18 years of age with chronic	N=236 13 weeks	Primary: Reduction of pain severity (BPI 24-hour average pain	Primary: There was a significantly greater reduction in the BPI 24-hour average pain in patients treated with duloxetine compared to placebo at all time points (-1.42 vs -0.78, respectively, P=0.016 at week 4; -2.06 vs -1.17,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
120 mg once daily vs placebo	low back pain		rating) Secondary: PGI-I, Roland Morris Disability Questionnaire (RMDQ-24), BPI-S, BPI-I, CGI-S, Athens Insomnia Scale response rates, health outcomes (EQ-5D and SF-36), work productivity and activity impairment instrument (WPAI)	respectively, P=0.001 at week 7; 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 at all time points (3.12 vs 3.51, respectively, P=0.007 at week 4; 2.82 vs 3.32, respectively, P=0.001 at week 7; 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). 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; 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 UK and US indexes of EQ-5D did not change significantly in patients treated with duloxetine compared to placebo. Among the 8 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				significantly (P=0.002) improved with duloxetine compared to placebo. Significantly more patients in the duloxetine group (13.9%) compared with placebo (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.[161] (2010) Duloxetine 60 to 120 mg once daily	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) Secondary: Response rates, PGI-I, Roland Morris Disability Questionnaire (RMDQ-24), BPI-S, BPI-I, CGI-S, Athens Insomnia Scale response rates, health outcomes (EQ-5D and SF-36)	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). 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 placebo-controlled 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 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.
Chappell et al.[150] (2009) Duloxetine 60 to 120 mg once daily vs	RCT, DB, PC, MC 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:	Primary: Duloxetine was more effective than placebo on the primary efficacy measure (weekly mean 24-hour pain scores) beginning at week 1 and continuing through the treatment period (P<0.05). There was a significant reduction in the average pain score in the duloxetine group compared with the placebo group at each week. The mean change from baseline to endpoint in the 24-hour average pain score also showed a significant

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo			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-h worst pain score, CGI-S, WOMAC pain and stiffness subscales, BPI-S and BPI-I, response to treatments and health outcomes and safety	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) groups. 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 7, there was a significant improvement in mean change in the weekly 24-h average pain score in the duloxetine 120 mg QD group compared with the duloxetine 60 mg QD group (P=0.039). No significant differences were observed between the two duloxetine groups in the MMRM analysis of the weekly 24-h average pain score or the 30% 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 (TEAEs).
Chappell et al.[140] (2010) Duloxetine 60 to 120 mg once daily vs placebo	RCT, DB, PC, MC Patients ≥40 years of age with osteoarthritis of the knee and pain for ≥14 days/month	N=256 13 weeks	Primary: Brief Pain Inventory (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	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 LS mean changes in the weekly mean 24-hour average pain rating was significantly reduced with duloxetine compared to placebo as early as at week 2 and remained significant at all time points.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			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 and health outcomes and safety	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 with placebo (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 with placebo. The other two WOMAC subscales (pain and stiffness) did not show significant improvement with duloxetine treatment. Both the U.K. and the U.S. 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.[147] (2011) Duloxetine 60 to 120 mg once daily vs	RCT, DB, MC, PC Patients ≥40 years of age with osteoarthritis of the knee and pain for ≥14 days/month and who were using	N=524 10 weeks	Primary: Weekly mean of the daily average pain rating at week 8 Secondary: Endpoint PGI-I	Primary: Patients receiving duloxetine experienced significantly greater pain reduction at week 8 than those receiving placebo. The estimated mean change was -2.46 for duloxetine compared with -1.55 for placebo (P<0.001).Duloxetine demonstrated greater improvement as early as week 1 (P<0.01), and at each subsequent week (P<0.001). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo Patients were also required to take an NSAID and PPI.	NSAIDs on most days of the week		and then change in WOMAC physical function	There was no significant difference in the use of acetaminophen as rescue medication for knee pain due to OA (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 (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 each). Treatment with duloxetine was associated with significantly more nausea, dry mouth, constipation, fatigue and decreased appetite than 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.[158] (2010) Escitalopram 20 mg once daily vs duloxetine 60 mg once daily	RCT Adult patients with non-radicular chronic low back pain (CLBP)	N=85 13 weeks	Primary: Weekly mean of the 24-hour average pain ratings Secondary: Clinical Global Impressions of Severity (CGI-S) and the 36-item Short-Form Health Survey (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 (SAEs) and the incidence of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				side effects did not differ significantly between treatment groups.
Obsessive-compulsive Disorder (OCD)				
Alaghband-Rad et al.[52] (2009) Fluoxetine 20 mg/day vs citalopram 20 mg/day	RCT, DB Children 8-17 years of age with OCD	N=29 6 weeks	Primary: Children's Yale–Brown obsessive-compulsive Scale (CY-BOCS) total score, CGI-OCD, adverse events	Primary: After 3 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 6 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.
Koran et al.[127] (1996) Fluvoxamine 100-300 mg/day vs clomipramine 100-250 mg/day	DB, RCT Patients with OCD	N=79 10 weeks	Primary: Y-BOCS, CGI, HAM-D	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 with 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.
Mundo et al.[129] (1997) Fluvoxamine 100-300 mg daily	RCT Patients with OCD	N=30 10 weeks	Primary: NIMH-OC, Y-BOCS, HAM-D, CGI	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-

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs paroxetine 20-60 mg daily vs citalopram 20-60 mg daily				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).
Denys et al.[128] (2003) Paroxetine 15-60 mg daily vs venlafaxine 75-300 mg daily	DB, PG, RCT Patients with OCD	N=150 12 weeks	Primary: Y-BOCS	Primary: Both paroxetine and venlafaxine were efficacious with a mean decrease of 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 3 (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.
Panic Disorder				
Stahl et al.[132] (2003) Citalopram vs escitalopram vs placebo	DB, PC, RCT Patients 18-80 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	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).
Dannon et al.[59]	OL	N=200	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2007) Citalopram 10-40 mg/day vs fluoxetine 10-40 mg/day vs fluvoxamine 50-200 mg/day vs paroxetine 10-40 mg/day	Adult patients with panic disorder (PD) or panic disorder with agoraphobia (PDA)	12 months	Panic Self-Questionnaire (PSQ), CGI-I	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 PSQ (P=0.13), VAS (P=0.43), or CGI-I (P=NS). There were no significant differences between the PD and the PDA groups in treatment response as measured at the 12 monthly follow-up visits.
Rampello et al.[133] (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 Hamilton scales for anxiety and depression and Cooper Disability Scale scores	Primary: No significant difference was observed at 8 weeks in the weekly rate of panic attacks. Secondary: No significant differences were observed at 8 weeks in the Hamilton scales for anxiety/depression, or in the Cooper Disability Scale scores. A significant improvement from baseline in outcome measures was observed in the escitalopram at 2 weeks and in the citalopram group at 4 weeks (P<0.001 and P<0.01 respectively).
Van Ameringen et al.[130] (2007) Nefazodone 300-600 mg daily	DB, MC, PC, RCT Patients 18-65 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	Primary: At endpoint, 31.4% of nefazodone-treated patients and 23.5% of placebo-treated patients were considered responders (P=0.38).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				
Sheehan et al.[131] (2005) Paroxetine CR 25 to 75 mg daily vs placebo	DB, MC, PC, RCT Patients with DSM-IV panic disorder with or without agoraphobia	N=889 10weeks	Primary: Patients free of panic attacks in the 2 weeks prior to endpoint Secondary: CGI-I, HAMA	Primary: Paroxetine CR was statistically more effective compared to placebo on the primary outcome measure: 63% vs 53%; P<0.005. 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.[135] (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, Hamilton Anxiety Rating Scale, Montgomery-Asberg Depression Rating Scale	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 4 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 Hamilton Anxiety Rating Scale (total) was observed for the 40 mg paroxetine group (in the end-

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				point but not in the completer analysis). Improvement in depressive symptoms (Montgomery-Asberg Depression Rating Scale total score) was significantly greater for the 40 mg paroxetine group than for the placebo group at week 10.
Bandelow et al.[134] (2004) Sertraline 50-150 mg daily vs paroxetine 40-60 mg daily	DB, MC, PG, RCT Patients with panic disorder between the ages of 18 and 65 years	N=225 12 weeks	Primary: Clinician-rated PAS Secondary: CGI-I score	Primary: Treatment with sertraline and paroxetine resulted in equivalent levels of improvement on the primary outcome measure from baseline, the PAS 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 with 78% of patients treated with paroxetine (P=0.320).
Pollack et al.[68] (2007) Venlafaxine ER 75 mg/day vs venlafaxine ER 225 mg/day vs paroxetine 40 mg/day vs placebo	RCT, DB, MC, PC 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 (PDSS) 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 PDSS total score compared with the placebo group at study endpoint. The venlafaxine ER 225 mg group had a significantly lower PDSS 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				75 mg, 41.0%; paroxetine 40 mg, 39.3%) than in the placebo group (26.8%).
Posttraumatic Stress Disorder (PTSD)				
Davidson et al.[136] (2005) Fluoxetine 10-60 mg daily vs placebo	OL, RCT Patients 18-70 years of age with PTSD	N=123 6 months	Primary: Rate of relapse defined by a change in CGI-I score that reverted back to no improvement relative to baseline or worse, CGI-I score which increased by at least 2 points Secondary: CGI-S, SPRINT	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). Secondary: Differences between the fluoxetine and the placebo group failed to meet significance for the SPRINT and CGI-S (P=0.08).
Friedman et al.[90] (2007) Sertraline 250-200 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 (PMDD)				
Pearlstein et al.[75] (2005) Paroxetine CR 12.5 mg daily or	DB, MC, PC, RCT Patients aged 18-45 years who had regular menstrual	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 versus placebo on the VAS-Mood (P<0.001) and for paroxetine CR 12.5 mg versus placebo (P=0.013).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
25 mg daily vs placebo	cycles with PMDD			Secondary: Paroxetine CR demonstrated greater mean reduction in VAS-Total scores compared with placebo at each time point. At the treatment cycle 3 last-observation-carried-forward endpoint, statistically significant differences in mean changes were observed in favor of paroxetine CR 25 mg versus placebo (P<0.001) as well as for paroxetine CR 12.5 mg versus placebo (P=0.011).
Steiner et al.[74] (2005) Paroxetine CR 12.5 mg daily vs paroxetine CR 25 mg daily vs placebo	DB, MC, PC, RCT Patients aged 18-45 years who had regular menstrual cycles with PMDD	N=373 3 menstrual cycles	Primary: VAS-Mood Secondary: Change form baseline to treatment cycle 3 in the sum of the 11VAS symptoms; change from baseline in the PMTS-O total score, change from baseline in the SDS total score	Primary: A statistically significant difference was demonstrated in favor of paroxetine CR 25 mg and 12.5 mg compared with 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 3 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 PMTS-O total score (paroxetine CR 25 mg vs placebo –3.21 mm; P=0.005; paroxetine CR 12.5 mg vs placebo –1.78 mm; P=0.093), the CGI-S (paroxetine CR 25 mg vs placebo –0.61 mm; P=0.004; paroxetine CR 12.5 mg vs placebo –0.27 mm; P=0.177). 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 with placebo.
Multiple Diseases				
Wernicke et al.[73] (2007) Duloxetine vs placebo	MA Patients diagnosed with either an MDD, diabetic peripheral neuropathy, fibromyalgia,	N=8,504 (42 trials) 4-12 weeks	Primary: Vital signs, ECG findings, cardiovascular side effects of the study drug	Primary: Patients receiving duloxetine were noted to have statistically significant changes from baseline in ECG findings (PR, RR, QRS, QT intervals) compared with 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	generalized anxiety disorder, or lower urinary tract infection			of ECG abnormality or vital sign changes between patients ≥65 years of age and a younger population. Although patients receiving duloxetine experienced statistically significant pulse and blood pressure elevations compared with 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), systolic blood pressure (P=0.740), or diastolic blood pressure (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 with placebo.
Mullins et al.[72] (2005) Sertraline vs paroxetine vs citalopram	RETRO Patients with depression, posttraumatic stress disorder, or social anxiety disorder	N=14,933 Data gathered from 1/1/99-6/30/02	Primary: Persistence, switching, discontinuation	Primary: Compared with 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).
Stein et al.[71] (2000) SSRIs, MAOIs, benzodiazepines, beta blockers, buspirone,	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) and RIMAs (N=6;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
gabapentin, olanzapine				RR=0.74; 95% CI: 0.59 to 0.91) supported the value of these agents. However, the SSRIs were significantly more effective than the RIMAs (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 3 comparisons from maintenance studies (RR=0.58; 95% CI: 0.39 to 0.85) and 5 comparisons from relapse prevention studies (RR=0.33; 95% CI: 0.22 to 0.49).

Study abbreviations: DB=double-blind, MA=meta-analysis, MC=multicenter, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial, RETRO=retrospective, SS=switch study

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, NINCDS/ADRDA=National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's disease and Related Disorders Association Cognition Efficacy Measures Key: BAI=Beck Anxiety Inventory, Beck Depression Inventory Fast Screen (BDI-FS), BDI-II=Beck Depression Inventory-II, 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, DNE=Diabetic Neuropathy Examination, DNS=Diabetic Neuropathy Symptom, EQ-5D=EuroQoL: 5 Dimensions Questionnaire, 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, IES=Impact of Event Scale, ITT-Intent-to-Treat Analysis, IU-GAM=Indiana University Generalized Anxiety Measurement Scale, LPS=Latency to Persistent Sleep, LSAS=Liebowitz Social Anxiety Scale, MADRS=Montgomery-Åsberg Depression Rating Scale, MAOIs=Monoamine Oxidase Inhibitors, MHID=Mantel-Haenszel Incidence Difference, MHRD=Mantel-Haenszel Exposure Time-adjusted Rate Difference, NAW=Number of Awakenings After Sleep Onset (NAW), NIMH-OC=National Institute of Mental Health-Obsessive-Compulsive Scale, NSS=Neuropathy Symptom Score, PAS=Panic and Agoraphobia Scale, PGI-C=Patient Global Impression of Change, PGI-I=Patient Global Impressions of Improvement, PMTS=Premenstrual Tension Scale, PTSD=Posttraumatic Stress Disorder, QoL=Quality of Life, Q-LES-Q=Quality of Life, Enjoyment, and Satisfaction Questionnaire, SE=Sleep Efficiency, SF-36=36-item Short-Form Health Status Survey, SSRIs=Selective Serotonin-reuptake Inhibitors, TST=Total Sleep Time, VAS=Visual Analog Scale, WASO=Wake Time After Sleep Onset, 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.[70] 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 4 treatment strategies in adolescents who continued to have depression despite initial treatment with an SSRI.[65] 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®	$$$$	N/A
Phenelzine	tablet	Nardil®*	$$$$	$$$$
Selegiline	transdermal patch	Emsam®	$$$$$	N/A
Tranylcypromine	tablet	Parnate®*	$$$$$	$$$$
Selective Serotonin- and Norepinephrine-reuptake Inhibitors				
Desvenlafaxine	extended-release tablet	Pristiq®	$$$$	N/A
Duloxetine	delayed-release capsule	Cymbalta®	$$$$	N/A
Venlafaxine	extended-release capsule, extended-release tablet, tablet	Effexor XR®*	$$$$-$$$$$	$-$$$$

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
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	Luvox CR®	$$$$$	$
Paroxetine	extended-release tablet, suspension, tablet	Paxil®*, Paxil CR®*, Pexeva®	$$$$-$$$$$	$-$$$
Sertraline	oral concentrate, tablet	Zoloft®*	$$$$$	$-$$
Serotonin Modulators				
Nefazodone	tablet	N/A	N/A	$-$$
Trazodone	extended-release tablet, tablet	Oleptro®	$$$$	$-$$$
Vilazodone	tablet	Viibryd®	$$$$	N/A
Tricyclics and Other Norepinephrine-reuptake Inhibitors				
Amitriptyline	tablet	N/A	N/A	$
Amitriptyline and chlordiazepoxide	tablet	N/A	N/A	$-$$
Amoxapine	tablet	N/A	N/A	$-$$
Clomipramine	capsule	Anafranil®*	$$$$$	$
Desipramine	tablet	Norpramin®*	$$-$$$$	$-$$$$
Doxepin	capsule, oral concentrate, tablet	Silenor®	$$$$	$
Imipramine	capsule, tablet	Tofranil®*, Tofranil-PM®*	$$$$$	$-$$$$$
Maprotiline	tablet	N/A	N/A	$$-$$$
Nortriptyline	capsule, solution	Pamelor®*	$$$$$	$
Protriptyline	tablet	Vivactil®*	$$$$-$$$$$	$$$$
Trimipramine	capsule	Surmontil®*	$$$$$	$$$$
Antidepressants, Miscellaneous				
Bupropion	extended-release tablet, sustained-release tablet, tablet	Aplenzin®, Wellbutrin®*, Wellbutrin SR®*, Wellbutrin XL®*	$$$-$$$$$	$-$$
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 and premenstrual dysphoric disorder.[1-32] 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.[1-32] The antidepressants are categorized into 6 different 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 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.[56,60,63,66-67,82-84,88,94,96-103,107-108,111,113,141,144-146,156]

Guidelines do not give preference to one agent over another.[35-36,38] Rather, the selection of an antidepressant should be based on adverse events, tolerability and patient preference.[35-36]

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.[47] 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.[39] 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.[52,55,59,61,64,68,122-123,125,127-129,131-134] Guidelines do not give preference to one agent over another.[39-43,47] The choice of treatment should be based on safety, adverse events, drug interactions, prior response to treatment and comorbid conditions.[40,47]

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.[9] 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.[140,147-148,150,155]

Vilazodone is a selective serotonin reuptake inhibitor and partial serotonin 5-HT_{1A} receptor agonist, which was approved by the FDA in January 2011 for the treatment of depression.[21] It has been shown to be more effective than placebo in two clinical trials, with effects seen as early as 1 week.[143,159] The SSRIs have also been shown to be effective after 1 week of use. There were no studies found in the medical literature directly comparing vilazodone to other antidepressants.

In 2010, the FDA approved an extended-release formulation of trazodone for the treatment of depression, as well as a low-dose (3 mg and 6 mg) formulation of doxepin for the treatment of insomnia characterized by difficulties with sleep maintenance.[20,23] Both agents have been shown to be more effective than placebo.[137,152-154,157,162] Trazodone (immediate-release tablets) and doxepin (10 mg/ml solution) are available in a generic formulation.

According to the boxed warning, antidepressants increased the risk of suicidal thinking and behavior in children, adolescents and young adults compared with placebo in short-term studies of major depressive disorder and other psychiatric disorders.[1-32] 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.[35]

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 and OTC products 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, generics and OTC products 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.

XII. References

1. Drug Facts and Comparisons. Drug Facts and Comparisons 4.0 [online]. 2012. Available from Wolters Kluwer Health, Inc. Accessed April 2012.
2. Lexi-Comp Online, Lexi-Drugs Online, Hudson, Ohio: Lexi-Comp, Inc.; 2012; April 2012.
3. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed April 2012.
4. Marplan® [package insert]. Parsippany, NJ: Validus Pharmaceuticals, LLC; March 2012.
5. Nardil® [package insert]. New York, NY: Pfizer Inc; October 2008.
6. Emsam® [package insert]. Morgantown, WV: Somerset Pharmaceuticals; May 2009.
7. Parnate® [package insert]. Research Triangle Park, NC: GlaxoSmithKline; November 2008.
8. Pristiq® [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals; October 2011.
9. Cymbalta® [package insert]. Indianapolis, IN: Eli Lilly and Company; September 2011.
10. Effexor XR® [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals Inc; November 2011.
11. Celexa® [package insert]. St. Louis, MO: Forest Pharmaceuticals; August 2011.
12. Lexapro® [package insert]. St. Louis, MO: Forest Pharmaceuticals; May 2011.
13. Prozac® [package insert]. Indianapolis, IN: Eli Lilly and Company; June 2011.
14. Sarafem® [package insert]. Rockaway, NJ: Warner-Chilcott; June 2009.
15. Luvox CR® [package insert]. Palo Alto, CA: Jazz Pharmaceuticals; May 2011.
16. Paxil® [package insert]. Research Triangle Park, NC: GlaxoSmithKline; July 2011.
17. Paxil CR® [package insert]. Research Triangle Park, NC: GlaxoSmithKline; July 2011.
18. Pexeva® [package insert]. Miami, FL: Noven Therapeutics; January 2011.
19. Zoloft® [package insert]. New York, NY: Pfizer Inc; September 2011.
20. Oleptro® [package insert]. Princeton, NJ: Angelini Labopharm, LLC; December 2010.
21. Viibryd® [package insert]. St. Louis, MO: Forest Pharmaceuticals, Inc.; March 2011
22. Anafranil® [package insert]. Hazelwood, MO: Mallinckrodt Inc; May 2007.
23. Silenor® [package insert]. San Diego, CA: Somaxon Pharmaceuticals, Inc.; March 2010.
24. Tofranil-PM® [package insert]. Hazelwood, MO: Mallinckrodt Inc; May 2007.
25. Pamelor® [package insert]. Hazelwood, MO: Mallinckrodt Inc; May 2007.
26. Surmontil® [package insert]. Pomona, NY: Duramed Pharmaceuticals; June 2007.
27. Aplenzin® [package insert]. Bridgewater, NJ: sanofi-aventis U.S. LLC; June 2011.
28. Wellbutrin® [package insert]. Research Triangle Park, NC: GlaxoSmithKline; August 2011.
29. Wellbutrin SR® [package insert]. Research Triangle Park, NC: GlaxoSmithKline; August 2011.
30. Wellbutrin XL® [package insert]. Bridgewater, NJ: BTA Pharmaceuticals; February 2010.
31. Remeron® [package insert]. Whitehouse Station, NJ: Merck & Co.; December 2011.
32. Remeron SolTab® [package insert]. Whitehouse Station, NJ: Merck & Co.; December 2011.
33. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th ed., text revision (DSM-IV-TR). Washington, DC: American Psychiatric Association; 2000:356.
34. Bril V, England J, Franklin GM, et al. Evidence-based guideline: Treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. Neurology 2011;76:1758-65.
35. American Psychiatric Association (APA). Practice guideline for the treatment of patients with major depressive disorder. 3rd ed. Arlington (VA): American Psychiatric Association (APA); 2010 Oct. 152 p. Available at: http://psychiatryonline.org/data/Books/prac/PG_Depression3rdEd.pdf. Accessed May 2012.
36. Qaseem A, Snow V, Denberg T, Forciea MA, Owens DK, Clinical Efficacy Assessment Subcommittee of American College of Physicians. Using second-generation antidepressants to treat depressive disorders: a clinical practice guideline from the American College of Physicians. Ann Intern Med 2008;18;149:725-33.
37. Birmaher B, Brent D, AACAP Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with depressive disorders. American Academy of Child and Adolescent Psychiatry (AACAP). J Am Acad Child Adolesc Psychiatry 2007;46:1503-1526.
38. National Institute for Clinical Excellence. Depression: the treatment and management of depression in adults (update). National Institute for Clinical Excellence (NICE); October 2009. Available at: http://guidance.nice.org.uk/CG90. Accessed May 2012.
39. National Institute for Clinical Excellence. Generalized anxiety disorder and panic disorder (with or without agoraphobia) in adults. National Institute for Clinical Excellence (NICE); January 2011. Available at: http://www.nice.org.uk/nicemedia/live/13314/52599/52599.pdf. Accessed May 2012.

40. Koran L, Hanna G, Hollander E, Nestadt G, Simpson H; American Psychiatric Association. Practice guideline for the treatment of patients with obsessive-compulsive disorder. Arlington (VA): American Psychiatric Association; July 2007. Available at: http://psychiatryonline.org/data/Books/prac/OCDPracticeGuidelineFinal05-04-07.pdf. Accessed May 2012.
41. National Institute for Clinical Excellence. Obsessive-compulsive disorder: core interventions in the treatment of obsessive-compulsive disorder and body dysmorphic disorder. National Institute for Clinical Excellence (NICE); November 2005. Available at http://www.nice.org.uk/CG031. Accessed May 2012.
42. Ursano RJ, Bell C, Eth S, Friedman M, Norwood A, Pfefferbaum B, et al; American Psychiatric Association. Practice guideline for the treatment of patients with acute stress disorder and posttraumatic stress disorder. American Psychiatric Association; November 2004. Available at: http://psychiatryonline.org/data/Books/prac/ASD_PTSD_Inactivated_04-16-09.pdf. Accessed May 2012.
43. Benedek D, Friedman M, Zatzick D, Ursano R. Guideline Watch (March 2009): Practice guideline for the treatment of patients with acute stress disorder and posttraumatic stress disorder. American Psychiatric Association; 2005. Available at: http://psychiatryonline.org/data/Books/prac/AcuteStressDisorder-PTSD_GuidelineWatch.pdf. Accessed May 2012.
44. American College of Obstetricians and Gynecologists. Premenstrual syndrome. ACOG Practice Bulletin 15. ACOG 2000; Washington, DC.
45. Attal N, Cruccu G, Baron R, et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. Eur J Neurol 2010;17:1113-e88.
46. Yager J, Devlin MJ, Halmi KA, et al. American Psychiatric Association (APA). Practice guidelines for the treatment of patients with eating disorders. Arlington, VA: American Psychiatric Association; 2006. Available at: http://psychiatryonline.org/data/Books/prac/EatingDisorders3ePG_04-28-06.pdf. Accessed May 2012.
47. Stein M, Goin M, Pollack M, et al. Practice guideline for the treatment of patients with panic disorder, second edition. American Psychiatric Association; 2009. Available at: http://psychiatryonline.org/data/Books/prac/PanicDisorder_2e_PracticeGuideline.pdf. Accessed May 2012.
48. Buckhardt C, Goldenberg D, Crofford L, et al. Guideline for the management of fibromyalgia syndrome pain in adults and children. American Pain Society (APS); 2005. Available at: http://www.ampainsoc.org/pub/fibromyalgia.html. Accessed November 2009.
49. Connolly S, Bernstein G, AACAP Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with anxiety disorders. American Academy of Child and Adolescent Psychiatry (AACAP). J Am Acad Child Adolesc Psychiatry 2007;46(2):267-283.
50. Mazeh D, Shahal B, Aviv A, et al. A randomized, single-blind, comparison of venlafaxine with paroxetine in elderly patients suffering from resistant depression. Int Clin Psychopharmacol 2007;22:371-5.
51. Thase ME, Kornstein SG, Germain JM, et al. An integrated analysis of the efficacy of desvenlafaxine compared with placebo in patients with major depressive disorder. CNS Spectr 2009;14:144-54.
52. Alaghband-Rad J, Hakimshooshtary M. A randomized controlled clinical trial of citalopram versus fluoxetine in children and adolescents with obsessive-compulsive disorder (OCD). Eur Child Adolesc Psychiatry 2009;18:131-5.
53. Cipriani A, Furukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. Lancet 2009;373:746-58.
54. Arnold LM, Hudson JI, Wang F, et al. Comparisons of the efficacy and safety of duloxetine for the treatment of fibromyalgia in patients with versus without major depressive disorder. Clin J Pain 2009;25:461-8.
55. Hartford J, Kornstein S, Liebowitz M, et al. Duloxetine as an SNRI treatment for generalized anxiety disorder: results from a placebo and active-controlled trial. Int Clin Psychopharmacol 2007;22:167-74.
56. Pigott TA, Prakash A, Arnold LM, et al. Duloxetine versus escitalopram and placebo: an 8-month, double-blind trial in patients with major depressive disorder. Curr Med Res Opin 2007;23:1303-18.
57. Russell IJ, Mease PJ, Smith TR, et al. Efficacy and safety of duloxetine for treatment of fibromyalgia in patients with or without major depressive disorder: Results from a 6-month, randomized, double-blind, placebo-controlled, fixed-dose trial. Pain 2008;136:432-44.
58. Yevtushenko VY, Belous AI, Yevtushenko YG, et al. Efficacy and tolerability of escitalopram versus citalopram in major depressive disorder: a 6-week, multicenter, prospective, randomized, double-blind, active-controlled study in adult outpatients. Clin Ther 2007;29:2319-32.
59. Dannon PN, Iancu I, Lowengrub K, et al. A naturalistic long-term comparison study of selective serotonin reuptake inhibitors in the treatment of panic disorder. Clin Neuropharmacol 2007;30:326-34.

60. Hewett K, Chrzanowski W, Schmitz M, et al. Eight-week, placebo-controlled, double-blind comparison of the antidepressant efficacy and tolerability of bupropion XR and venlafaxine XR. J Psychopharmacol 2009;23:531-8.
61. Nicolini H, Bakish D, Duenas H, et al. Improvement of psychic and somatic symptoms in adult patients with generalized anxiety disorder: examination from a duloxetine, venlafaxine extended-release and placebo-controlled trial. Psychol Med 2009;39:267-76.
62. Blier P, Gobbi G, Turcotte JE, et al. Mirtazapine and paroxetine in major depression: a comparison of monotherapy versus their combination from treatment initiation. Eur Neuropsychopharmacol 2009;19:457-65.
63. Wade A, Gembert K, Florea I, et al. A comparative study of the efficacy of acute and continuation treatment with escitalopram versus duloxetine in patients with major depressive disorder. Curr Med Res Opin 2007;23:1605-14.
64. Bose A, Korotzer A, Gommoll C, et al. Randomized placebo-controlled trial of escitalopram and venlafaxine XR in the treatment of generalized anxiety disorder. Depress Anxiety 2008;25:854-61.
65. Brent D, Emslie G, Clarke G, et al. Switching to another SSRI or to venlafaxine with or without cognitive behavioral therapy for adolescents with SSRI-resistant depression: the TORDIA randomized controlled trial. JAMA 2008;299:901-13.
66. Lenox-Smith AJ, Jiang Q. Venlafaxine extended release versus citalopram in patients with depression unresponsive to a selective serotonin reuptake inhibitor. Int Clin Psychopharmacol 2008;23:113-9.
67. Kok RM, Nolen WA, Heeren TJ. Venlafaxine versus nortriptyline in the treatment of elderly depressed inpatients: a randomised, double-blind, controlled trial. Int J Geriatr Psychiatry 2007;22:1247-54.
68. Pollack M, Mangano R, Entsuah R, et al. A randomized controlled trial of venlafaxine ER and paroxetine in the treatment of outpatients with panic disorder. Psychopharmacology (Berl) 2007;194:233-42.
69. Perahia DG, Pritchett YL, Kajdasz DK, et al. A randomized, double-blind comparison of duloxetine and venlafaxine in the treatment of patients with major depressive disorder. J Psychiatr Res 2008;42:22-34.
70. Claxton A, de Klerk E, Parry M, Robinson JM, Schmidt ME. Patient compliance to a new enteric-coated weekly formulation of fluoxetine during continuation treatment of major depressive disorder. J Clin Psychiatry. 2000 Dec;61(12):928-32.
71. Stein DJ, Ipser JC, van Balkom AJ. Pharmacotherapy for social anxiety disorder. Cochrane Database Syst Rev. 2000 (4):CD001206. doi: 10.1002/14651858.CD001206.pub2.
72. Mullins CD, Shaya FT, Meng F, Wang J, Harrison D. Persistence, switching, and discontinuation rates among patients receiving sertraline, paroxetine, and citalopram. Pharmacotherapy. 2005;25(5):660-7.
73. Wernicke J, Lledo A, Raskin J, et al. An evaluation of the cardiovascular safety profile of duloxetine. Drug Safety.2007;30(5):437-55.
74. Steiner M, Hirschberg AL, Bergeron R, Holland F, Gee M, Van Erp E. Luteal phase dosing with paroxetine controlled release in the treatment of premenstrual dysphoric disorder. Am J Obstet Gynecol. 2005;193:352-60.
75. Pearlstein TB, Bellew KM, Endicott J, Steiner M. Paroxetine controlled release for premenstrual dysphoric disorder: Remission analysis following a randomized, double-blind, placebo-controlled trial. Prim Care Companion J Clin Psychiatry. 2005;7:53-60.
76. Moncrieff J, Wessely S, Hardy R. Active placebos versus antidepressants for depression. Cochrane Database Syst Rev. 2004;(1):CD003012.
77. Walsh BT, Seidman SN, Sysko R, et al. Placebo response in studies of major depression: variable, substantial, and growing. JAMA. 2002;287:1840-7.
78. Geddes JR, Carney SM, Davies C, et al. Relapse prevention with antidepressant drug treatment in depressive disorders: a systematic review. Lancet. 2003;361:653-61.
79. Acharya N, Rosen AS. Polzer JP, D'Souza DN, Perahia DG, Cavazzoni PA, Baldessarini RJ. Duloxetine: meta-analyses of suicidal behaviors and ideation in clinical trials for major depressive disorder J Clin Psychopharmacol. 2006; 26(6):587-94.
80. Feighner J, Targum S, Bennet M et al. A double-blind, placebo-controlled trial of nefazodone in the treatment of patients hospitalized for major depression. J Clin Psychiatry. 1998;59(5):246-53.
81. Dunner DL, Lipshitx A, Pitts C, Davies JT. Efficacy and tolerability of controlled-release paroxetine in the treatment of severe depression; post hoc analysis of pooled data from a subset of subjects in four double-blind clinical trials. Clin Ther. 2005;27:1901-11.
82. Weihs KL, Settle EC Jr, Batey SR, et al: Bupropion sustained release versus paroxetine for the treatment of depression in the elderly. J Clin Psychiatry. 2000 Mar;61(3):196-202.

83. Kavoussi RJ, Segraves RT, Hughes AR, et al: Double-blind comparison of bupropion sustained release and sertraline in depressed outpatients. J Clin Psychiatry. 1997;58(12):532-537.
84. Rocca P, Calvarese P, Faggiano F, Marchiaro L, Mathis F, Rivoira E, Taricco B, Bogetto F. Citalopram versus sertraline in late-life non-major clinically significant depression: a 1 year follow-up clinical trial. J Clin Psychiatry 2005;66:360-9.
85. Van Baardewijk M, Vis PMJ, Einarson TR. Cost effectiveness of duloxetine compared with venlafaxine-XR in the treatment of major depressive disorder. Curr Med Res Opin. 2005;21(8):1271-79.
86. Moore N, Verdoux H, Fantino B. Prospective, multicentre, randomized, double-blind study of the efficacy of escitalopram versus citalopram in outpatient treatment of major depressive disorder. Int Clin Psychopharmacol. 2005 May;20(3):131-7.
87. Lam RW, Andersen HF. The influence of baseline severity on efficacy of escitalopram and citalopram in the treatment of major depressive disorder: an extended analysis. Pharmacopsychiatry. 2006 Sep;39(5):180-4.
88. Colonna L, Andersen HF, Reines EH. A randomized, double-blind, 24-week study of escitalopram (10 mg/day) versus citalopram (20 mg/day) in primary care patients with major depressive disorder. Curr Med Res Opin. 2005 Oct;21(10):1659-68.
89. Gorman JM, Korotzer A, Su G. Efficacy comparison of escitalopram and citalopram in the treatment of major depressive disorder: pooled analysis of placebo-controlled trials. CNS Spectr. 2002 Apr;7(4 Suppl 1):40-4.
90. Friedman MJ, Marmar CR, Baker DG, Sikes CR, Farfel GM. Randomized, double-blind comparison of sertraline and placebo for posttraumatic stress disorder in a department of veterans affairs setting. J Clin Psychiatry 2007;61:711-20.
91. Khan A, Bose A, Alexopoulos GS, Gommoll C, Li D, Gandhi C. Double-blind comparison of escitalopram and duloxetine in the acute treatment of major depressive disorder. Clin Drug Investig. 2007;27(7):481-92.
92. Boulenger JP, Huusom AK, Florea I, Baekdal T, Sarchiapone M. A comparative study of the efficacy of long-term treatment with escitalopram and paroxetine in severely depressed patients. Curr Med Res Opin. 2006 Jul;22(7):1331-41.
93. Ventura D, Armstrong EP, Skrepnek GH, Haim Erder M. Escitalopram versus sertraline in the treatment of major depressive disorder: a randomized clinical trial. Curr Med Res Opin. 2007 Feb;23(2):245-50.
94. Montgomery SA, Huusom AK, Bothmer J. A randomised study comparing escitalopram with venlafaxine XR in primary care patients with major depressive disorder. Neuropsychobiology. 2004;50(1):57-64.
95. Thase ME, Rush AJ, Howland RH, et al. Double-blind switch study of imipramine or sertraline treatment of antidepressant-resistant chronic depression. Arch Gen Psychiatr. 2002;59:233-9.
96. Versiani M, Moreno R, Ramakers-van Moorsel CJ, Schutte AJ. Comparative Efficacy Antidepressants Study Group. Comparison of the effects of mirtazapine and fluoxetine in severely depressed patients. CNS Drugs. 2005;19(2):137-46.
97. Wheatley D, Kremer CME: A randomized, double-blind comparison of mirtazapine and fluoxetine in patients with major depression. J Clin Psychiatry. 1998 Jun;59(6):306-12.
98. Behke K, Søgaard J, Martin S, et al: Mirtazapine orally disintegrating tablet versus sertraline. J Clin Psychopharmacol. 2003 Aug;23:4.
99. Guelfi D, Ansseau M, Timmerman L, et al: Mirtazapine versus venlafaxine in hospitalized severely depressed patients with melancholic features. J Clin Psychopharmacol. 2001;21:425-31.
100. Birkenhager TK, van den Broek WW, Mulder PG, et al. Efficacy and tolerability of tranylcypromine versus phenelzine: a double-blind study in antidepressant-refractory depressed inpatients. J Clin Psychiatry. 2004;65(11):1505-10.
101. Rossini D, Serretti A, Franchini L, Mandelli L, Smeraldi E, Ronchi DD, Zanardi R. Sertraline versus fluvoxamine in the treatment of elderly patients with major depression. J Clin Psychopharmacol 2005;25:471-5.
102. Bielski RJ, Ventura D, Chang C. A double-blind comparison of escitalopram and venlafaxine extended-release in the treatment of major depressive disorder. J Clin Psychiatry. 2004;65:1190-6.
103. Benkert O, Grunder G, Wetzel H, et al: A randomized, double-blind comparison of a rapidly escalating dose of venlafaxine and imipramine in inpatients with major depression and melancholia. J Psychiatr Res. 1996:30(6):441-51.
104. Stahl S, Zivkov M, Reimitz PE, et al. Meta-analysis of randomized, double-blind, placebo-controlled, efficacy and safety studies of mirtazapine versus amitriptyline in major depression. Acta Psychiatr Scand. 1997;96(suppl 391):22-30.
105. Clayton AH, Croft HA, Horrigan JP, Wightman DS, Krishen A, Richard NE, Modell JG. Bupropion extended release compared with escitalopram: effects on sexual functioning and antidepressant efficacy in 2 randomized, double-blind, placebo-controlled studies. J Clin Psychiatry 2006;67:736-46.

106. Llorca PM, Azorin JM, Despiegel N, Verpillat P. Efficacy of escitalopram in patient with severe depression: a pooled analysis. Int J Clin Pract. 2005 Mar;59(3):268-75.
107. Burke WJ, Gergel I, Bose A. Fixed-dose trial of the single isomer SSRI escitalopram in depressed outpatients. J Clin Psychiatry. 2002;63:331-36.
108. Nierenberg AA, Greist JH, Mallinckrodt CH, Prakash A, Sambunaris A, Tollefson GD, Wohlreich MM. Duloxetine versus escitalopram and placebo in the treatment of patients with major depressive disorder: onset of antidepressant action, a non-inferiority study. Curr Med Res Opin. 2007 Feb;23(2):401-16.
109. Goldstein DJ, Lu Y, Detke MJ, et al: duloxetine in the treatment of depression a double-blind placebo-controlled comparison with paroxetine. J Clin Psychopharmacol. 2004;24:389-99.
110. Vis PM. van Baardewijk M. Einarson TR. Duloxetine and venlafaxine-XR in the treatment of major depressive disorder: a meta-analysis of randomized clinical trials. Ann Pharmacother. 2005;39(11):1798-807.
111. Nemeroff CB, Michael E: A double-blind, placebo-controlled comparison of venlafaxine and fluoxetine treatment in depressed outpatients. J Psychiatr Res. 2007;41:351-9.
112. Rudolph RL, Feiger AD: A double-blind, randomized, placebo-controlled trial of once-daily venlafaxine extended release (XR) and fluoxetine for the treatment of depression. J. Affective Disorders. 1999:56:171-81.
113. Fava M, Hoog SL, Judge RA, Kopp JB, Nilsson ME, Gonzales JS. Acute efficacy of fluoxetine versus sertraline and paroxetine in major depressive disorder including effects of baseline insomnia. J Clin Psychopharmacol. 2002;22(2):137-47.
114. Perahia DG. Wang F. Mallinckrodt CH. Walker DJ. Detke MJ**.** Duloxetine in the treatment of major depressive disorder: a placebo- and paroxetine-controlled trial. Eur Psychiatry. 2006;21(6):367-78.
115. Thase ME, Trivedi MH, Rush AJ. MAOIs in the Contemporary Treatment of Depression. Neuropsychopharmacology. 1995;12(3):185-219.
116. Cipriani A, Brambilla P, Furukawa T, Geddes J, Gregis M, Hotopf M, et al. Fluoxetine versus other types of pharmacotherapy for depression. Cochrane Database Syst Rev. 2005 Oct 19;(4):CD004185.
117. Bull SA, Hu XH, Hunkeler EM, et al. Discontinuation of use and switching of antidepressants: influence of patient-physician communication. JAMA. 2002 Sep 18;288(11):1403-09.
118. Anderson IM. Selective serotonin reuptake inhibitors versus tricyclic antidepressants: a meta-analysis of efficacy and tolerability. J Affect Disord. 2000 Apr;58(1):19-36.
119. MacGillivray S, Arroll B, Hatcher S, et al. Efficacy and tolerability of selective serotonin reuptake inhibitors compared with tricyclic antidepressants in depression treated in primary care: systematic review and meta-analysis. BMJ. 2003;326:1014-9.
120. Steffens DC, Ranga K, Krishnan MD, et al. Are SSRIs better than TCAs? Comparison of SSRIs and TCAs: a meta-analysis. Depress Anxiety. 1997;6:10-8.
121. Davidson JR, Bose A, Wang Q. Safety and efficacy of escitalopram in the long-term treatment of generalized anxiety disorder. J Clin Psychiatry 2005;66:1441-6.
122. Goodman WK, Bose A, Wang Q. Treatment of generalized anxiety disorder with escitalopram: pooled results from double-blind, placebo-controlled trials. J Affect Disord. 87;2005;161-7.
123. Dahl AA, Ravindran A, Allgulander C, Kutcher SP, Austin C, Burt T. Sertraline in generalized anxiety disorder: efficacy in treatment in psychic an somatic anxiety factors. Acta Psychiatr Sand 2005;111:429-35.
124. Bielski RJ, Bose A, Chang CC. A double-blind comparison of escitalopram and paroxetine in the long-term treatment of generalized anxiety disorder. Ann Clin Psychiatry. 2005 Apr;17(2):65-69.
125. Ball S, Kuhn A, Wall D, Shekhar A, Goddard AW. Selective serotonin reuptake inhibitor for generalized anxiety disorder: a double-blind, prospective comparison between paroxetine and sertraline. J Clin Psychiatry 2005;66:94-9.
126. Schmitt R, Gazalle FK, Lima MS, Cunha A, Souza J, Kapczinski F. The efficacy of antidepressants for generalized anxiety disorder: a systematic review and meta-analysis. Rev Bras Psiquiatr. 2005 Mar;27(1):18-24.
127. Koran LM, McElroy SL, Davidson JRT, et al. Fluvoxamine versus clomipramine for obsessive-compulsive disorder: a double-blind comparison. J Clin Psychopharmacol. 1996;16:121-9.
128. Denys D, van der Wee N, van Megen HJ, Westenberg HG. A double blind comparison of venlafaxine and paroxetine in obsessive-compulsive disorder. J Clin Psychopharmacol. 2003;23:568-75.
129. Mundo E, Bianchi L, Bellodi L. Efficacy of Fluvoxamine, paroxetine, and Citalopram in the treatment of obsessive-compulsive disorder: A single-blind study. J Clin Psychopharmacol. 1997;17(4):267-71.
130. Van Ameringen M, Mancini C, Oakman J, Walker J, Kjernisted K, Chokka P, Johnston D, Bennett M, Patterson B. Nefazodone in the treatment of generalized social phobia; a randomized, placebo-controlled trial. J Clin Psychiatry 2007;68:288-95.

131. Sheehan DV, Burnham DB, Iyengar MK, Perea P. Efficacy and tolerability of controlled-release paroxetine in the treatment of panic disorder. J Clin Psychiatry 2005;66:34-40.
132. Stahl SM, Gergel I, Li D. Escitalopram in the treatment of panic disorder: a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry. 2003 Nov;64(11):1322-7.
133. Rampello L, Alvano A, Raffaele R, Malaguarnera M, Vecchio I. New possibilities of treatment for panic attacks in elderly patients: escitalopram versus citalopram. J Clin Psychopharmacol. 2006 Feb;26(1):67-70.
134. Bandelow B, Behnke K, Lenoir S, Hendriks GJ, Alkin T, Goebel C, et al. Sertraline versus paroxetine in the treatment of panic disorder: An acute, double-blind noninferiority comparison. J Clin Psych. 2004;65(3):405-13.
135. Ballenger JC, Wheadon DE, Steiner M, Bushnell W, Gergel IP. Double-blind, fixed-dose, placebo-controlled study of paroxetine in the treatment of panic disorder. Am J Psychiatry. 1998;155:36-42.
136. Davidson JR, Connor KM, Hertzberg MA, Weisler RH, Wislon WH, Payne VM. Maintenance therapy with fluoxetine in posttraumatic stress disorder. J Clin Psychopharmacol 2005;25:166-9.
137. Sheehan DV, Croft HA, Gossen ER, et al. Extended-release trazodone in major depressive disorder: a randomized, double-blind, placebo-controlled study. Psychiatry (Edgmont) 2009;6:20-33.
138. Robinson DS, Kajdasz DK, Gallipoli S, et al. A 1-year, open-label study assessing the safety and tolerability of vilazodone in patients with major depressive disorder. J Clin Psychopharmacol 2011;31:643-6.
139. Kaur H, Hota D, Bhansali A, et al. A comparative evaluation of amitriptyline and duloxetine in painful diabetic neuropathy: a randomized, double-blind, cross-over clinical trial. Diabetes Care 2011;34:818-22.
140. Chappell AS, Desaiah D, Liu-Seifert H, et al. A double-blind, randomized, placebo-controlled study of the efficacy and safety of duloxetine for the treatment of chronic pain due to osteoarthritis of the knee. Pain Pract 2010;11:33-41.
141. Martinez JM, Katon W, Greist JH, et al. A pragmatic 12-week, randomized trial of duloxetine versus generic selective serotonin-reuptake inhibitors in the treatment of adult outpatients in a moderate-to-severe depressive episode. Int Clin Psychopharmacol 2012;27:17-26.
142. Gaynor PJ, Gopal M, Zheng W, et al. A randomized placebo-controlled trial of duloxetine in patients with major depressive disorder and associated painful physical symptoms. Curr Med Res Opin 2011;27:1849-58.
143. Khan A, Cutler AJ, Kajdasz DK, et al. A randomized, double-blind, placebo-controlled, 8-week study of vilazodone, a serotonergic agent for the treatment of major depressive disorder. J Clin Psychiatry 2011;72:441-7.
144. Rosso G, Rigardetto S, Bogetto F, et al. A randomized, single-blind, comparison of duloxetine with bupropion in the treatment of SSRI-resistant major depression. J Affect Disord 2012;136:172-6.
145. Rush AJ, Trivedi MH, Stewart JW, et al. Combining medications to enhance depression outcomes (CO-MED): acute and long-term outcomes of a single-blind randomized study. Am J Psychiatry 2011;168:689-701.
146. Soares CN, Thase ME, Clayton A, et al. Desvenlafaxine and escitalopram for the treatment of postmenopausal women with major depressive disorder. Menopause 2010;17:700-11.
147. Frakes EP, Risser RC, Ball TD, et al. Duloxetine added to oral nonsteroidal anti-inflammatory drugs for treatment of knee pain due to osteoarthritis: results of a randomized, double-blind, placebo-controlled trial. Curr Med Res Opin 2011;27:2361-72.
148. Skljarevski V, Zhang S, Desaiah D, et al. Duloxetine versus placebo in patients with chronic low back pain: a 12-week, fixed-dose, randomized, double-blind trial. J Pain 2010;11:1282-90.
149. Gaynor PJ, Gopal M, Zheng W, et al. Duloxetine versus placebo in the treatment of major depressive disorder and associated painful physical symptoms: a replication study. Curr Med Res Opin 2011;27:1859-67.
150. Chappell AS, Ossanna MJ, Liu-Seifert H, et al. Duloxetine, a centrally acting analgesic, in the treatment of patients with osteoarthritis knee pain: a 13-week, randomized, placebo-controlled trial. Pain 2009;146:253-60.
151. Tanenberg RJ, Irving GA, Risser RC, et al. Duloxetine, pregabalin, and duloxetine plus gabapentin for diabetic peripheral neuropathic pain management in patients with inadequate pain response to gabapentin: an open-label, randomized, noninferiority comparison. Mayo Clin Proc 2011;86:615-26.
152. Krystal AD, Durrence HH, Scharf M, et al. Efficacy and safety of doxepin 1 mg and 3 mg in a 12-week sleep laboratory and outpatient trial of elderly subjects with chronic primary insomnia. Sleep 2010;33:1553-61.
153. Krystal AD, Lankford A, Durrence HH, et al. Efficacy and safety of doxepin 3 and 6 mg in a 35-day sleep laboratory trial in adults with chronic primary insomnia. Sleep 2011;34:1433-42.
154. Roth T, Heith Durrence H, Jochelson P, et al. Efficacy and safety of doxepin 6 mg in a model of transient insomnia. Sleep Med 2010;11:843-7.

155. Skljarevski V, Desaiah D, Liu-Seifert H, et al. Efficacy and safety of duloxetine in patients with chronic low back pain. Spine 2010;35:E578-85.
156. Ou JJ, Xun GL, Wu RR, et al. Efficacy and safety of escitalopram versus citalopram in major depressive disorder: a 6-week, multicenter, randomized, double-blind, flexible-dose study. Psychopharmacology (Berl) 2011;213:639-46.
157. Scharf M, Rogowski R, Hull S, et al. Efficacy and safety of doxepin 1, 3 and 6 mg in elderly patients with primary insomnia. J Clin Psychiatry 2008; 69:1557-64
158. Mazza M, Mazza O, Pazzaglia C, et al. Escitalopram 20 mg versus duloxetine 60 mg for the treatment of chronic low back pain. Expert Opin Pharmacother 2010;11:1049-52.
159. Rickels K, Athanasiou M, Robinson DS, et al. Evidence for efficacy and tolerability of vilazodone in the treatment of major depressive disorder: a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry 2009;70:326-33.
160. Mease PJ, Russell IJ, Kajdasz DK, et al. Long-term safety, tolerability, and efficacy of duloxetine in the treatment of fibromyalgia. Semin Arthritis Rheum 2010;39:454-64.
161. Skljarevski V, Zhang S, Chappell AS, et al. Maintenance of effect of duloxetine in patients with chronic low back pain: a 41-week uncontrolled, dose-blinded study. Pain Med 2010;11:648-57.
162. Roth T, Rogowski R, Hull S, et al. Efficacy and safety of doxepin 1, 3 and 6 mg in adults with primary insomnia. Sleep 2007;30: 1555-61
163. Carville SF, Arendt-Nielsen S, Bliddal H, et al. EULAR evidence-based recommendations for the management of fibromyalgia syndrome. Ann Rheum Dis 2008;67:536-41.
164. National Collaborating Centre for Primary Care. Low back pain. Early management of persistent non-specific low back pain. London (UK): National Institute for Health and Clinical Excellence (NICE); 2009. Available at: http://www.nice.org.uk/CG88. Accessed May 2012.
165. Chou R, Qaseem A, Snow V, 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. Ann Intern Med 2007;147:478-491.
166. Hegmann KT, ed. Low back disorders. In: Glass LS, editor(s). Occupational medicine practice guidelines: evaluation and management of common health problems and functional recovery in workers. 2nd ed. Elk Grove Village (IL): American College of Occupational and Environmental Medicine (ACOEM); 2007. p. 366. Available at: http://www.guideline.gov/content.aspx?id=12540&search=low+back+disorder. Accessed May 2012.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Cerebral Stimulants/Agents Used for ADHD
Central Alpha-Agonists, AHFS Class 240816
Amphetamines, AHFS Class 282004
Anorexigenic Agents and Respiratory and Cerebral Stimulants, Miscellaneous AHFS Class 282092
Central Nervous System Agents, Miscellaneous, AHFS Class 289200
August 8, 2012

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.[21,23-24] The key diagnostic feature is a persistent pattern of inattention and/or hyperactivity-impulsivity that is more frequent/severe than seen in individuals at a comparable level of development.[21] 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.[21] Untreated (or undertreated) ADHD is associated with adverse sequelae, including delinquent behavior, antisocial personality traits, substance abuse and other comorbidities.[24]

There are several central nervous system (CNS) 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.[4-10,12-19,145-146] 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.[5-10,12-19] 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.[4,145-146]

The cerebral stimulants are also used to treat a variety of sleep disorders. Narcolepsy is a sleep disorder characterized by excessive daytime sleepiness and intermittent manifestations of REM sleep during wakefulness.[29] Obstructive sleep apnea (OSA) is the most common form of breathing-related sleep disorder, which is caused by obstruction of the airway.[21] Individuals with OSA often suffer from excessive daytime sleepiness, as well as other serious health conditions (e.g., depression, hypertension and cardiovascular/cerebrovascular disease).[32] 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.[21,31] Modafinil and armodafinil (the longer half-life enantiomer of modafinil) are both approved to improve wakefulness in adult patients with excessive sleepiness associated with narcolepsy, OSA and shift work sleep disorder.[11,20] 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.[11,20] As a result, these agents are classified as Schedule IV controlled substances. Sodium oxybate is gamma-hydroxybutyric acid (GHB), a known drug of abuse.[147] 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 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 February 2010.

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®	none
Amphetamines			
Amphetamine aspartate, amphetamine sulfate, and dextroamphetamine	extended-release capsule, tablet	Adderall®*, Adderall XR®*‡	Adderall XR®*‡
Dextroamphetamine	sustained-release capsule, solution, tablet	Dexedrine®*, ProCentra®	dextroamphetamine
Lisdexamfetamine	capsule	Vyvanse®	Vyvanse®
Methamphetamine	tablet	Desoxyn®*	methamphetamine
Anorexigenic Agents and Respiratory and Cerebral Stimulants, Miscellaneous			
Armodafinil	tablet	Nuvigil®	none
Dexmethylphenidate	extended-release capsule, tablet	Focalin®*, Focalin XR®	dexmethylphenidate, Focalin XR®
Methylphenidate	chewable tablet, extended-release capsule and tablet, sustained-release tablet, solution, tablet, transdermal patch	Concerta®*, Daytrana®, Metadate CD®, Metadate ER®*, Methylin®*, Ritalin®*, Ritalin LA®*, Ritalin-SR®*	methylphenidate, Ritalin®*, Ritalin-SR®*
Modafinil	tablet	Provigil®*	modafinil
Central Nervous System Agents, Miscellaneous			
Atomoxetine	capsule	Strattera®	none
Guanfacine	extended-release tablet	Intuniv®	none
Sodium oxybate	solution	Xyrem®	none

*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[1-20,145-147]

Generic Name(s)	Short-Acting	Intermediate-Acting	Long-Acting
Central Alpha-Agonists			
Clonidine			Kapvay®
Amphetamines			
Amphetamine aspartate, amphetamine sulfate, and dextroamphetamine	amphetamine aspartate, amphetamine sulfate, and dextroamphetamine, Adderall®*		amphetamine aspartate, amphetamine sulfate, and dextroamphetamine, Adderall XR®*
Dextroamphetamine	dextroamphetamine, ProCentra®	dextroamphetamine, Dexedrine®*	
Lisdexamfetamine			Vyvanse®
Methamphetamine		methamphetamine, Desoxyn®*	
Anorexigenic Agents and Respiratory and Cerebral Stimulants, Miscellaneous			
Armodafinil			Nuvigil®
Dexmethylphenidate	dexmethylphenidate, Focalin®*		Focalin XR®
Methylphenidate	methylphenidate, Methylin®*, Ritalin®*	methylphenidate SR, Metadate ER®*, Ritalin SR®*	methylphenidate, Concerta®*, Daytrana®, Metadate CD®, Ritalin LA®*
Modafinil			Provigil®
Central Nervous System Agents, Miscellaneous			
Atomoxetine			Strattera®
Guanfacine			Intuniv®
Sodium oxybate	Xyrem®		

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the cerebral stimulants/agents used for 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 (AAP): **Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit Hyperactivity Disorder in Children and Adolescents[26] (2011)**	Preschool-Aged Children (4–5 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 in the child's function. Elementary School–Aged Children (6–11 years of age) • The primary care clinician should prescribe FDA-approved medications for 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). Adolescents (12–18 years of age) • 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. General Considerations • Stimulant medications are highly effective for most children in reduction core symptoms of ADHD. • Atomoxetine, extended-release guanfacine and extended-release clonidine reduce core symptoms; however, 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 medication 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 OROS methylphenidate). • Primary care clinicians should titrate doses of medication for ADHD to achieve maximum benefit with minimum adverse effects.
Institute for Clinical Systems Improvement (ICSI): **Diagnosis and Management of Attention Deficit Hyperactivity Disorder in Primary Care for School-Age Children and Adolescents[25] (2012)**	Medication Trials • Prescribe FDA-approved treatments for ADHD in children, including psychostimulants and/or non-stimulants. • The decision to use medication 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. • Optimal medication management alone is superior to other modalities

Clinical Guideline	Recommendation(s)
	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 with other stimulants. • 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 and atomoxetine trials are unsuccessful (due to either poor response or side effects in spite of adjustment), or if associated comorbidity is present, alternative medication trials may 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 (NICE): **Attention Deficit Hyperactivity Disorder: Diagnosis and Management of ADHD in Children, Young People, and Adults**[27] **(2008)**	<u>Treatment for Children and Adolescents with ADHD</u>
	• Methylphenidate, atomoxetine and dexamfetamine 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

Clinical Guideline	Recommendation(s)
	controlled drugs 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 dexamfetamine can be tried. • Caution should be exercised when prescribing dexamfetamine to those likely to be at risk of stimulant misuse or diversion.
American Academy of Child and Adolescent Psychiatry (AACAP): **Practice Parameter for the Assessment and Treatment of Children and Adolescents With Attention-Deficit/Hyperactivity Disorder**[24] **(2007)**	• Initial pharmacologic therapy should be with an agent approved by the FDA for the treatment of ADHD. This includes dextroamphetamine, methylphenidate (MPH), mixed salts of amphetamine, and atomoxetine. • Stimulants have been shown to be highly effective for the treatment of ADHD in many clinical trials. • Available evidence suggests that both MPH and amphetamines are equally efficacious in the treatment of ADHD. • Immediate-release stimulant medications have the disadvantage that they must be taken two to three times per day to control ADHD symptoms throughout the day. • The long-acting formulations are equally efficacious as immediate-release formulations. • Long-acting formulations may be used as initial therapy. There is no need to titrate to the appropriate dose on short-acting forms and then transfer children to a long-acting form. Short-acting stimulants are often used as initial treatment in small children (<16 kg in weight), for whom there are no long-acting forms in a sufficiently low dose. • Once a medication is initiated, the dose should be titrated every 1 to 3 weeks until the maximum dose is reached, the symptoms of ADHD remit, or side effects prevent further titration. • It is recommended that the patient be in contact with the physician during the titration period and visit the physician after 1 month of therapy to assess effectiveness and determine long-term therapy plans. • Some patients may respond similarly to different stimulant classes; whereas, other patients may preferentially respond to only one class of stimulants. There is no method to predict which stimulant will produce the best response in a given patient. • For the treatment of preschoolers, the available evidence suggests that the titration of stimulants be done slowly and that lower doses may be effective. This may be due to slower metabolism of MPH in preschoolers. • In studies published comparing atomoxetine to stimulants, greater efficacy was seen in those patients treated with stimulants. • Atomoxetine may have less pronounced effects on appetite and sleep than stimulants, although they may produce relatively more nausea or sedation. • Atomoxetine may be considered as a first-line agent in patients with an active substance abuse problem, comorbid anxiety, tics, or in those who experience severe side effects while taking stimulants. • It is the choice of the family and the clinician as to which agent should be used for the patient's treatment, and each patient's treatment must

Clinical Guideline	Recommendation(s)
	be individualized.
British Association of Psychopharmacology (BAP): **Evidence-Based Guidelines for the Management of Attention Deficit Hyperactivity Disorder in Adolescents in Transition to Adult Services and in Adults[28] (2006)**	Treatment Recommendations for Children • Proven first-line treatments in children include psychostimulants and atomoxetine. • Second-line treatment options include imipramine and bupropion. • Clonidine and guanfacine may be used as adjunctive treatments. • Qualitative assessments suggest that all agents are more effective than placebo and have similar efficacy; however, there have been few head-to-head comparisons. • The agents are not equivalent in terms of adverse events. • The response to different agents varies between individuals and with different doses. Treatment Recommendations for Adults • Drug treatment needs to be chosen and adapted to best fit the individual, including the patient's preferences and concerns. • Use of methylphenidate in adults has been shown to demonstrate similar drug response effect to that seen in children. • There is limited evidence suggesting that psychostimulants have better efficacy than other treatments for core symptoms. However, amphetamines, methylphenidate and atomoxetine are all effective but not equivalent, since they have different actions and hazards. 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 (AASM): **Practice Parameters for the Treatment of Narcolepsy and Other Hypersomnias of Central Origin[29] (2007)**	• Most of the agents used to treat excessive sleepiness have little effect on cataplexy or other REM sleep associated symptoms. Most antidepressants and anti-cataplectics 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 (SSRIs) 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 (EFNS): **Guidelines on Management of Narcolepsy[30] (2006)**	• Modafinil, 100-400 mg/day is recommended as the first-line pharmacological treatment of excessive daytime sleepiness and irresistible episodes of sleep. • Methylphenidate 10-60 mg/day is recommended as the second-line pharmacological treatment of excessive daytime sleepiness and irresistible episodes of sleep.

Clinical Guideline	Recommendation(s)
	• Nonpharmacological treatment recommendations include taking planned naps throughout the day scheduled on a patient-by-patient basis.
American Academy of Sleep Medicine (AASM): **Clinical Guideline for the Evaluation, Management and Long-term Care of Obstructive Sleep Apnea in Adults**[32] **(2009)**	Weight Reduction • Successful dietary weight loss may improve the apnea-hypopnea index (AHI) in obese obstructive sleep apnea (OSA) patients. • Dietary weight loss should be combined with a primary treatment for OSA. • Bariatric surgery may be adjunctive in the treatment of OSA in obese patients. Pharmacologic Agents • Modafinil is recommended for the treatment of residual excessive daytime sleepiness in OSA patients who have sleepiness despite effective PAP treatment and who are lacking any other identifiable cause for their sleepiness. • Selective serotonergic uptake inhibitors (SSRIs), protriptyline, methylxanthine derivatives (aminophylline and theophylline), and estrogen therapy are not recommended for treatment of OSA. Supplemental Oxygen • Oxygen supplementation is not recommended as a primary treatment for OSA. Medical Therapies Intended to Improve Nasal Patency • Short-acting nasal decongestants are not recommended for treatment of OSA. • Topical nasal corticosteroids may improve the AHI in patients with OSA and concurrent rhinitis, and thus may be a useful adjunct to primary therapies for OSA. Positional Therapies • Positional therapy is an effective secondary therapy or can be a supplement to primary therapies for OSA in patients who have a low AHI in the non-supine versus that in the supine position.
American Academy of Sleep Medicine (AASM): **Practice Parameters for the Clinical Evaluation and Treatment of Circadian Rhythm Sleep Disorders**[31] **(2007)**	Shift Work Disorder (SWD) • 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 SWD. • Caffeine is indicated to enhance alertness during the night shift for SWD.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the cerebral stimulants/agents used for 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[1-20,145-147]

Generic Name(s)	ADHD	Narcolepsy	Exogenous Obesity	Obstructive Sleep Apnea	Shift Work Sleep Disorder
Central Alpha-Agonists					
Clonidine	✔ *				
Amphetamines					
Amphetamine aspartate, amphetamine sulfate, and dextroamphetamine	✔ †	✔			
Dextroamphetamine	✔	✔			
Lisdexamfetamine	✔				
Methamphetamine	✔		✔		
Anorexigenic Agents and Respiratory and Cerebral Stimulants, Miscellaneous					
Armodafinil		✔		✔	✔
Dexmethylphenidate	✔				
Methylphenidate	✔ †‡§	✔ †‡			
Modafinil		✔		✔	✔
Central Nervous System Agents, Miscellaneous					
Atomoxetine	✔				
Guanfacine	✔ *				
Sodium oxybate		✔			

*As monotherapy and as adjunctive therapy to stimulant medications
§Extended-release formulations
†Immediate-release formulations
‡Sustained-release formulations

IV. Pharmacokinetics

The pharmacokinetic parameters of the cerebral stimulants/agents used for ADHD are listed in Table 5.

Table 5. Pharmacokinetic Parameters of the Cerebral Stimulants/Agents Used for ADHD[1-20,145-147]

Generic Name(s)	Onset (hours)	Duration (hours)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Central Alpha-Agonists							
Clonidine	0.5-1	6-10	89	20-40	Liver	Renal (40-60)	12-16
Amphetamines							
Amphetamine aspartate, amphetamine sulfate, and dextroamphetamine†	1-3	IR: 4-6 XR: 10-12	Well absorbed	20	Liver	Renal (67-73)	7-31
Dextroamphetamine	2-3	IR: 4-6 SR: 6-8	Well absorbed	Not reported	Liver	Renal (17-73)	10-12
Lisdexamfetamine	Not reported	10	Rapid	Not reported	Liver Intestinal wall	Renal (96)	<1
Methamphetamine	Not reported	Not reported	Rapid	Not reported	Liver	Renal (62)	4-5
Anorexigenic Agents and Respiratory and Cerebral Stimulants, Miscellaneous							
Armodafinil	Not reported	Not reported	Rapid	60	Liver	Renal	15
Dexmethylphenidate	1	IR: 5-6 XR: 12	22-25	12-15	Liver	Renal (90)	3
Methylphenidate	IR: 0.5-1 SR: 4-7 ER: 1-2 XR: 0.5-1 TD: 2	IR: 3-5 SR: 3-8 ER: 10-12 XR: 8-12 TD: 10-12	10-52	10-33	Liver	Renal (67-97)	3-4
Modafinil	Not reported	Not reported	Rapid	60	Liver	Renal (80)	7.5-15
Central Nervous System Agents, Miscellaneous							
Atomoxetine	1 week	Not reported	63-94	98	Liver	Renal Feces (<17)	4-22
Guanfacine	Not reported	Not reported	Well absorbed	70	Liver (50)	Renal (50)	18
Sodium oxybate	0.25-0.75	2-3	25	<1	Liver	Renal (1-5)	<1

ER=extended-release (osmotic), IR=immediate-release, SR=sustained-release, TD=transdermal, XR=extended-release (non-osmotic)
†Values are for amphetamine sulfate; data for mixed amphetamine salts are not available.

V. Drug Interactions

Significant drug interactions with the cerebral stimulants/agents used for ADHD are listed in Table 6.

Table 6. Significant Drug Interactions with the Cerebral Stimulants/Agents Used for ADHD[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Central Alpha-Agonists			
Clonidine	2	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	2	Tizanidine	The potential for symptomatic additive hypotension exists when tizanidine is coadministered with clonidine.
Clonidine	2	Tricyclic antidepressants	The antihypertensive effects of clonidine may be decreased by tricyclic antidepressants. Tricyclic antidepressants may worsen rebound reactions from abrupt clonidine withdrawal.
Amphetamines			
Amphetamines	1	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	1	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	2	Guanethidine	Interaction may lead to a decrease in guanethidine effectiveness, probably due to antagonistic pharmacologic activity.
Amphetamines	2	Urinary alkalinizers	Interaction may lead to pH-dependent diminished urinary elimination of amphetamines and increases risk of amphetamine toxicity.
Anorexigenic Agents and Respiratory and Cerebral Stimulants, Miscellaneous			

Generic Name(s)	Significance Level	Interaction	Mechanism
Armodafinil, modafinil	1	Contraceptives, oral	Armodafinil or modafinil may cause induction of gastrointestinal and hepatic metabolism of oral contraceptives. Pharmacologic effects of oral contraceptives may be decreased.
Methylphenidates	1	MAOIs	Pharmacologic effects of methylphenidates may be increased. Headache, GI symptoms and hypertension may occur. The mechanism of this interaction is not clear. Liberation of intraneuronal catecholamine stores may play a role.
Methylphenidates	2	Halogenated anesthetics	Coadministration of methylphenidates and halogenated anesthetics may cause a sudden increase in blood pressure during surgery. The mechanism of this interaction is unknown.
Central Nervous System Agents, Miscellaneous			
Atomoxetine	1	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.
Sodium oxybate	1	Barbiturates	Concurrent use of sodium oxybate and barbiturates may result in an increase in sleep duration and central nervous system depression.
Sodium oxybate	1	Benzodiazepines	Concurrent use of sodium oxybate and benzodiazepines may result in an increase in sleep duration and central nervous system depression.
Sodium oxybate	1	Buspirone	Concurrent use of sodium oxybate and buspirone may result in an increase in sleep duration and central nervous system depression.
Sodium oxybate	1	CNS depressants	Concurrent use of sodium oxybate and CNS depressants may result in an increase in sleep duration and central nervous system depression.

Generic Name(s)	Significance Level	Interaction	Mechanism
Sodium oxybate	1	Zolpidem	Concurrent use of sodium oxybate and zolpidem may result in an increase in sleep duration and central nervous system depression.
Atomoxetine	2	Quinidine	Plasma concentrations and pharmacologic effects of atomoxetine may be increased by quinidine. Quinidine may decrease the metabolism of atomoxetine and increase atomoxetine plasma concentrations.
Atomoxetine	2	Serotonin-reuptake inhibitors	Certain SSRIs may inhibit the metabolism (CYP2D6) of atomoxetine and increase plasma concentrations.
Guanfacine	2	Tizanidine	An additive effect on alpha$_2$-adrenergic receptors by tizanidine and guanfacine may occur. The potential for symptomatic additive hypotension exists when tizanidine is coadministered with guanfacine.
Guanfacine	2	Tricyclic antidepressants	Tricyclic antidepressants may antagonize the pharmacodynamic action of guanfacine at the CNS alpha-$_2$ adrenergic receptor. The antihypertensive effect of guanfacine may be decreased by tricyclic antidepressants.

Significance Level 1 = major severity
Significance Level 2 = moderate severity

VI. Adverse Drug Events

The most common adverse drug events reported with the cerebral stimulants/agents used for ADHD are listed in Tables 7-10. The boxed warnings for the cerebral stimulants/agents used for ADHD are listed in Tables 11-15. 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.[21-22,34-35] 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[4]

Adverse Events	Clonidine
Cardiovascular	
Atrioventricular block	✔

Adverse Events	Clonidine
Bradycardia	≤4
Cardiac arrhythmia	✔
Chest pain	✔
CHF	✔
ECG abnormalities	✔
Orthostatic hypotension	✔
Pallor	✔
Palpitations	1
Reynaud's phenomenon	✔
Syncope	✔
Tachycardia	1
Central Nervous System	
Abnormal sleep-related event	1-3
Aggressive behavior	✔
Agitation	✔
Anxiety	✔
Behavioral change	✔
Crying	1-3
Delirium	✔
Dizziness	2-5
Emotional disorder	3-4
Fatigue/lethargy	12-15
Fever	✔
Hallucinations	✔
Headache	1-11
Insomnia	≤5
Irritability	3-6
Malaise	✔
Mental depression	1
Nervousness	1-3
Nightmares	✔
Paresthesia	✔
Restlessness	✔
Sleep terror	3
Somnolence	26-33
Tremor	✔
Vivid dreams	✔
Dermatological	
Flushing	✔
Rash	1
Urticaria	✔
Gastrointestinal	
Abdominal pain	≤3
Anorexia	1
Constipation	1-6
Diarrhea	≤1
Dry mouth	✔
Nausea	1-4
Thirst	1-3
Vomiting	✔
Weight gain	<1
Genitourinary	
Dysuria	✔
Enuresis	4

Adverse Events	Clonidine
Erectile dysfunction	2-3
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	2-4
Nasal dryness	✔
Nasopharyngitis	2
Upper respiratory tract infection	2-7
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	3-5
Thrombocytopenic purpura	✔
Viral infection	≤3

✔ Percent not specified

Table 8. Adverse Drug Events (%) Reported with the Amphetamines[5-10]

Adverse Events	Amphetamine Aspartate/ Amphetamine Sulfate/ Dextroamphetamine	Dextro-amphetamine	Lisdex-amfetamine	Meth-amphetamine
Cardiovascular				
Blood pressure increased	-	-	3	-
Cardiomyopathy	✔ †	✔	✔	-
Heart rate increased	-	-	2	-
Hypertension	✔ †	✔	✔	✔
Myocardial infarction	✔ *	✔	✔	-
Palpitations	✔ †, 2-4*	✔	✔	✔
Sudden death	✔ *	✔	✔	-
Tachycardia	✔ †, 6*	✔	✔	✔
Central Nervous System				
Aggressive behavior	✔ †*	✔	-	-
Agitation	8*	-	3	-

Adverse Events	Amphetamine Aspartate/ Amphetamine Sulfate/ Dextroamphetamine	Dextro-amphetamine	Lisdex-amfetamine	Meth-amphetamine
Anxiety	8*	-	6	-
Depression	✔ †*	-	✔	-
Dizziness	2-7*	✔	5	✔
Dyskinesia	✔ †*	✔	✔	-
Dysphoria	✔ †*	✔	✔	✔
Euphoria	✔ †*	✔	✔	✔
Fever	5*	-	2	-
Headache	✔ †, 26*	✔	12	✔
Insomnia	12-27*	✔	4-27	✔
Irritability	✔ †*	-	10	-
Labile affect	-	-	3	-
Mania	-	✔	✔	-
Nervousness	6*	-	-	-
Overstimulation	✔ †	✔	✔	✔
Psychotic episodes	✔ †	✔	✔	✔
Restlessness	✔ †*	✔	3	✔
Seizures	✔ *	-	✔	-
Somnolence	2-4*	-	2	-
Speech disorder	2-4*	-	-	-
Stroke	✔ *	✔	✔	-
Tic exacerbation	✔ †*	✔	2	✔
Tourette's exacerbation	✔ †*	✔	✔	✔
Tremor	✔ †*	✔	2	✔
Twitching	2-4*	-	-	-
Dermatological				
Diaphoresis	2-4*	-	-	-
Hyperhidrosis	-	-	3	-
Photosensitivity	2-4*	-	-	-
Rash	✔ †*	✔	3	✔
Stevens-Johnson syndrome	✔ †*	-	✔	-
Toxic epidermal necrolysis	✔ †*	-	✔	-
Urticaria	✔ †*	✔	✔	✔
Gastrointestinal				
Abdominal pain	11-14*	-	12	-
Anorexia	-	✔	5	✔
Appetite decreased	22-36*	-	27-39	-
Constipation	✔ †, 2-4*	✔	✔	✔
Diarrhea	2-6*	✔	7	✔
Dry mouth	2-35*	✔	5-26	✔
Dyspepsia	2-4*	-	-	-
Nausea	2-8*	-	6-7	✔
Other GI disturbances	-	✔	-	✔
Unpleasant taste	✔ †*	✔	✔	✔
Vomiting	2-7*	-	9	✔
Weight loss	4-11*	✔	9	✔
Genitourinary				
Changes in libido	2-4*	✔	≤2	✔
Impotence	2-4*	✔	✔	✔
Urinary tract infection	5*	-	-	-
Other				
Anaphylaxis	✔ *	-	✔	-

Adverse Events	Amphetamine Aspartate/ Amphetamine Sulfate/ Dextroamphetamine	Dextro-amphetamine	Lisdex-amfetamine	Meth-amphetamine
Angioedema	-	-	✔	-
Blurred vision	✔ †*	✔	✔	-
Dysmenorrhea	2-4*	-	-	-
Dyspnea	2-4*	-	2	-
Growth suppression	-	-	-	✔
Hypersensitivity reactions	-	-	✔	-
Infection	2-4*	-	-	-
Tolerance	-	-	-	✔
Weakness	2-6*	-	-	-

†Immediate-release formulation
*Extended-release formulation
✔ Percent not specified
- Event not reported

Table 9. Adverse Drug Events (%) Reported with the Anorexigenic Agents and Respiratory and Cerebral Stimulants, Miscellaneous[11-20]

Adverse Events	Armodafinil	Dexmethylphenidate	Methylphenidate	Modafinil
Cardiovascular				
Angina	-	✔	✔	-
Cardiac arrhythmia	-	✔	✔	-
Chest pain	-	-	✔	3
Hypertension	-	✔	✔	3
Hypotension	-	✔	✔	-
Myocardial infarction	-	-	✔	-
Palpitations	2	✔	✔	2
Pulse increase/decrease	1	✔	✔	-
Raynaud's phenomenon	-	-	✔	-
Sudden death	-	✔	-	-
Systolic BP increased	✔	-	-	-
Tachycardia	-	3	✔	2
Vasodilation	-	-	-	2
Central Nervous System				
Aggressive behavior	-	✔	✔	-
Agitation	1	-	-	1
Anxiety	4	5-11	-	5
Attention disturbance	1	-	-	-
Cerebral arteritis	-	✔	✔	-
Cerebral occlusion	-	✔	✔	-
Depression	1-3	✔	✔	2
Dizziness	5	6	✔	5
Drowsiness	-	✔	✔	-
Dyskinesia	-	✔	✔	1
Emotional instability	-	-	6†	-
Fatigue/lethargy	2	-	-	-
Fever	1	5	✔	-
Hallucinations	-	-	✔ †	-
Headache	14-23	25-39	✔, 28†	34
Hyperkinesia	-	-	-	1
Hypertonia	-	-	-	1
Insomnia	4-6	✔	✔, 13-30†	5
Jittery feeling	-	12	-	-
Labile affect	-	-	✔	-
Mania	-	-	✔	✔

Adverse Events	Armodafinil	Dexmethylphenidate	Methylphenidate	Modafinil
Migraine	1	-	-	-
Nervousness	1	✔	✔	7
Neuroleptic malignant syndrome	-	✔	✔	-
Overstimulation	-	-	-	1
Paresthesia	1	-	✔	2
Psychotic episodes	-	-	-	✔
Restlessness	-	12	-	-
Seizures	-	-	✔ †	-
Somnolence	-	-	-	2
Tic	-	-	✔ , 7†	-
Tourette's exacerbation	-	✔	✔	-
Toxic psychosis	-	✔	✔	-
Tremor	1	-	-	1
Vertigo	-	-	-	1
Dermatological				
Alopecia	-	-	✔	-
Application site reaction	-	-	✔ †	-
Dermatitis	1	-	-	-
Diaphoresis	-	-	-	1
Erythema	-	-	✔	-
Erythema multiforme	-	✔	✔	✔ -
Exfoliative dermatitis	-	✔	✔	-
Hair loss	-	✔	✔	-
Herpes simplex	-	-	-	1
Hyperhidrosis	1	-	✔	-
Rash	1-4	✔	✔	-1
Stevens-Johnson syndrome	-	-	-	✔
Toxic epidermal necrolysis	-	-	✔	-
Urticaria	-	✔	✔	-
Gastrointestinal				
Abdominal pain	2	15	✔	-
Anorexia	1	5-7	✔ , 5-46†	4
Appetite decreased	1	30	✔ , 26†	-
Bruxism	-	-	✔	-
Constipation	1	-	✔	2
Diarrhea	4	-	✔	6
Dry mouth	2-7	7-20	✔	4
Dyspepsia	2	5-9	✔	5
Flatulence	-	-	-	1
Mouth ulceration	-	-	-	1
Nausea	-	9	✔ , 12†	11
Stomach cramps	-	✔	-	-
Thirst	-	-	-	1
Unpleasant taste	-	-	-	1
Vomiting	1	-	✔ , 10†	-
Weight loss	-	✔	✔ , 9†	-
Genitourinary				
Abnormal urine	-	-	-	1
Erectile disturbance	-	-	✔	-
Hematuria	-	-	-	1
Libido decreased	-	-	✔	-
Polyuria	1	-	-	-
Pyuria	-	-	-	1

Adverse Events	Armodafinil	Dexmethylphenidate	Methylphenidate	Modafinil
Hematologic				
Agranulocytosis	-	-	-	✔
Anemia	-	✔	✔	-
Eosinophilia	-	-	-	1
Leukopenia	-	✔	✔	-
Pancytopenia	✔	-	✔	-
Thrombocytopenic purpura	-	✔	✔	-
Hepatic				
Hepatic coma	-	✔	✔	-
Liver function test abnormalities	✔	✔	✔	2
Musculoskeletal				
Arthralgia	-	✔	✔	-
Back pain	-	-	-	6
Respiratory				
Cough	-	-	✔	-
Dyspnea	1	-	✔	-
Epistaxis	-	-	-	1
Lung disorder	-	-	-	2
Nasal congestion	-	-	✔, 6†	-
Nasopharyngitis	-	-	✔, 5†	-
Pharyngitis	-	-	✔	4
Pharyngolaryngeal pain	-	4-7	✔	-
Respiratory tract infection	-	-	✔	-
Rhinitis	-	-	✔	7
Sinusitis	-	-	✔	-
Special Senses				
Abnormal vision	-	-	-	1
Accommodation difficulties	-	✔	✔	1
Amblyopia	-	-	-	1
Blurred vision	-	✔	✔	1
Dry eyes	-	-	✔	-
Eye pain	-	-	-	1
Mydriasis	-	-	✔	-
Other				
Accidental injury	-	-	✔	-
Allergic contact sensitization	-	-	✔ †	-
Anaphylaxis	✔	-	✔ †	✔
Dysmenorrhea	-	-	✔	-
Edema	-	-	-	1
Flu-like syndrome	1	-	-	4
Growth suppression	-	-	✔	-
Hypersensitivity reactions	-	✔	✔	✔
Necrotizing vasculitis	-	✔	✔	-
Pain	1	-	-	-
Thirst	1	-	-	-
Viral infection	-	-	28†	-

†Transdermal formulation
✔ Percent not specified
- Event not reported

Table 10. Adverse Drug Events (%) Reported with the Central Nervous System Agents, Miscellaneous[145-147]

Adverse Events	Atomoxetine	Guanfacine	Sodium Oxybate
Cardiovascular			
Atrioventricular block	-	✔	-

Adverse Events	Atomoxetine	Guanfacine	Sodium Oxybate
Chest pain	-	-	✔
Diastolic blood pressure increased	≤ 4	-	-
Flushing	≥2	-	-
Hypertension	1-9	✔	6
Hypotension	<2	4	-
Palpitations	3	-	-
QT prolongation	<1	-	-
Reynaud's phenomenon	✔	-	-
Sinus arrhythmia	-	✔	-
Stroke	✔	-	-
Systolic blood pressure increased	4-5	-	-
Tachycardia	≤2	-	<1
Central Nervous System			
Abnormal dreams	4	-	3-9
Aggressive behavior	✔	-	-
Agitation	✔	✔	✔
Akathisia	✔	-	-
Anxiety	✔	✔	3-6
Ataxia	-	-	✔
Attention disturbance	-	-	3-9
Chills	3	-	✔
Confusion	-	-	3-6
Crying	2	-	-
Depression	-	✔	6
Disorientation	-	-	6
Dizziness	5-6	2	17
Early morning awakening	<2	-	-
Fatigue/lethargy	6-9	14	≤6
Fever	3	-	-
Hallucinations	-	✔	-
Headache	2-19	5	22
Hostility	✔	-	-
Insomnia	2-15	-	5
Irritability	≤ 6	2	-
Jittery feeling	2	-	-
Mania	✔	-	-
Mood swings	1-2	-	-
Nervousness	-	-	✔
Nightmare	-	✔	3-6
Panic disorder	✔	-	-
Paresthesia	4	-	-
Rigors	3	-	-
Seizure	-	✔	✔
Sleep disorder	-	-	3-6
Sleep disturbance	3	-	-
Sleep paralysis	-	-	3-11
Sleep walking	-	-	6
Somnolence	4-11	26	8
Suicidal ideation	✔	-	✔
Syncope	✔	✔	✔
Tremor	2	-	✔
Dermatological			
Dermatitis	2-4	-	-
Diaphoresis	2	-	3-11

Adverse Events	Atomoxetine	Guanfacine	Sodium Oxybate
Flushing	2	-	-
Hyperhidrosis	4	-	3-6
Rash	2	-	✔
Urticaria	✔	-	-
Endocrine and Metabolic			
Dysmenorrhea	6	-	3-6
Hot flushes	8	-	-
Menstrual disturbances	2-3	-	-
Gastrointestinal			
Abdominal pain	7-18	2	3-11
Anorexia	<3	-	-
Appetite decreased	11-16	2	-
Constipation	1-9	3	✔
Diarrhea	4	-	6-8
Dry mouth	4-21	3	-
Dyspepsia	4-6	✔	3
Fecal incontinence	-	-	<1
Flatulence	2	-	✔
Nausea	7-21	4	21
Stomach discomfort	-	✔	-
Vomiting	3-11	✔	8
Weight increase	-	✔	✔
Weight loss	2-3	-	-
Genitourinary			
Dysuria	3	-	-
Ejaculatory disturbance	3	-	-
Enuresis	-	✔	3-17
Erectile disturbance	9	-	-
Impotence	3	-	-
Libido decreased	4	-	✔
Orgasm abnormal	2	-	-
Prostatitis	2	-	-
Urinary incontinence	-	-	7
Urinary retention	7	-	-
Hepatic			
Hepatotoxicity	✔	-	-
Jaundice	✔	-	-
Musculoskeletal			
Hypoesthesia	-	-	6
Myalgia	-	-	✔
Myasthenia	-	-	3-6
Weakness	-	-	6-8
Respiratory			
Asthma	-	✔	-
Bronchitis	-	-	✔
Cough	11	-	✔
Dyspnea	-	-	✔
Nasopharyngitis	-	-	8
Rhinitis	-	-	8
Rhinorrhea	4	-	-
Sinus headache	3	-	-
Sinusitis	6	-	-
Upper respiratory infection	-	-	3
Special Senses			

Adverse Events	Atomoxetine	Guanfacine	Sodium Oxybate
Amblyopia	-	-	6
Blurred vision	-	-	3
Mydriasis	<2	-	-
Tinnitus	-	-	6
Other			
Accidental injury	-	-	-
Allergic contact sensitization	✔	-	✔
Ear infection	3	-	-
Ear pain	-	-	✔
Flu-like syndrome	✔	-	✔
Hypersensitivity reactions	<1	✔	✔
Influenza	3	-	-
Pain	-	-	3
Pallor	-	✔	✔
Thirst	-	-	✔
Viral infection	-	-	6

✔ Percent not specified
- Event not reported

Table 11. Boxed Warning for the Amphetamines[1]

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[1]

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 (6- 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 with placebo. The average risk of suicidal ideation in patients receiving atomoxetine was 0.4% (5/1,357 patients), compared with none in placebo-treated patients (0/851 patients). No suicides occurred in these trials

Table 13. Boxed Warning for Dexmethylphenidate[1]

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 Methylphenidate[1]

WARNING
Drug dependence: Give methylphenidate cautiously to emotionally unstable patients such as those with a history of drug dependence or alcoholism, because such patients may increase dosage at their own initiative. Long-term 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. Long-term follow-up may be required because of the patient's basic personality disturbances.

Table 15. Boxed Warning for Sodium Oxybate[1]

WARNING
Sodium oxybate is a gamma hydroxybutyrate (GHB), a known drug of abuse. Abuse has been associated with some important CNS adverse reactions, including death. Even at recommended doses, use has been associated with confusion, depression, and other neuropsychiatric reactions. Reports of respiratory depression occurred in clinical trials. Almost all of the patients who received sodium oxybate during clinical trials were receiving CNS stimulants. Important CNS adverse reactions associated with abuse of sodium oxybate include respiratory depression, seizure, and profound decreases in level of consciousness, with instances of coma and death. For reactions that occurred outside of clinical trials, in people taking sodium oxybate for recreational purposes, the circumstances surrounding the reactions often are unclear (e.g., dose of sodium oxybate taken, the nature and amount of alcohol or any concomitant drugs). Sodium oxybate is available through the Xyrem Success Program, using a centralized pharmacy (1-866-997-3688). The Success Program provides educational materials to the prescriber and the patient explaining the risks and proper use of sodium oxybate and the required prescription form. Once it is documented that the patient has read and/or understands the materials, the drug will be shipped to the patient. The Xyrem Success Program also recommends patient follow-up every 3 months. Health care providers are expected to report all serious adverse reactions to the manufacturer.

VII. Dosing and Administration

The usual dosing regimens for the cerebral stimulants/agents used for ADHD are listed in Table 16.

Table 16. Usual Dosing Regimens for the Cerebral Stimulants/Agents Used for ADHD[1-20,145-147]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Central Alpha-Agonists			
Clonidine	Safety and efficacy has not been established in adults.	ADHD: ≥6 years of age: Initial, 0.1 mg at bedtime; increase by 0.1 mg/day every 7 days until desired response; doses should be administered twice daily; maximum, 0.4 mg/day	Tablet (SR): 0.1 mg 0.2 mg
Amphetamines			
Amphetamine aspartate, amphetamine sulfate, and dextroamphetamine	ADHD (Capsule ER): 20 mg daily; may titrate at weekly intervals to appropriate efficacy and tolerability as indicated	ADHD (Capsule ER): 6-12 years of age: 5-10 mg once daily; may increase dose by 5-10 mg daily at weekly intervals	Capsule (ER): 5 mg 10 mg 15 mg 20 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	ADHD (Tablet): 5 mg once or twice daily; may increase daily dose in 5 mg increments at weekly intervals until optimal response obtained. Give first dose upon awakening and additional doses (1 or 2) at intervals of 4 to 6 hours. Narcolepsy (Tablet): 5-60 mg daily in divided doses. Give first dose upon awakening and additional doses (1 or 2) at intervals of 4 to 6 hours.	13-17 years of age: 10 mg once daily; may increase to 20 mg daily after one week if ADHD symptoms not adequately controlled ADHD (Tablet): 3-5 years of age: 2.5 mg once daily; may increase dose by 2.5 mg daily at weekly intervals until optimal response obtained ≥6 years of age: 5 mg once or twice daily; may increase dose by 5 mg daily at weekly intervals. Give first dose upon awakening and additional doses (1 or 2) at intervals of 4 to 6 hours. Narcolepsy (Tablet): 6-12 years of age: 5 mg once daily; may increase dose daily dose in 5 mg increments at weekly intervals until optimal response is obtained. Give first dose upon awakening and additional doses (1 or 2) at intervals of 4 to 6 hours. ≥12 years of age: 10 mg once daily; may increase daily dose in 10 mg increments weekly. Give first dose upon awakening and additional doses (1 or 2) at intervals of 4 to 6 hours.	25 mg 30 mg Tablet: 5 mg 7.5 mg 10 mg 12.5 mg 15 mg 20 mg 30 mg
Dextroamphetamine	ADHD (IR): 5 mg once or twice daily; may increase daily dose in 5 mg increments at weekly intervals until optimal response obtained. Give first dose upon awakening and additional doses (1 or 2) at intervals of 4 to 6 hours. ADHD (SR): 5 mg once or twice daily; may increase daily dose in 5 mg	ADHD (IR): 3-5 years of age: 2.5 mg once daily; may increase by 2.5 mg daily at weekly intervals until optimal response is obtained. Give first dose upon awakening and additional doses (1 or 2) at intervals of 4 to 6 hours. ≥6 years of age: 5 mg once or twice daily;	Capsule (SR): 5 mg 10 mg 15 mg Solution (IR): 5 mg/5 ml Tablet (IR): 5 mg 10 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	increments at weekly intervals until optimal response obtained. SR capsules may be used for once daily dosing when appropriate. Narcolepsy (IR): 5-60 mg daily in divided doses. Give first dose upon awakening and additional doses (1 or 2) at intervals of 4 to 6 hours. Narcolepsy (SR): 5-60 mg daily in divided doses. SR capsules may be used for once daily dosing when appropriate.	may increase dose in 5 mg increments at weekly intervals until optimal response is reached. Give first dose upon awakening and additional doses (1 or 2) at intervals of 4 to 6 hours. ADHD (SR): ≥6 years of age: 5 mg once or twice daily; may increase daily dose in 5 mg increments at weekly intervals until optimal response is reached. SR capsules may be used for once daily dosing when appropriate. Narcolepsy (IR): 6-12 years of age: 5 mg daily; may increase dose daily dose in 5 mg increments at weekly intervals until optimal response is obtained. Give first dose upon awakening and additional doses (1 or 2) at intervals of 4 to 6 hours. Narcolepsy (SR): 6-12 years of age: 5 mg once daily; may increase dose daily dose in 5 mg increments at weekly intervals until optimal response is obtained. SR capsules may be used for once daily dosing when appropriate. ≥12 years of age: 10 mg once daily; may increase daily dose in 10 mg increments at weekly intervals until optimal dose obtained. SR capsules may be used for once daily dosing when appropriate.	
Lisdexamfetamine	ADHD: 30 mg once daily in the morning; may increase dose in 10-20 mg increments at weekly intervals	ADHD: 6-12 years of age: 30 mg once daily in the morning; may increase dose in 10-20 mg increments at weekly intervals	Capsule: 20 mg 30 mg 40 mg 50 mg 60 mg 70 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Methamphetamine	ADHD: 5 mg once or twice daily; may increase in 5 mg increments at weekly intervals until optimum response is achieved. The total daily dose may be given in two divided doses. Obesity: 5 mg tablet 30 minutes before each meal; treatment should not exceed a few weeks in duration	ADHD: ≥6 years of age: 5 mg once or twice daily; may increase in 5 mg increments at weekly intervals until optimum response is achieved. The total daily dose may be given in two divided doses. Obesity: ≥12 years of age: 5 mg tablet 30 minutes before each meal; treatment should not exceed a few weeks in duration	Tablet: 5 mg
Anorexigenic Agents and Respiratory and Cerebral Stimulants, Miscellaneous			
Armodafinil	Narcolepsy: 150-250 mg once daily in the morning Obstructive Sleep Apnea: 150-250 mg once daily in the morning Shift Work Sleep Disorder: 150 mg daily given 1 hour prior to start of work shift	Safety and efficacy in children have not been established.	Tablet: 50 mg 150 mg 250 mg
Dexmethylphenidate	ADHD (Capsule ER): Methylphenidate naïve patients: 10 mg once daily; may increase by 10 mg increments at weekly intervals Patients already using methylphenidate: initiate dexmethylphenidate at half (1/2) the current total daily dose of racemic methylphenidate Patients already using dexmethylphenidate immediate-release tablets: switch to the same daily dose ADHD (Tablet): Methylphenidate naïve patients: 2.5 mg twice daily; may increase by 2.5-5 mg increments at weekly intervals Patients already using methylphenidate: initiate dexmethylphenidate at half (1/2) the dose of racemic	ADHD (Capsule ER): ≥6 years of age: Methylphenidate naïve patients: 5 mg once daily; may increase by 5 mg increments at weekly intervals Patients already using methylphenidate: initiate dexmethylphenidate at half (1/2) the current total daily dose of racemic methylphenidate Patients already using dexmethylphenidate immediate-release tablets: switch to the same daily dose ADHD (Tablet): ≥6 years of age: Methylphenidate naïve patients: 2.5 mg twice daily; may increase by 2.5-5 mg increments at weekly intervals	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

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	methylphenidate	Patients already using methylphenidate: initiate dexmethylphenidate at half (1/2) the dose of racemic methylphenidate	
Methylphenidate	ADHD: Capsule ER (Metadate CD®): Initial, 20 mg once daily in the morning; may increase in 10-20 mg increments at weekly intervals Capsule ER (Ritalin LA®): Initial, 20 mg once daily in the morning; may increase in 10 mg increments at weekly intervals Solution (Methylin®), tablet (Ritalin®, Methylin®): Initial, administer in divided doses 2 or 3 times daily. Average dosage is 20 to 30 mg daily. Some patients may require 40 to 60 mg daily. In others, 10 to 15 mg daily will be adequate. Tablet ER Osmotic (Concerta®): Initial, 18-36 mg once daily; may increase in 18 mg increments at weekly intervals Tablet SR (Ritalin SR®, Metadate ER®): SR tablets may be used in place of IR tablets when the 8-hour dosage of SR tablets corresponds to the titrated 8-hour dosage of IR tablets. Transdermal patch (Daytrana®): 10 mg (week 1), 15 mg (week 2), 20 mg (week 3), 30 mg (week 4); titrate to effect. Apply 2 hours before an effect is needed and remove 9 hours after application. Narcolepsy: Solution (Methylin®), tablet (Ritalin®, Methylin®): Initial, administer in divided doses 2 or 3 times daily. Average dosage is 20 to 30 mg daily.	ADHD: ≥6 years of age: Capsule ER (Metadate CD®): Initial, 20 mg once daily in the morning; may increase in 10-20 mg increments at weekly intervals Capsule ER (Ritalin LA®): Initial, 20 mg once daily in the morning; may increase in 10 mg increments at weekly intervals Solution (Methylin®), tablet (Ritalin®, Methylin®): Initial, 5 mg twice daily; may increase in 5-10 mg increments at weekly intervals Tablet ER Osmotic (Concerta®): Initial, 18 mg once daily; may increase in 18 mg increments at weekly intervals Tablet SR (Ritalin SR®, Metadate ER®): SR tablets may be used in place of IR tablets when the 8-hour dosage of SR tablets corresponds to the titrated 8-hour dosage of IR tablets. Transdermal patch (Daytrana®): 10 mg (week 1), 15 mg (week 2), 20 mg (week 3), 30 mg (week 4); titrate to effect. Apply 2 hours before an effect is needed and remove 9 hours after application. Narcolepsy: ≥6 years of age: Solution (Methylin®), tablet (Ritalin®, Methylin®): Initial, 5 mg twice daily;	Capsule (ER): 10 mg 20 mg 30 mg 40 mg 50 mg 60 mg Chewable tablet: 2.5 mg 5 mg 10 mg Solution: 5 mg/5 ml 10 mg/5 ml Tablet (ER): 18 mg 27 mg 36 mg 54 mg Tablet (IR): 5 mg 10 mg 20 mg Tablet (SR): 10 mg 20 mg Transdermal patch: 10 mg/9 hours 15 mg/9 hours 20 mg/9 hours 30 mg/9 hours

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Some patients may require 40 to 60 mg daily. In others, 10 to 15 mg daily will be adequate. Tablet SR (Ritalin SR®, Metadate ER®): SR tablets may be used in place of IR tablets when the 8-hour dosage of SR tablets corresponds to the titrated 8-hour dosage of IR tablets.	may increase in 5-10 mg increments at weekly intervals Tablet SR (Ritalin SR®, Metadate ER®): SR tablets may be used in place of IR tablets when the 8-hour dosage of SR tablets corresponds to the titrated 8-hour dosage of IR tablets.	
Modafinil	Narcolepsy: 200 mg once daily in the morning Obstructive Sleep Apnea: 200 mg once daily in the morning Shift Work Sleep Disorder: 200 mg as a single dose 1 hour prior to start of work shift	Safety and efficacy in children have not been established.	Tablet: 100 mg 200 mg
Central Nervous System Agents, Miscellaneous			
Atomoxetine	ADHD: Initial, 40 mg per day; may be increased after a minimum of 3 days to a target total daily dose of approximately 80 mg	ADHD: Children and adolescents ≤70 kg: Initial, 0.5 mg/kg per day; may be increased after a minimum of 3 days to a target total daily dose of approximately 1.2 mg/kg Children and adolescents >70 kg: Initial, 40 mg per day; may be increased after a minimum of 3 days to a target total daily dose of approximately 80 mg	Capsule: 10 mg 18 mg 25 mg 40 mg 60 mg 80 mg 100 mg
Guanfacine	Safety and efficacy have not been established in adults.	ADHD: 6-17 years of age: Initial, 1 mg once daily; adjust in increments of no more than 1 mg/week. Maintain the dose within the range of 1-4 mg once daily, depending on clinical response and tolerability.	Tablet (ER): 1 mg 2 mg 3 mg 4 mg
Sodium oxybate	Narcolepsy: Initial, 4.5 g/night in 2 divided doses; first dose to be given at bedtime after the patient is in bed, and second dose to be given 2.5-4 hours later. Dose may be increased or adjusted in 2-week intervals; maximum, 9 g/day	Safety and efficacy in children have not been established.	Solution: 500 mg/ml

ER=extended-release, IR=immediate-release, SR=sustained-release

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the cerebral stimulants/agents used for ADHD are summarized in Table 17.

Table 17. 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 (ADHD)				
McCracken et al.[65] (2003) AMP-IR (Adderall®) 10 mg daily vs AMP-XR (Adderall XR®) 10-30 mg daily vs placebo	DB, PC, RCT, XO Children 6-12 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.[64] (2000) AMP-IR (Adderall®) 12.5 mg daily vs MPH-IR 25 mg daily vs placebo	DB, PC, PG, RCT Children in grades 1 through 5 diagnosed with ADHD	N=58 3 weeks	Primary: CGI-S (parent and teacher)	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%) in the MPH-IR group received 2 or more doses per day (P=0.003).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Pelham et al.[66] (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 5-12 years of age diagnosed with ADHD	N=25 6 weeks	Primary: Time course and dose-dependent response information	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.
Faraone et al.[68] (2002) AMP-IR (Adderall®) vs MPH-IR	MA Patients diagnosed with ADHD	N=216 (4 trials) 3-8 weeks	Primary: CGI-S (parent, teacher and investigator)	Primary: Combined results showed slightly greater efficacy with AMP-IR versus 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).
Biederman et al.[47] (2002) AMP-XR (Adderall XR®) 10-30 mg daily vs placebo	DB, MC, PC, RCT Children 6-12 years of age diagnosed with ADHD (hyperactive-impulsive or combined subtypes)	N=584 3 weeks	Primary: CGI-S (teachers and parents) Secondary: Variation in responses based on morning and afternoon assessments	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 placebo (P<0.001) at each assessment. The CGI-S teacher scores in the AMP-XR group were statistically

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				significantly improved at all time points compared to those in the placebo group (P<0.001).
Goodman et al.[48] (2005) AMP-XR (Adderall XR®) 10-60 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 treatment 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 treatment groups reported significant improvements in all quality of life measurements (all P<0.0001) measured by the SF-36, including physical functioning and mental health parameters.
Biederman et al.[58] (2002) Atomoxetine 1.2-1.8 mg/kg/day vs placebo	DB, MC, PC, RCT (2 trials) Girls 7-13 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).
Michelson et al.[59] (2001) Atomoxetine 1.2-1.8 mg/kg/day vs placebo	MC, OL, PC, RCT Children 8-18 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 mg/kg/day 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Atomoxetine 1.8 mg/kg showed significant increase in all scales of CHQ (P<0.05).
Kratochvil et al.[104] (2011) Atomoxetine 0.5-1.8 mg/kg/day vs placebo	DB, MC, PC, RCT Children 5-6 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. A total of 40% of children treated with atomoxetine and 22% who received placebo had CGI-I scores much to 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 of moderately or severely ill at the end of the study compared with 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.[60] (2002) Atomoxetine up to 90 mg daily vs placebo	DB, MC, PC, RCT (pooled data) Children 7-13 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 1 and P<0.001 for study 2). 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).
Dittmann et al.[105] (2011) Atomoxetine 0.5 mg/kg/day x 7 days, then 1.2 mg/kg/day (fast	DB, PC, RCT Patients 6-17 years of age ADHD with comorbid oppositional defiant disorder (ODD) or	N=181 9 week	Primary: SNAP-ODD, SNAP-ADHD Secondary: CGI-S	Primary: Treatment with atomoxetine once daily at week 9, using either fast or slow titration to a target dose=1.2 mg/kg/day, was significantly better than placebo in reducing ODD symptoms measured by SNAP-ODD scores (P<0.001). Comparing fast and slow titration separately, the decrease in ODD

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
titration) vs atomoxetine 0.5 mg/kg/day x 7 days, then 0.8 mg/kg/day x 7days, then 1.2 mg/kg/day (slow titration) vs placebo	conduct disorder (CD)			symptoms severity was significant for both individual titration groups (atomoxetine-fast: 8.6, 95% CI: 7.2-9.9; atomoxetine-slow: 9.0, 95% CI: 7.7-10.3; placebo: 12.0, 95% CI: 10.6-13.5). Atomoxetine was significantly more effective than placebo in reducing the severity of ADHD symptoms measured by SNAP-ADHD scores. Scores reflecting severity of CD symptoms, attention-deficit and disruptive behavior, were significantly reduced after 9 weeks of atomoxetine treatment. 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 3 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.[103] (2009) Atomoxetine 0.5-1.4 mg/kg/day	OL, PRO Children 6-17 years of age diagnosed with ADHD who had a prior trial of stimulant treatment	N=34 6 weeks	Primary: ADHD-RS, CGI	Primary: There was a significant reduction in ADHD RS symptoms compared with 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. Commonly reported adverse events (>10%) included gastrointestinal problems, headache and sedation.
Adler et al.[46] (2008)	OL, MC	N=384	Primary: CAARS-Inv:SV	Primary: The mean CAARS-Inv:SV Total ADHD Symptom scores decreased

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Atomoxetine 60-120 mg/day	Adults diagnosed with ADHD	4 years	Total ADHD Symptom score Secondary: CAARS-Self:SV, CGI-ADHD-S, $HAMD_{17}$, HAMA, WRAADDS, and Sheehan Disability Scale	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; both P<0.001). Sheehan Disability Scale total and subscale scores improved 25.3% (-3.8, P<0.001). A slight increase was noted in $HAMD_{17}$ 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). Heart rate, diastolic blood pressure, and systolic blood pressure increased. Weight loss over the course of the study was statistically significant (-0.94 kg, P<0.001).
Biederman et al.[71] (2006) Atomoxetine 0.5-1.2 mg/kg daily vs AMP-XR (Adderall XR®) 10-30 mg daily	DB, FD, MC, RCT Girls 6-12 years of age diagnosed with ADHD	N=57 18 days	Primary: SKAMP-A SKAMP-D Academic testing Secondary: Adverse events	Primary: 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				were of mild or moderate severity.
Kemner et al.[81] (2005) Atomoxetine 0.5 mg/kg once daily vs MPH-ER (Concerta®) 18 mg once daily	MC, OL, PRO, R Children 6-12 years of age diagnosed with ADHD	N=1,323 3 weeks	Primary: Investigator-related ADHD-RS and CGI-I, performed at weeks 1, 2, and 3; parental satisfaction questionnaire (PSQ)	Primary: The ADHD-RS change from baseline measured at each time point showed that both treatments were effective. Methylphenidate ER produced significantly greater improvements in ADHD-RS scores at weeks, 1, 2, and 3 (P<0.001). At week 3, rates of treatment response (i.e., ≥25% reduction in ADHD-RS score) were significantly greater with methylphenidate ER than were seen with atomoxetine (P<0.001). Significantly more children treated with methylphenidate ER than with atomoxetine achieved a CGI-I score of ≤2 after week 3 (P<0.001). Parent-rated PSQ scores revealed statistically significantly greater improvements with methylphenidate ER than with atomoxetine.
Newcorn al.[42] (2008) Acute Comparison Trial Atomoxetine 0.8-1.8 mg/kg/day administered twice daily vs MPH-ER (Concerta®) 18-54 mg once daily vs placebo	RCT, DB, PC, XO Children 6-16 years of age diagnosed with ADHD (any subtype)	Acute Comparison Trial N=516 6 weeks Crossover 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). Crossover 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 crossover trial. Of the 69 patients who did not respond to atomoxetine in the second trial,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Crossover Trial Atomoxetine 0.8-1.8 mg/kg/day administered twice daily Patients on MPH-ER were switched to atomoxetine during the crossover 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.[82] (2005) Atomoxetine 0.5 mg/kg once daily vs MPH-ER (Concerta®) 18 mg once daily	OL, RCT African-American children 6-12 years of age diagnosed with ADHD	N=183 3 weeks	Primary: Investigator-related ADHD-RS and CGI-I, performed at weeks 1, 2, and 3; parental satisfaction questionnaire (PSQ)	Primary: For the ADHD-RS scores, both treatment groups achieved significant improvements from baseline at all time points (P<0.001). Improvements from baseline, defined as ADHD-RS score reductions of ≥30% or ≥50%, were significantly greater in the methylphenidate ER group starting at week 3 (P<0.03 for ≥30% reduction, P<0.006 for ≥50% reduction). Significantly more children treated with methylphenidate ER than atomoxetine achieved a CGI-I score of ≤2 after week 3 (P<0.01). Parent-rated PSQ scores revealed statistically significantly greater improvements with methylphenidate ER than with atomoxetine.
Wang et al.[72] (2007) Atomoxetine 0.8-1.8 mg/kg/day vs MPH-IR 0.2-0.6 mg/kg/day in two divided doses	DB, MC, RCT Children 6-16 years of age diagnosed with ADHD	N=330 8 weeks	Primary: ADHD-RS Secondary: CPRS-RS, CGI-S TEAEs, weight	Primary: Atomoxetine was not significantly different than methylphenidate in improving ADHD symptoms based on ADHD-RS scores (atomoxetine, 77.4%; methylphenidate, 81.5%; P=0.404). Secondary: Both atomoxetine and MPH-IR treatment groups significantly improved CPRS-RS and CGI-S scores from baseline (all P<0.001), the groups were not statistically significant from each other in both measures (P>0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				TEAEs that occurred significantly more frequently in the atomoxetine group, compared with the methylphenidate 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 8 weeks compared to those in the methylphenidate group (-1.2 kg vs -0.4 kg; P<0.001).
Kratochvil et al.[80] (2002) Atomoxetine titrated up to 2 mg/kg/day vs MPH-IR titrated up to 60 mg daily	HTH, MC, OL Boys 7-15 years of age and girls 7-9 year of age diagnosed with ADHD	N=228 10 weeks	Primary: ADHD-RS Secondary: CPRS-R, CGI-S, side effects	Primary: Both atomoxetine and MPH-IR were associated with marked 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 blood pressure were seen with both atomoxetine and MPH-IR (P<0.05). The authors state that these changes were incremental and unlikely to be clinically important.
Sutherland et al.[116] (2012) Atomoxetine 40-100 mg/day vs atomoxetine 40-100 mg/day and buspirone 15-45 mg/day	DB, MC, PC, RCT Men and women 18-60 years of age diagnosed with ADHD	N=241 8 weeks	Primary: AISRS	Primary: There was a significantly greater decrease in the AISRS total score for atomoxetine + buspirone than placebo at weeks 1-7, with an estimated mean difference -4.80 (P=0.001). There was a greater decrease in the AISRS total score for atomoxetine + buspirone than for atomoxetine at weeks 1-7, but only statistically significant at week 4 (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 + buspirone treatment

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				group. Discontinuations due to treatment-related adverse events were 15.5% for atomoxetine + buspirone, 11.3% for atomoxetine, and 14.9% for placebo.
Prasad et al.[62] (2007) Atomoxetine 0.5-1.8 mg/kg/day vs standard current therapy (SCT)	MC, OL, RCT Children 7-15 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 SCT 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 SCT group (all P<0.001). The atomoxetine group was significantly better in improving the HSPP Social Acceptance domain over the SCT 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.[61] (2007) Atomoxetine vs placebo	MA Patients diagnosed with ADHD	N=1,828 (9 trials) Variable duration	Primary: ADHD-RS Secondary: CTRS-RS, CPRS-RS, CGI-S, CHQ	Primary: Atomoxetine significantly improved ADHD-RS scores compared to placebo (all P<0.01). Secondary: Atomoxetine significantly improved CTRS-RS, CPRS-RS, and CGI-S scores compared to placebo (all P<0.01). Atomoxetine significantly improved quality of life as measured by the CHQ compared to placebo (P<0.01).
Hazell et al.[110] (2003) CLON 0.1-0.2 mg/day	PC, RCT, TB Children 6-14 years of age with ADHD and co-morbid oppositional defiant	N=67 6 weeks	Primary: CBC (subscales conduct and hyperactive index)	Primary: Significantly more children treated with clonidine than placebo improved on the CBC-Conduct scale (21 of 37 versus 6 of 29; P<0.01) but not the Hyperactive Index (13 of 37 versus 5 of 29; P=0.16). Compared with placebo, clonidine was associated with a greater

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	or conduct disorder			reduction in standing systolic blood pressure 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 with placebo.
Jain et al.[108] (2011) CLON-XR 0.2 mg/day vs CLON-XR 0.4 mg/day vs placebo	RCT, DB, PC Children and adolescents 6-17 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, TEAEs	Primary: Improvement from baseline to week 5 in ADHD-RS total score was significantly greater in both CLON-XR groups versus placebo (P<0.001). A significant improvement in ADHD-RS total score occurred beginning week 1 for the CLON-XR 0.2-mg/day group (P=0.02) and week 2 for the CLON-XR 0.4-mg/day group (P<0.0001) as compared to placebo and continued throughout the treatment period. Secondary: A significant improvement in mean change in ADHD-RS inattention score at week 5 versus baseline was -7.7 for both CLON-XR groups versus -3.4 for the placebo group (P<0.001 for CLON-XR 0.2 mg/day; P<0.006 for CLON-XR 0.4 mg/day). Improvements from baseline to week 5 in ADHD-RS hyperactivity score were -4.1 in the placebo group, -7.9 in the CLON-XR 0.2-mg/day group, and -8.8 in the CLON-XR 0.4-mg/day group (P<0.0012). Mean improvement in CPRS-R total score was significantly greater than placebo in both CLON-XR groups (P<0.01) at weeks 3 and 5. Improvement in CGI-S and CGI-I from baseline to week 5 was significantly greater in both treatment groups versus 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 versus placebo was observed at week 2 (P<0.001) and was maintained through week 7 (P<0.02) in the CLON-XR

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				0.2-mg/day group and through week 5 in the CLON-XR 0.4-mg/day group (P<0.009). The most common TEAE was mild-to-moderate somnolence. Changes on electrocardiogram were minor and due to the pharmacology of clonidine.
Kollins et al.[122] (2011) CLON-XR 0.1 to 0.4 mg/day + psychostimulant vs placebo + 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 5, study patients in the CLON-XR + psychostimulant group experienced a greater improvement in ADHD-RS total score compared to patients in the placebo + 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 CLON-XR + psychostimulant group compared with the placebo + psychostimulant group. The most commonly TEAEs reported were mild to moderate in severity and included somnolence, headache, fatigue, upper abdominal pain, and nasal congestion.
Wigal et al.[67] (2004) DXM (Focalin®) 2.5-10 mg twice daily vs MPH-IR 5-20 mg twice daily vs placebo	DB, MC, PC, RCT Children 6-17 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 3:00 P.M. and 6:00 P.M. assessments compared to placebo (P<0.0001 and P=0.0003 respectively). The MPH-IR group significantly decreased 3:00 P.M. SNAP-P assessments compared to placebo (P=0.0073) but did not reach statistical significance at the 6:00 P.M. 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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.[49] (2006) DXM-XR (Focalin XR®) 5-30 mg daily vs placebo	DB, MC, PC, RCT Children 6-17 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% vs 11.9%, P<0.001). 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.[50] (2007) DXM-XR (Focalin XR®) 20-40 mg daily vs placebo	DB, MC, PC, RCT Adults 18-60 years of age diagnosed with ADHD (any subtype), childhood onset of symptoms, and a baseline ADHD-RS score of ≥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 of ≥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%. All doses DXM-XR significantly improved CGI-I scores over placebo (all P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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 reported as "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 (all P<0.05). None of the groups improved Q-LES-Q scores from baseline nor were there significant differences between groups.
Adler et al.[113] (2009) DXM-XR (Focalin XR®) 20-40 mg/day vs placebo After completion of double-blind phase, patients could enter an OL extension phase with flexible dosing 20-40 mg/day for 6 months.	DB, MC, RCT Men and women 18-60 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%), and decreased appetite (17.6%). Most adverse events were considered mild or moderate by the study investigator. Secondary: 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.
Stein et al.[128] (2011) DXM-XR (Focalin XR®)	DB, PC, RCT Children and adolescents 9-17 years of age with	N=56 8 weeks	Primary: ADHD-RS, CGI-I, CGI-S, WFIS, SSERS	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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
10-30 mg/day vs AMP-XR (Adderall XR®) 10-30 mg/day	ADHD			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 (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.
Muniz et al.[112] (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	DB, MC, RCT Children 6-12 years of age diagnosed with ADHD and stabilized on MPH for at least 2 weeks	N=84 10 weeks	Primary: SKAMP	Primary: Mean change in combined SKAMP score at 2 hours post-dose was significantly larger for MPH-ER 20 mg/day versus MPH-ER 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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(Concerta®) 54 mg/day vs placebo				
Scahill et al.[111] (2001) Guanfacine 0.5 mg at bedtime, day 4 added 0.5 mg in the morning, day 8 added 0.5 mg afternoon dose vs placebo	DB, PC, PG, RCT Children 7-15 years of age diagnosed with ADHD and tic disorder	N=34 8 weeks	Primary: ADHD-RS, CGI-I, CPRS-R (hyperactivity index), YGTSS, CPT	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 with 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 with 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 blood pressure and pulse.
Kollins et al.[130] (2011) GXR 1 to 3 mg once daily vs	DB, MC, PC, RCT Children and adolescents 6-17 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 GXR 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). GXR treatment was associated with significant improvement in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				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.[93] (2009) GXR 1 to 4 mg once daily vs placebo	RCT, DB, MC, PC Patients 6 to 17 years of age with ADHD and a baseline score of 24 on the ADHD Rating Scale-IV	N=324 9 weeks	Primary: ADHD Rating Scale IV (ADHD-RS-IV) total score Secondary: CPRS-R, CGI-I, and PGA	Primary: The mean reduction in ADHD-RS-IV total scores from baseline to endpoint across all GXR dose groups was -19.6 compared with -12.2 for placebo. 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 GXR 1 mg, 2 mg, 3 mg, 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 GXR 1 mg, 2 mg, 3 mg, 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 GXR 1 mg, 2 mg, 3 mg, and 4 mg, respectively. Secondary: Using placebo-adjusted LS mean differences in change from baseline at endpoint in CPRS-R total scores, the 4 mg GXR dose demonstrated significant efficacy at 8 hours (-10.2; P=0.004) and 12 hours (-7.5; P=0.04). The 3 mg GXR dosage group demonstrated significant improvements in CPRS-R results at 8 (-11.8; P=0.002), 12 (-9.6; P=0.01), and 14 hours (-9.8; P=0.0156) postdose. The 2 mg GXR dosage group demonstrated significant improvements in CPRS-R scores at 8 hours (-9.0; P=0.01) postdose. For the 1 mg GXR dosage group, the placebo-adjusted LS mean differences in CPRS-R at 8, 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 improvement were 30% (placebo), 54% (GXR 1 mg; P=0.007 vs placebo), 43% (GXR 2 mg; P=0.1404 vs placebo), 55% (GXR 3 mg;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				P=0.006 vs placebo), and 56% (GXR 4 mg; P=0.004 vs placebo). Improvements in PGA scores were 30% (placebo), 51% (GXR 1 mg; P=0.030 vs placebo), 36% (GXR 2 mg; P=0.4982 vs placebo), 62% (GXR 3 mg; P=0.002 vs placebo), and 57% (GXR 4 mg; P=0.0063 vs placebo). Mild to moderate treatment-emergent adverse events (TEAEs) in patients taking GXR 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 GXR. GXR was not associated with abnormal changes in height or weight. Systolic BP (SBP), diastolic BP (DBP), and pulse rate (PR) decreased as the GXR 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 GXR randomized dose groups.
Sallee et al.[94] (2009) GXR 1 to 4 mg once daily	OL, ES Patients 6 to 17 years of age with ADHD and a baseline score of 24 on the ADHD Rating Scale-IV	N=257 24 months	Primary: ADHD-RS-IV, CPRS-R, CGI-I, CHQ-PF50, CTRS-R, and PGA	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 (AEs). 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 diastolic blood pressure (DBP) was found in 3.5% of patients, decreased blood pressure in 2.7% of patients, and decreased systolic BP in 2.3% of patients. Decreased appetite (13.2%), irritability (13.2%), and pharyngitis (11.3%) were among the most common treatment-emergent AEs that differed in the subgroup coadministered psychostimulants relative to monotherapy or the overall safety population. Mean changes in ADHD-RS-IV total score from baseline to end point

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				showed significant improvement: overall, -20.1 (P<0.001), and for all GXR dose groups, -23.8, -22.5, -20.0, and -18.4 for the 1 mg, 2 mg, 3 mg, 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).
Connor et al.[95] (2010) GXR 1 to 4 mg once daily vs placebo	RCT, DB, PC, MC Patients 6–12 years of age with a diagnosis of attention-deficit hyperactivity disorder (ADHD) and the presence of oppositional symptoms	N=217 9 weeks	Primary: Change from baseline to endpoint in the oppositional subscale of the CPRS-R:L Secondary: Change in ADHD-RS-IV total score and safety	Primary: The mean change from baseline in the oppositional subscale of the CPRS-R:L was -10.9 for those receiving GXR and -6.8 for those receiving placebo (P<0.001). The mean percentage reductions from baseline were 56.3% with GXR 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 GXR compared with 11.5 for placebo (P<0.001). The mean percentage reductions from baseline were 56.7% with GXR and 26.5% with placebo (P<0.001). Adverse events (AEs) were reported in 84.6% of those receiving GXR group and 60.3% of those receiving placebo. Treatment-emergent AEs (TEAEs) occurred more frequently with GXR than with placebo (83.8% vs 57.7%, respectively). The most common TEAEs in the GXR group were somnolence (50.7%), headache (22.1%), sedation

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(13.2%), upper abdominal pain (11.8%) and fatigue (11.0%).
Biederman et al.[89] (2008) GXR 2 to 4 mg once daily vs placebo	RCT, DB, MC, PC Patients 6 to 17 years of age with ADHD combined subtype, predominantly inattentive subtype, or predominantly hyperactive-impulsive subtype	N=345 8 weeks	Primary: ADHD Rating Scale IV (ADHD-RS-IV) total score observed during the last treatment week of the dosage escalation period (weeks 1–5) Secondary: CGI-S, CGI-I, PGA, CPRS-R, and CTRS-R observed during the last treatment week of the dosage escalation period (weeks 1–5)	Primary: The mean reduction in ADHD-RS-IV score at end point across all GXR groups was -16.7 compared with -8.9 for placebo. Placebo-adjusted LS mean end point changes from baseline in the GXR 2 mg, 3 mg, 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 GXR 2 mg, 3 mg, 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 GXR 2 mg, 3 mg, and 4 mg groups, respectively. Improvement in CGI-I scores was significant in the GXR 2 mg group compared with the placebo group by week 2 (P=0.0194) and in all GXR groups by week 3 continuing through week 5 (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 GXR 2 mg, 3 mg, 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 mg, 3 mg, and 4 mg doses, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The most commonly reported treatment-emergent adverse events (TEAEs) were somnolence, fatigue, upper abdominal pain and sedation. The incidence of somnolence in patients who were receiving GXR 1 mg, 2 mg, 3 mg, and 4 mg doses was 12.7%, 11.4%, 20.9%, and 17.5%, respectively. Systolic BP (SBP), diastolic BP (DBP), and pulse rate decreased as GXR 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 GXR 2 mg, 3 mg, 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 3 and 5), and -10.1 mm Hg (week 4) and -7.1 mm Hg (week 4), respectively. The greatest mean changes from baseline in pulse rate for patients who were receiving GXR 2 mg, 3 mg, and 4 mg doses were -5.7 beats per minute (bpm; week 3), -8.1 bpm (week 3), and -8.0 bpm (week 4), respectively. Mean changes in height and weight from baseline to end point were not significant across the treatment groups.
Biederman et al.[90] (2008) GXR 2 to 4 mg once daily	OL, ES Patients 6 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 (AEs). Changes from baseline to endpoint in systolic blood pressure, diastolic blood pressure, and pulse rate were -0.8 mm Hg, -0.4 mm Hg, and -1.9 beats per minute (bpm), 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% 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 with 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.[92] (2009) GXR 1 to 4 mg once daily added to existing stimulant therapy	MC, OL Patients 6 to 17 years of age with ADHD (combined, predominantly inattentive, or predominantly hyperactive-impulsive subtype) and who were on a stable regimen of either methylphenidate (MPH) or amphetamine (AMP) for at least 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	Primary: The most common treatment-related adverse events (AEs) were fatigue (34.7%), headache (33.3%), upper abdominal pain (32.0%), irritability (32.0%), somnolence (18.7%), and insomnia (16.0%). Most AEs were mild to moderate in severity. The incidences of the TEAEs were comparable between both psychostimulant subgroups except for fatigue (28.6% in the GXR+MPH subgroup vs 18.2% in the GXR+AMP subgroup) and irritability (14.3% in the GXR+MPH subgroup vs 33.3% in the GXR+AMP subgroup). Twenty patients have a decrease in blood pressure judged to be of clinical interest. Twelve patients exhibited orthostatic blood pressure decreases. None of the patients with blood pressure decreases reported syncope or lightheadedness. At baseline, the mean Pediatric Daytime Sleepiness Scale (PDSS) score was 15.0. Decreases were observed at visit 6 (-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 Pittsburgh Side Effects Rating Scale (PSERS). There was a decrease in the number of patients with clinically significant loss of appetite and trouble sleeping. The psychostimulant

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				subgroups were generally comparable. Significant decreases from baseline (psychostimulant only) to end point in ADHD-RS-IV total score were observed overall and in both psychostimulant combination subgroups, indicating improvement in ADHD symptoms (overall -16.1, GXR+MPH group -17.8, GXR+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; all P<0.0001). 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).
Wilens et al.[120] (2012) GXR 1-4 mg/day in the morning and placebo at bedtime vs placebo in the morning and GXR 1-4 mg/day in the afternoon vs	DB, MC, PC, RCT Children and adolescents 6-17 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, GXR treatment groups showed significantly greater improvement from baseline ADHD-RS total scores compared with placebo plus psychostimulant (GXR AM, P=0.002; GXR PM, P<0.001). Secondary: Significant benefits of GXR treatment compared to placebo plus psychostimulant were observed on the CGI-S (GXR AM, P=0.013; GXR PM, P<0.001) and CGI-I (GXR AM, P=0.024; GXR PM, P=0.003). At study endpoint, small mean decreases in pulse, systolic, and diastolic blood pressure were observed in GXR treatment groups versus placebo plus psychostimulant.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo Patients continued stable dose of psychostimulant given in the morning.				The most common TEAEs were mild to moderate in severity and included headache, somnolence and upper respiratory infections.
Faraone et al.[91] (2010) GXR 1 to 4 mg once daily	MA Patients 6 to 17 years of age with ADHD (combined subtype, predominantly inattentive subtype, or predominantly hyperactive-impulsive subtype)	N=813 6 to 9 weeks	Primary: Predictors of efficacy and sedation using various models	Primary: Actual Dose Model The presence or absence of ADHD symptoms was influenced by the 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 AEs 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 AEs 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The only significant influence on the frequency of sedation-related AEs was treatment duration (P=0.034).
Biederman et al.[51] (2007) LDX 30-70 mg daily vs placebo	DB, MC, PC, RCT Children 6-12 years of age diagnosed with ADHD and with an ADHD-RS score of ≥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 with placebo (P<0.001). The greatest efficacy was seen in the 70 mg treatment group with a mean ADHD-RS change of –4.91 from baseline between the 30 mg and 70 mg groups (P<0.05). Secondary: Each LDX treatment group significantly improved CPRS-R scores throughout the day compared to placebo (all, P<0.01). Mean CGI-S scale scores significantly improved from baseline to treatment end point for all LDX treatment groups compared with placebo (all, P<0.001). CGI-I ratings were either "very much improved" or "much improved" in ≥70% of patients in the LDX groups compared with 18% of patients in the placebo group (all, P<0.001).
Biederman et al.[52] (2007) LDX 30-70 mg daily vs placebo (AMP-XR 10-30 mg was used as a control arm)	DB, MC, PC, RCT, XO Children 6-12 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 placebo (both, P<0.0001). Secondary: PERMP scores for both the LDX and AMP-XR groups significantly decreased compared to the placebo group (both, P<0.0001). The CGI-I scores significantly improved in the both LDX and AMP-XR compared with placebo (P<0.0001).
Findling et al.[124] (2011) LDX 30-70 mg daily	DB, PC, RCT Adolescents 13-17 years of age diagnosed with	N=314 4 weeks	Primary: ADHD-RS Secondary: CGI-I, YQOL-R,	Primary: Differences in ADHD-RS total scores favored all LDX doses compared with placebo at all weeks (P<0.0076). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	ADHD		TEAEs	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 with placebo. The most common TEAEs for all combined LDX doses included decreased appetite, headache, insomnia, decreased weight, and irritability. The severity of TEAEs was generally mild or moderate Clinically insignificant mean increases in pulse, blood pressure and ECG changes were noted with LDX.
Findling et al.[98] (2008) LDX 30-70 mg daily	MC, OL, SA Children 6-12 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 4 weeks, improvements in ADHD-RS scores were maintained throughout 11 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 blood pressure or electrocardiographic parameters.
Weisler et al.[99] (2009) LDX 30-70 mg daily	DB, PC, RCT, SA Adults aged 18-55 years of age diagnosed with	N=349 12 months	Primary: ADHD-RS Secondary: CGI-S, CGI-I	Primary: Mean ADHD-RS total scores improved at week 1 of treatment and sustained throughout the 11 month treatment period (P<0.001). Mean ADHD-RS total scores improved by 24.8 points from baseline to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	ADHD			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 1, 2, 3, and 4, 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 investigator. Small but statistically significant increases in pulse and blood pressure noted at treatment endpoint.
Wigal et al.[106] (2011) MPH-ER (Concerta®) 18-54 mg daily vs placebo	DB, PC, RCT Children 9-12 years of age diagnosed with ADHD	N=78 5 months	Primary: PERMP, SKAMP, TOVA, Finger Windows forward and backward subtest	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 placebo-treated children 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.
Casas et al.[126] (2011) MPH-ER	DB, MC, PC, RCT Men and women 18-65 years of age	N=279 13 weeks	Primary: CAARS-Inv: SV Secondary:	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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(Concerta®) 54- 72 mg/day vs placebo	diagnosed with ADHD		CGI-S, CGI-C, CAARS-Self: SV, SDS, AIMA-A	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. 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.
Wilens et al.[53] (2004) MPH-ER (Concerta®) 18-54 mg daily	MC, OS, PRO Children 6-13 years of age diagnosed with ADHD	N=432 1 year	Primary: Heart rate (HR) and blood pressure after 1 year	Primary: Compared to baseline, MPH-ER was associated with minor clinical, although statistically significant, diastolic blood pressure elevations (1.5 mm Hg, P<0.001), systolic blood pressure elevations (3.3 mm Hg, P<0.001) and HR (3.9 bpm, P<0.0001) at the 12-month end point.
Mattos et al.[129] (2012) MPH-ER (Concerta®) 18-72 mg/day	MC, OL Men and women 18-65 years of age diagnosed with ADHD	N=60 12 weeks	Primary: ASRS, AAQoL, STAI, HAM-D, CGI-I	Primary: ADHD symptom severity improved with the ASRS scores (total score, inattention and hyperactivity) significantly reduced from baseline, to weeks 4, 8 and 12 (P<0.001). AAQoL subscales (P<0.001), as well as AAQoL total score (P<0.001),

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				significantly improved from baseline to week 12. A significant reduction in STAI, CGI-I, and HAM-D, 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.
Cox et al.[74] (2006) MPH-ER (Concerta®) 36 mg once daily on days 1-5, then 72 mg once daily on days 6-17 vs AMP-XR (Adderall XR®) 15 mg once daily on days 1-5, then 30 mg once daily on days 6-17 vs placebo	DB, PC, RCT, XO Adolescents 16-19 years of age diagnosed with ADHD and licensed to drive	N=35 21-38 days	Primary: Impaired Driving Score (IDS), assessed using an Atari Research Driving Simulator on days 10 and 17; subjective ratings of driving performance by participants and investigators	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 (P=0.008).
Yang et al.[118] (2011) MPH-ER 18-54 mg/day	RCT, SB Children and adolescents 7-14 years of age diagnosed with	N=142 4-6 weeks	Primary: Rey Complex Figure Test (RCFT), Digit span, Stroop color word test	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs atomoxetine 0.5-1.4 mg/kg/day	ADHD			Although word interference time was more improved than the control group, there was no statistically significant difference (P>0.05).
Wolraich et al.[73] (2001) MPH-ER (Concerta®) 18-54 mg daily vs MPH-IR 5-15 mg three times daily vs placebo	DB, PC, PG, RCT Children 6-12 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 1 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 treatment groups at week 1 (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. CGI-I scores significantly improved in the MPH-ER and MPH-IR groups compared with placebo (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 placebo (P<0.001).
Pelham et al.[75] (2001) MPH-ER (Concerta®) 18-54 mg daily vs MPH-IR 5-15 mg	DB, PC, RCT, XO Children 6-12 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)	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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
three times daily vs placebo				
Gau et al.[70] (2006) MPH-ER (Concerta®) 18-36 mg daily vs MPH-IR 5-10 mg three times daily	OL, RCT Children 6-15 years of age diagnosed with ADHD (any subtype) who were taking MPH (10-40 mg daily)	N=64 28 days	Primary: CTRS-RS, CPRS-RS, SKAMP-A, SKAMP-D Secondary: SAICA, CGI	Primary: Each of the 4 treatment groups displayed a significant decrease in all measures of CTRS-RS, CPRS-RS, SKAMP-A, SKAMP-D at each of the follow-up visits (all P<0.001) compared to baseline, but there were no significant differences between the treatment groups (all P>0.05). 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). 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.[76] (2003) MPH-ER (Concerta®) 18-36 mg daily vs MPH-XR (Ritalin LA®) 20 mg daily	DB, PC, RCT Children 6-12 years of age diagnosed with ADHD who were previously stabilize on MPH (equivalent dose of 10 mg twice daily)	N=36 28 days	Primary: SKAMP scales	Primary: Both MPH-ER and MPH-XR statistically improved SKAMP scale scores compared to placebo (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				
Swanson et al.[77] (2004) MPH-ER (Concerta®) 18-54 mg daily vs MPH-XR (Metadate CD®) 20-60 mg daily vs placebo	DB, MC, PC, RCT, XO Children 6-12 years of age diagnosed with ADHD (inattentive type, hyperactive-impulsive type, or combined type) being treated with MPH in doses of 10-60 mg daily	N=184 7 weeks	Primary: SKAMP scales, PERMP	Primary: MPH-ER and MPH-XR demonstrated similar efficacy, and both were better than placebo in SKAMP and PERMP scores (P<0.016).
Silva et al.[79] (2005) MPH-ER (Concerta®) 18 mg vs MPH-ER (Concerta®) 36 mg vs methylphenidate extended-release (ER-MPH) 20 mg	MC, RCT, SB, XO Children 6-12 years of age diagnosed with ADHD and stabilized on MPH (20-40 mg/day)	N=54 6 weeks	Primary: SKAMP-A rating subscale Secondary: SKAMP-D and SKAMP-C rating subscales and written math tests	Primary: 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 mg and 40 mg showed significantly greater differences from predose on the SKAMP-A than did methylphenidate ER, 36 mg at 2 hours postdose, and also when scores were integrated over 0-4 hours (P=0.022 for the 20 mg dose and P=0.001 for the 40 mg dose), but showed no significant improvement over 8-12 hours. Secondary: Single morning doses of ER-MPH and methylphenidate 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
vs methylphenidate extended-release (ER-MPH) 40 mg vs placebo All medications were dosed once per study day (6 consecutive Saturdays). Patients continued their regular ADHD medications on Sunday through Thursday of the study weeks, with no medications allowed on Friday.				
Jahromi et al.[96] (2009) MPH-IR 0.125 mg/kg/dose BID for 1 week (low dose) vs MPH-IR 0.25 mg/kg/dose BID	DB, RCT, XO Children 5-13 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	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 with 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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
for 1 week (medium dose) vs MPH-IR 0.50 mg/kg/dose BID for 1 week (high dose) vs placebo for 1 week				No significant improvement in self-regulation behaviors for the clean-up task for any of the three dose levels of MPH compared with 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 (<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>05).
Spencer et al.[101] (2011) MPH-IR 3 times daily vs MPH-ER once daily (OROS-MPH)	PG, RCT, SB Patients 19-60 years of age diagnosed with ADHD who were on stable therapy with MPH-IR	N=61 6 weeks	Primary: AISRS	Primary: MPH-IR responders randomized to MPH-IR or OROS-MPH 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 OROS-MPH remained satisfied over 71% of the time. MPH-IR treatment group missed significantly more doses than the OROS-MPH treatment group (7.3 vs 3.3; P=0.02).
Efron et al.[69] (1997) MPH-IR 0.3 mg/kg/dose twice daily vs DEX-IR 0.15 mg/kg/dose twice daily	DB, RCT, XO Children 5-15 years of age diagnosed with ADHD	N=125 4 weeks	Primary: SERS	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Patients received 1 drug for 2 weeks then crossed over to the other stimulant for 2 weeks.				
Pelham et al.[78] (1990) MPH-IR 10 mg twice daily vs MPH-SR (Ritalin SR®) 20 mg daily vs DEX-SR (Dexedrine®) 10 mg daily vs pemoline 56.25 mg daily vs placebo	DB, PC, RCT, XO Boys 8-13 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	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 2 hours, and the effects lasted for 9 hours vs placebo (P<0.025).
Palumbo et al.[109] (2008) MPH-IR 5-60 mg/day	DB, MC, PC, RCT Children 7-12 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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs CLON 0.05-0.6 mg/day vs MPH-IR and CLON vs placebo				Secondary: Study patients treated with CLON had greater improvements on the CASQ-P and CGAS, but a higher rate of sedation compared with patients not treated with clonidine.
Greenhill et al.[54] (2002) MPH-XR (Metadate CD®) 20-60 mg daily vs placebo	DB, MC, PC, RCT Children 6-16 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 versus 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 1 adverse event vs 38% from the placebo group (P=0.014). The rate of anorexia was more significant in the MPH-XR group versus placebo (9.7% vs 2.5%, P=0.007).
McGough et al.[55] (2006) Methylphenidate transdermal system	RCT, OL (first 5 weeks) then DB, PC Children 6-12 years of age diagnosed	N=80 7 weeks	Primary: Evaluate time course effects of MTS vs PTS via SKAMP-A,	Primary: Mean SKAMP-D scores were improved with MTS 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
(MTS) 10-27 mg daily vs placebo transdermal system (PTS)	with ADHD		SKAMP-D, PERMP, ADHD-RS-IV, CPRS-R, CGI-I, and PGA rating scales Secondary: Acute efficacy and tolerability of MTS	Mean (SKAMP-A) scores were improved with MTS 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 MTS 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 MTS vs placebo (P<0.0001). Those in the MTS group (79.8%) were more likely to be deemed improved on clinician rated CGI-I scores vs placebo (79.85% and 11.6%, respectively; P<0.0001). Statistically significant differences were observed with PGA ratings; 71.1% of MTS participants and 15.8% of placebo participants were rated as improved (P<0.0001). Secondary: More treatment-emergent adverse events were recorded with MTS therapy (39 events, 24 participants) vs placebo (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.[56] (2005) Methylphenidate transdermal system (MTS): 6.25 cm^2 (0.45 mg/hour), 12.5 cm^2 (0.9 mg/hour), and 25 cm^2 (1.8 mg/hour),	DB, DR, MC, RCT Children 7–12 years of age diagnosed with ADHD	N=36 8 days	Primary: MTS efficacy and influence of exposure time on morning effects	Primary: All doses of MTS 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 MTS patches were observed at all time points after application of the patch and were still seen for 3 hours after the patch had been removed (i.e., throughout the 12-hour assessment). Incidence of skin rash was reported as 40%-50%.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
worn for at least 12 hours daily Each participant received single applications of MTS 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).				
Pelham et al.[57] (2005) Methylphenidate transdermal system (MTS): 12.5 cm^2, 25 cm^2, and 37.5 cm^2 plus behavior modification (BMOD) Each participant had 2 days on each treatment without concomitant BMOD and 4 days on each treatment with BMOD.	DR, RCT Children aged 6-12 years diagnosed with ADHD	N=27 6 weeks	Primary: Proportion that reached individual target goals in Daily Report Card (DRC) scores	Primary: The percentage of individualized target criteria met by children in their DRC assessment was significantly (all P<0.05) higher with MTS 12.5 cm^2, 25 cm^2, and 37.5 cm^2 vs placebo, both without BMOD (41.9%, 63.1% and 66.2% vs 20.8%) and with BMOD (73.7%, 87.5% and 86.2% vs 54.7%; all P<0.05). Response rates were higher in the MTS 25 cm^2 group than in the 12.5 cm^2 group, both with and without BMOD (both P<0.05); increasing the size of the patch to 37.5 cm^2 added no further advantage.
Faraone et al.[43] (2009) Methylphenidate transdermal system	RCT, DB, MC, PC Children 6-12 years of age diagnosed with ADHD	N=268 5 weeks	Primary: Children's Sleep Habits Questionnaire (CSHQ)	Primary: 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(MTS) 10-30 mg daily worn for 9 hours per day or MPH-ER (Concerta®) 18-54 mg daily vs placebo	(predominantly hyperactive-impulsive, predominantly inattentive, or combined type)			observed between MTS/MPH-ER and placebo (P≥ 0.554). There was no significant effect of methylphenidate dosage on sleep problems (P=0.135). The effects of each methylphenidate treatment and the various doses of these treatments on each CSHQ subscale were identical to the effects observed for the total CSHQ scale.
Findling et al.[97] (2008) Methylphenidate transdermal system (MTS) 10-30 mg daily or MPH osmotic-release capsule (OROS-MPH) 18-54 mg daily vs placebo	DB, PC, RCT Children 6-12 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 MTS, OROS-MPH, 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 MTS and OROS-MPH compared with placebo (P<0.001). There was a 2-fold improvement of ADHD symptoms in active treatments compared to placebo from baseline to study endpoint. Secondary: MTS and OROS-MPH showed improvements over placebo in mean total parent and teacher scores from baseline to endpoint. More study patients receiving MTS and OROS-MPH compared with placebo were rated as improved by clinicians and parents (P<0.001). Adverse events included decreased appetite, nausea, vomiting and insomnia. Most adverse events were considered mild or moderate by the study investigator.
Faraone et al.[63] (2006) AMP-IR,	MA Patients diagnosed with ADHD	N=2,988 (29 trials) Variable	Primary: Effect sizes	Primary: All of the drugs groups produced a significant measure of effect compared to placebo (P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
AMP-XR, atomoxetine, bupropion, DEX-IR, DEX-ER, DEXM-IR, modafinil, MPH-ER, MPH-IR, MPH-XR, MTS, pemoline		duration		The effect sizes for nonstimulant medications were significantly less than those for immediate-release stimulants (P<0.0001) or long-acting stimulants (P=0.0008). The 2 classes of stimulant medications (short acting and long acting) did not differ significantly from one another (P=0.14).
Schelleman et al.[127] (2011) ADHD medications vs nonusers	RETRO Children 3-17 years of age who were dispensed a prescription for an amphetamine, atomoxetine, or methylphenidate	N=241,417 Variable duration	Primary: Sudden cardiac death, or ventricular arrhythmia, stroke, MI Secondary: All-cause death	Primary: 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: 0.19–13.60) or all-cause death (HR: 0.76; 95% CI: 0.52–1.12). None of the strokes identified during exposed time to ADHD medications were validated. No myocardial infarctions 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– 6.61); stroke (HR, 0.89; 95% CI: 0.11–7.11); stroke/MI (HR, 0.72; 95% CI: 0.09 –5.57); or all-cause death (HR, 0.77; 95% CI: 0.56–1.07).
Olfson et al.[125] (2012) AMP and MPH vs nonusers	RETRO Patients 6 to 21 years of age diagnosed with ADHD who were prescribed AMP or MPH	N=171,126 Variable duration	Primary: Cardiac events (inpatient diagnosis of chest pain, cardiac dysrhythmia or transient cerebral ischemia) and cardiac symptoms (tachycardia,	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 with no stimulant use was not associated with less severe cardiovascular event (adjusted OR, 0.69; 95% CI: 0.42–1.12). Past stimulant use compared with no stimulant use was not associated with less severe cardiovascular event (adjusted OR, 1.18; 95% CI

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			palpitations, or syncope)	0.83–1.66). The adjusted odds ratios for cardiac symptoms were 1.18 (95% CI: 0.89 –1.59) for current and 0.93 (95% CI: 0.71–1.21) for past stimulant use when compared with 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: 0.82–5.63) or symptoms (adjusted OR, 1.08, 95% CI: 0.66 –1.79) for current methylphenidate use compared with amphetamine use.
Schelleman et al.[115] (2012) AMP, atomoxetine, MPH	RETRO Patients 3 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	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: 0.19–13.60) or all-cause death (HR: 0.76; 95% CI: 0.52–1.12). None of the strokes identified during exposed time to ADHD medications were validated. No myocardial infarctions 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– 6.61; stroke: 0.89, 95% CI: 0.11–7.11; stroke/myocardial infarction: 0.72, 95% CI: 0.09 –5.57; and all-cause death: 0.77, 95% CI: 0.56–1.07).
Hanwella et al.[117] (2011) Atomoxetine vs MPH	MA Children and adolescents 6-16 years of age diagnosed with ADHD	N=2,762 (5 trials) Variable duration	Primary: ADHD-RS	Primary: The meta-analysis did not find a significant difference in efficacy between MPH and atomoxetine when comparing standardized mean differences (SMD) in ADHD-RS scores (SMD=0.09; 95% CI -0.08-0.26). There was no significant difference in response rates between the two medications (RR=0.93; 95% CI, 0.76-1.14). Treatment effects between the formulations of MPH showed a

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				significant standardized mean difference in ADHD-RS favoring OROS-MPH (SMD=0.32; 95% CI, 0.12-0.53). MPH-IR was not superior to atomoxetine (SMD=-0.04; 95% CI, -0.19-0.12). There was no significant difference in acceptability between atomoxetine and methylphenidate (RR=1.22; 95% CI, 0.87-1.71).
Bloch et al [131] (2009) ADHD medications	MA Children diagnosed with ADHD and Tourette's	N=77 (11 trials) Variable duration	Primary: ADHD severity (ADHD-RS, CADS-P, CADS-T, CTRS-R) and tic severity (YGTSS, STSSS, HMVTS, and GTSS)	Primary: MPH, alpha-2 agonists, desipramine, and atomoxetine demonstrated efficacy in improving ADHD symptoms in children with co-morbid tics. Alpha-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.
Narcolepsy				
Harsh et al.[45] (2006) Armodafinil 150-250 mg once daily vs placebo	RCT, DB, MC, PC Patients 18-65 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 min from baseline in the 150 mg, 250 mg, and armodafinil combined groups, respectively, and decreased 1.9 min 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 min from baseline in the placebo group. The differences for the armodafinil combined group versus placebo and the 150 mg group versus placebo 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 with placebo (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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				3%, respectively, for placebo. Power of attention was significantly improved in the armodafinil 150 mg/day and armodafinil combined groups compared with placebo at the final visit (P<0.05). There were not significant effects on mean continuity of attention between the treatment groups. 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 with placebo at weeks 8 (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; 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 with 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	DB, MC, PC, RCT	N=283	Primary: ESS	Primary: Both modafinil treatment groups reduced mean ESS scores and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Group[83] (1998) Modafinil 200-400 mg daily vs placebo	Adults 18-68 years of age diagnosed with narcolepsy	9 weeks	Secondary: MSLT, MWT, CGI-C	subjective sleepiness at each time point (weeks 3, 6, and 9) compared to placebo (P<0.001). The two modafinil groups did not differ from each other. Secondary: Mean sleep latency for MSLT significantly increased in both modafinil treatment groups compared to placebo (P<0.001). Modafinil groups did not differ from each other. Mean sleep latencies for MWT significantly increased in each of the modafinil treatment groups compared to placebo (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 treatment 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[84] (2000) Modafinil 200-400 mg daily vs placebo	DB, MC, PC, RCT Adults 17-67 years of age diagnosed with narcolepsy	N=271 9 weeks	Primary: MWT, CGI-C Secondary: MSLT, ESS	Primary: MWT improved for both modafinil groups versus placebo (P<0.001) at each follow-up visit (weeks 3, 6, 9). The percent of patients with improvement in CGI-C scores at week 9 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 versus 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) versus placebo.
Broughton et al.[85] (1997) Modafinil 200-400 mg daily	MC, PC, RCT, XO Patients 27-59 years of age diagnosed with narcolepsy	N=75 6 weeks	Primary: MWT results, patient assessed sleepiness	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 with placebo. There was not a significant difference between modafinil treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo			Secondary: ESS	Both modafinil treatment 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 placebo (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 placebo.
Billiard et al.[86] (1994) Modafinil 100 mg in the morning and 200 mg at noon (or vice versa) vs placebo	DB, MC, PC, RCT, XO Patients 27-54 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 treatment groups compared to placebo (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.[87] (1993) Modafinil 200 mg in morning and 100 mg at noon vs placebo	DB, PC, RCT, XO Patients 31-61 years of age with a history of EDS, cataplexy, at least two sleep onset REM periods and MSLT of <5 minutes	N=10 12 weeks	Primary: Subjectively assessed sleepiness, FCRTT, PLM, nocturnal sleep organization	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=NS).
Thorpy et al.[88] (2003)	OL, RCT Adults 17-65 years	N=40 5 weeks	Primary: ESS, tolerability	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Modafinil 200 - 400 mg/day	of age diagnosed with narcolepsy who had been receiving MPH for EDS for a month			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% in the washout group, and 21% in the taper/titrate group.
U.S. Xyrem Multicenter Study Group[137] (2004) Phase 1 (2 weeks) Continue sodium oxybate at the dose previously prescribed. Phase 2 (2 weeks) 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 3-9 g/day	N=55 4 weeks	Primary: Cataplexy attacks; TEAEs	Primary: During the 2-week double-blind 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.
Xyrem International Study Group[132] (2005) Sodium oxybate 4.5- 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,	Primary: Study patients displayed dose related decreases in median ESS scores and frequency of weekly inadvertent naps, which were significant at the 6 gram and 9 gram doses (for each, P<0.001). Study patients treated with 9 grams of sodium oxybate nightly displayed a significant median increase of >10 minutes in the MWT (P<0.001). Improvements in excessive daytime sleepiness were incremental in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				those study patients who 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.
Xyrem International Study Group[134] (2005) Sodium oxybate 4.5- 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	Primary: Compared to placebo, nightly doses of 4.5, 6 and 9 g of sodium oxybate for 8 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 8 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.
Black et al.[140] (2010) Sodium oxybate 4.5- 9 g/day administered at bedtime	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	Primary: Following 4 weeks (P<0.001) and 8 weeks (P<0.001) of sodium oxybate treatment, study patients demonstrated significant dose-related increases in the duration of stage 3 and 4 sleep, reaching a median increase of 52.5 minutes in patients receiving 9 grams nightly. Compared to placebo-treated patients, delta power was significantly increased in all treatment dose groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				Stage 1 sleep and the frequency of nocturnal awakenings were each significantly decreased at the 6 and 9 gram/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 with placebo. Adverse events were mild to moderate in severity and appeared to be dose-related as documented by study investigators.
Weaver et al.[133] (2006) Sodium oxybate 4.5-9 g/day in 2 divided doses taken at bedtime and again 2.5-4 hours later vs placebo	DB, MC, RCT Patients 16-75 years of age with narcolepsy who were experiencing cataplexy and excessive daytime sleepiness with recurrent episodes for ≥3 months	N=285 4 weeks	Primary: FOCS	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 FOCS (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 6.0-g per day dose of sodium oxybate to large effects for the 9.0 g/day dose.
Wang et al.[136] (2009) Sodium oxybate	RETRO Patients receiving sodium oxybate	N=~26,000 68 months	Primary: Occurrence of abuse/misuse of sodium oxybate	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, 4 cases (0.016%) meeting DSM-IV dependence criteria, 8 cases (0.031%, including 3 of the previous 4) with withdrawal symptoms reported after discontinuation of sodium oxybate, 2 confirmed cases (0.008%) of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				sodium oxybate–facilitated sexual assault, 8 cases (0.031%) of overdose with suicidal intent, 21 deaths (0.08%) in patients receiving sodium oxybate treatment with 1 death known to be related to sodium oxybate, and 3 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 5 incidents (0.0009%) of diversion were reported.
Black et al.[138] (2006) Sodium oxybate 6-9 g/day vs modafinil 200-600 mg/day vs sodium oxybate 6-9 g/day and modafinil 200-600 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 excessive daytime sleepiness	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 8 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 excessive daytime sleepiness as previously administered modafinil. In the sodium oxybate + modafinil group, there was an increase in daytime sleep latency from 10.43 minutes 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 + 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 with the placebo-treated study patients. The placebo and the modafinil-treated study patients demonstrated no significant change in symptoms.
Black et al.[139] (2009)	DB, PC, RCT	N=278	Primary: Sleep architecture,	Primary: Following 8 weeks of treatment, there was no significant change in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Sodium oxybate 6 g/day vs modafinil 200-600 mg/day vs sodium oxybate 6 g/day and modafinil 200-600 mg/day vs placebo	Patients ≥18 years of age with narcolepsy taking modafinil 200-600 mg/day for the treatment of excessive daytime sleepiness (EDS)	8 weeks	MWT	total sleep time for any treatment group. Significant changes in total non-REM sleep among patients receiving sodium oxybate and sodium oxybate + modafinil included a median increase in Stage 3 and 4 sleep (43.5 and 24.25 min, 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 + 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 8 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 + modafinil-treated patients experienced significant improvements in ESS scores (for each, P<0.001). There was no change in ESS scores in the group maintained on modafinil alone.
Obstructive Sleep Apnea (OSA)				
Hirshkowitz et al.[41] (2007) Armodafinil 150 mg/day vs placebo	RCT, DB, MC, PC Patients 18-65 years of age with a diagnosis of obstructive sleep apnea/hypopnea syndrome who complained of residual excessive	N=263 12 weeks	Primary: MWT, CGI-C Secondary: CDR, ESS, BFI	Primary: Armodafinil significantly improved wakefulness compared with placebo. The mean MWT sleep latency increased from baseline by 2.3 min in the armodafinil group and decreased by 1.3 min in the placebo group (P=0.0003). Armodafinil significantly improved MWT sleep latency compared with placebo at each visit (all P<0.01). The proportion of patients with at least ‘‘minimal improvement’’ on

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	sleepiness (ES) during continuous positive airway pressure therapy			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 with 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 (all P<0.01). As assessed on the BFI, armodafinil significantly reduced global fatigue and worst fatigue in the past 24 hours at weeks 4 and 12 and at the final visit compared with placebo (all P<0.05).
Roth et al.[44] (2006) Armodafinil 150-250 mg/day vs placebo	RCT, DB, MC, PC Patients 18-65 years of age with a diagnosis of moderate obstructive sleep apnea/hypopnea syndrome and residual excessive sleepiness (ES) despite effective, regular, and stable use of nCPAP treatment	N=395 12 weeks	Primary: MWT, CGI-C Secondary: ESS, CDR, BFI	Primary: The mean changes in MWT sleep latency across the first 4 tests were significantly greater in the armodafinil 150 mg/day, 250 mg/day, and combined groups compared with placebo at the final visit (all, P<0.001). 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 with placebo (all, P<0.001). 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 with placebo at the final visit (P<0.001). Mean changes in global fatigue scores were significantly greater in the armodafinil combined group compared with placebo at all visits (all, P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The mean change in score for worst fatigue during the past 24 hours was statistically greater in the armodafinil combined group compared with placebo at week 8 (P<0.05). Mean changes in quality of episodic secondary memory score were significantly greater with armodafinil 150 and 250 mg/day compared with placebo at week 4 (both, P<0.05) and with armodafinil 250 mg/day versus placebo at week 8 (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 4 or last 3 sessions at any assessment. At week 8, mean changes in continuity of attention across the first 4 sessions were significantly greater in the armodafinil 150 mg/day, 250 mg/day, and combined groups compared with placebo (all, P<0.05). The most frequently reported adverse event (AE) 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 AEs was generally mild or moderate in patients receiving armodafinil (58.4%) or placebo (46.9%).
Krystal et al.[100] (2010) Armodafinil 200 mg/day vs placebo	DB, PC, PG, RCT Patients 18-65 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: ESS	Primary: The proportion of patients with least minimal improvement on CGI-C was significantly greater in the armodafinil treatment group (69%) compared to placebo (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: Mean ESS scores were significantly reduced in study patients treated with armodafinil (-6.3) compared to placebo (-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 and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				study investigator.
Black et al.[33] (2005) Modafinil 200-400 mg/day vs placebo	DB, MC, PC, RCT Adults 18-70 years of age with obstructive sleep apnea/hypopnea syndrome and having residual excessive sleepiness during continuous positive airway pressure therapy	N=305 12 weeks	Primary: MWT, ESS Secondary: CGI-C, Functional Outcomes of Sleep	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 (each P>0.15). Secondary: At the end of the study, modafinil had significant improvements in CGI-C compared to placebo (P<0.001). Modafinil improved mean Functional Outcomes of Sleep questionnaire scores compared to placebo (P<0.02) for vigilance, general productivity, and activity level.
Weaver et al.[142] (2009) Modafinil 200-400 mg/day vs placebo	DB, MC, PC, RCT (Pooled analysis) Patients 24-76 years of age diagnosed with obstructive sleep apnea (OSA) and residual excessive sleepiness associated with continuous positive airway pressure (CPAP)	N=480 (2 trials) 4 to 12 weeks	Primary: FOSQ	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 with placebo. A greater proportion of patients who received modafinil were considered responders compared with 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 1 point for significantly more patients who received modafinil (P<0.05).
Williams et al.[141] (2010) Modafinil 200 mg/day	DB, RCT, XO Men diagnosed with obstructive sleep apnea (OSA) who	N=21 2 days	Primary: Driving simulation, subjective sleepiness	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	were modafinil-naïve			task (mean 1/reaction time and lapses, both P<0.0002), and subjective sleepiness (P <0.01).
Shift Work Sleep Disorder (SWSD)				
Czeisler et al.[40] (2009) Armodafinil 150 mg daily administered 30-60 minutes before the start of work shift vs placebo	RCT, DB, MC, PC Patients 18-65 years of age who exhibited signs and symptoms of shift work disorder (SWD) of moderate or greater severity, as documented by a CGI-S rating of 4 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 (2-8 AM) by 3.1 minutes to 5.3 minutes compared with an increase of 0.4 minutes 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 with 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 with placebo. Armodafinil significantly improved the mean score for the quality of episodic secondary memory factor compared with placebo at each visit (P<0.001 at weeks 4 and 8; P=0.002 at week 12; P<0.001 at final visit) and during the first 4 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; P=0.006 at 6:30 AM). Armodafinil significantly improved speed of memory from baseline compared with placebo at week 8 (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 and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				study visit (P=0.005 at week 4; P=0.006 at week 8; P=0.005 at week 12; P=0.001 at final visit) and during the first 4 tests on the final night shift compared with 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 with 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.
Czeisler et al.[114] (2012) Armodafinil 150 mg daily administered 30-60 minutes before the start of work shift vs placebo	DB, MC, PG, RCT Patients 18-65 years of age with excessive sleep associated with chronic (≥3 months) shift work disorder (SWD) of moderate or greater severity	N=254 12 weeks	Primary: Sleep propensity during night shift hours, clinical impression of severity, patient-reported sleepiness, and cognitive function	Primary: Armodafinil significantly improved mean sleep latency from 2.3 minutes at baseline to 5.3 minutes at the end of the study, compared with a change from 2.4 minutes to 2.8 minutes in the placebo group (P<0.001). Clinical condition improved in more patients receiving armodafinil (79%) compared to placebo (59%; P=0.001). As reported by study patients' diaries, armodafinil significantly reduced sleepiness during laboratory nights (P<0.001), night shifts at work (P<0.001), and the commute home (P=0.003). Armodafinil improved memory (P<0.001) and attention (power, P=0.001; continuity, P<0.001) compared with placebo. Armodafinil was well tolerated and did not affect daytime sleep.
Tembe et al.[123] (2011) Armodafinil 150 mg administered 1 hour prior to night shift	DB, MC, RCT Patients 18-60 years of age suffering from excessive sleepiness associated with shift work sleep disorder	N=211 12 weeks	Primary: Proportion of patients showing ≥2 grades of improvement (responder) based on SSS in both groups	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs modafinil 200 mg administered 1 hour prior to night shift	(SWSD)		Secondary: Improvement in mean SSS grades, compliance, patients' as well as physicians' global assessment for efficacy, safety	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 (42.87%; P=0.78). The most commonly TEAEs reported were mild to moderate in severity and included headache, nausea, and dry mouth.
Czeisler et al.[36] (2005) Modafinil 200 mg daily administered 30-60 minutes before the start of work shift vs placebo	DB, MC, PC, RCT Adults 18-60 years of age diagnosed with SWSD 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	Primary: The modafinil treatment 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 treatment group significantly improved the CGI-C test scores with 74% of the patients rated as at least minimally improved compared with 36% in the placebo group (P<0.001). The modafinil treatment group produced a significant decrease in mean number of lapses of attention during the Psychomotor Vigilance Test from baseline versus placebo (P=0.005).
Miscellaneous				
Black et al.[143] (2010) Armodafinil 100-250 mg/day (OSA) or 100-250 mg/night 30 minutes to 1 hour before night shift but no later than 23:00 (SWD)	DB, MC, OL Men and women 18-65 years of age with a diagnosis of obstructive sleep apnea (OSA), shift work disorder (SWD) or narcolepsy	N=743 ≥12 months	Primary: Tolerability and efficacy (CGI-C, ESS, BFI)	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 blood pressure (3.6/2.3 mm Hg), heart rate (6.7 beats per minute) across all study patient groups with most of the changes occurring by month 3. Greater improvement, compared to baseline, on the CGI-C was reported in the 3 study groups (75% to 92%) at the final visit with the SWD

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				group reporting the greatest improvement. Study patients reported significant improvement at the final visit by 65% with treated OSA (95% CI: 60.2, 68.9), 88% with SWD (95% CI: 81.3, 93.9), and 62% with narcolepsy (95% CI: 54.2, 69.8). Armodafinil improved wakefulness, measured by the ESS, in the treated OSA and narcolepsy groups, at all follow-up visits compared with 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.
Schwartz et al.[144] (2010) Armodafinil 100-250 mg/day (OSA and narcolepsy) or 100-250 mg/day 30 minutes to 1 hour before the start of night shift but no later than 23:00 (SWD)	MC, OL Patients 18-65 years of age who had a complaint of excessive sleepiness associated with obstructive sleep apnea (OSA), shift work disorder (SWD) or narcolepsy	N=328 12 months	Primary: CGI, ESS, adverse events	Primary: At the final visit, 80% (95% CI: 74.1-86.7) of patients with OSA and 84% (95% CI: 72.7-94.8) 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: 95.2-100.0) 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%–24%). The adverse event was mild to moderate in severity as noted by the study investigators.
Jean-Pierre et al.[107] (2010) Modafinil 200 mg/day vs	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	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				Modafinil had no statistically significant effect on depression (P>0.05).
Orlikowski et al.[102] (2009) Modafinil 300 mg/day vs placebo	DB, MC, PC, RCT Patients ≥18 years of age diagnosed with myotonic muscular dystrophy type 1 (MMD1) experiencing hypersomnia	N=28 2.5 years	Primary: MWT Secondary: MLST, ESS, global assessment (patient and physician), HAM-D, and SF-36	Primary: At 4 weeks, the mean MWT score was 16.4 minutes in the modafinil treatment 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 treatment groups in disturbances of personality and mood or quality-of-life. A total of 8 patients reported ≥1 adverse event, including digestive, neurologic and skin symptoms. The adverse events were considered mild or moderate by the study investigator.

Drug regimen abbreviations: AM=morning, AMP=mixed amphetamine salts, BID=twice a day, CLON=clonidine, DEX=dextroamphetamine, DXM=dexmethylphenidate, ER=extended release, FD=forced dose, GXR= guanfacine extended-release, IR=immediate release, LDX=lisdexamfetamine, MPH=methylphenidate, MTS=methylphenidate transdermal system, OROS=osmotic-release oral system, PC=placebo capsule, PM=evening, PTS=placebo transdermal system, QD=daily, SR=sustained release, TID=three times a day, XR=extended release
Study abbreviations: CI=confidence interval, DB=double blind, DD=double dummy, HR=hazard ratio, HTH=head-to-head trial, 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, SA=single arm, SB=single blind, TB=triple blind, XO=crossover design
Other abbreviations: AAQoL=Adult ADHD quality of life scale, 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, 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-T=Conners ADHD/DSM IV scale-teacher version, CADS-P=Conners ADHD/DSM IV scale-parent 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, CDR=Cognitive Drug Research, 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, CGI-S=clinical global impression scale, CHIP-CE=Child Health and Illness Profile-Child Edition, CHQ=child health questionnaire, CPRS=Conners parent rating scale, CHIP-CE=child health and illness profile-child edition, CHQ=child health questionnaire, 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, DBP=diastolic blood pressure, EDS=excessive daytime sleepiness, DSST=Digit Symbol Substitution Task/Coding Test, ESS=Epworth sleep scale, FCRTT=four-choice reaction time test, FIBM=Family Burden of Illness Module, FOSQ=Functional outcomes of sleep questionnaire, HAMA=Hamilton Anxiety Rating Scale, GTSS=Global tic severity scale, $HAMD_{17}$=Hamilton 17-item Depression Rating scale, HR=heart rate, HSPP=Harter Self-Perception Profile, I/O=inattention/overactivity, HMVTS=Hopkins motor/vocal tic scale, JAMES=Joint Attention Measure from the EScs (Early and Social Communication Scale), KSS=Karolinska Sleepiness Scale, MI=myocardial infarction, MSLT=multiple sleep latency test, MWT=maintenance of wakefulness test, nCAP=Nasal continuous positive airway pressure, O/D=oppositional/defiance, PDD=pervasive developmental disorders, PERMP=permanent product measure of performance, PGA=parent global assessment, PLM=periodic leg movements, PSG=Polysomnogram, POMS-DD=depression-dejection subscale of profile of mood states, Q-LES-Q=quality of life, enjoyment, and satisfaction questionnaire, QU.E.S.T.=Quality of life, effectiveness, safety, and tolerability, REM=rapid eye movement, SAICA=Social Adjustment Scale for Children and Adolescents, SDS=Sheehan disability scale, SF-36=36-item Short Form Health Survey, SERS=side effect ratings scale, SOREM=Sleep-onset rapid eye movement, SKAMP=Swanson, Kotkin, Agler, M-Flynn, and Pelham, SKAMP-A=SKAMP-Attention, SKAMP-D=SKAMP-Deportment, 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, SSS=Stanford sleepiness score, STAI=State and trait anxiety inventory, TOVA=test of variables of attention, STSSS=Shapiro tourette syndrome severity scale, TEAEs=treatment-emergent adverse events, 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®).[37] 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 18. Relative Cost of the Cerebral Stimulants/Agents Used for ADHD

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

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Anorexigenic Agents and Respiratory and Cerebral Stimulants, Miscellaneous				
Armodafinil	tablet	Nuvigil®	$$$$-$$$$$	N/A
Dexmethylphenidate	extended-release capsule, tablet	Focalin®*, Focalin XR®	$$-$$$$	$-$$
Methylphenidate	chewable tablet, extended-release capsule, extended-release tablet sustained-release tablet, solution, tablet, transdermal patch	Concerta®*, Daytrana®, Metadate CD®, Metadate ER®*, Methylin®*, Ritalin®*, Ritalin LA®*, Ritalin-SR®*	$$-$$$$$	$-$$$$$
Modafinil	tablet	Provigil®*	$$$$$	$$$$$
Central Nervous System Agents, Miscellaneous				
Atomoxetine	capsule	Strattera®	$$$$	N/A
Guanfacine	extended-release tablet	Intuniv®	$$$$	N/A
Sodium oxybate	solution	Xyrem®	$$$$$	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 treat Attention-Deficit/Hyperactivity Disorder (ADHD) and to improve wakefulness in patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnea (OSA) and shift work sleep disorder.[1-20,145-147] The cerebral stimulants are classified as Schedule II (amphetamines and methylphenidate derivatives) or Schedule IV (armodafinil and modafinil) controlled substances. Sodium oxybate is a central nervous system depressant and is classified as a Schedule III controlled substance. 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 FDA for the initial pharmacologic treatment of ADHD and they do not give preference to one agent over another.[24-26] The central nervous system agents have been shown to be effective for the treatment of ADHD in numerous clinical trials.[24,47-57,64-68,70,73,75-79,89-90,93-99,101,103-106,108-109,112-113,118,124,126,128-130] 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.).[42,64-69,70-73,75-82,97,101,109,118] Extended-release clonidine and extended-release guanfacine are approved for the treatment of ADHD as monotherapy and as adjunctive therapy to stimulants.[4,92,120,122,146]

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.[24-25,27] The advantage of a once-daily formulation is that 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.

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.[29] Modafinil is also recommended as one of several initial treatment options for individuals with excessive sleepiness due to OSA and shift work sleep disorder.[31-32] Armodafinil was approved by the FDA in June 2007 and is not addressed in the available guidelines. Armodafinil, modafinil and sodium oxybate have been shown to be more effective than placebo in patients with narcolepsy, OSA and shift work sleep disorder[33,36,40-41,44-45,83-88,100,114, 132,134,137-142]

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

Therefore, all brand cerebral stimulants/agents used for ADHD within the class reviewed are comparable to each other and to the generics and OTC 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.

XII. References

1. Drug Facts and Comparisons. Drug Facts and Comparisons 4.0 [online]. 2012. Available from Wolters Kluwer Health, Inc. Accessed April 2012.
2. Lexi-Comp Online, Lexi-Drugs Online, Hudson, Ohio: Lexi-Comp, Inc.; 2012; April 2012.
3. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed April 2012.
4. Kapvay® [package insert]. Atlanta, GA: Shionogi Pharma, Inc.; September 2010.
5. Adderall® [package insert]. Pomona, NY: Barr Laboratories; March 2007.
6. Adderall XR® [package insert]. Wayne, PA: Shire US, Inc.; February 2012.
7. Dexedrine® [package insert]. Middlesex, NJ: Amedra Pharmaceuticals, LLC; December 2010.
8. ProCentra® [package insert]. Charlotte, NC: FSC Laboratories; June 2010.
9. Vyvanse® [package insert]. Wayne, PA: Shire US, Inc.; January 2012.
10. Desoxyn® [package insert]. Deerfield, IL: Ovation Pharmaceuticals; March 2007.
11. Nuvigil® [package insert]. Fraser, PA: Cephalon, Inc.; October 2010.
12. Focalin® [package insert]. East Hanover, NJ: Novartis Pharmaceuticals; December 2010.
13. Focalin XR® [package insert]. East Hanover, NJ: Novartis Pharmaceuticals; April 2011.
14. Concerta® [package insert]. Titusville, NJ: McNeil Pediatrics; November 2010.
15. Daytrana® [package insert]. Miami, FL: Noven Therapeutics, LLC.; November 2010.
16. Metadate CD® [package insert]. Smyrna, GA: UCB, Inc.; June 2009.
17. Methylin® [package insert]. Atlanta, GA: Shionogi Pharma, Inc.; September 2010.
18. Ritalin®, Ritalin-SR® [package insert]. East Hanover, NJ: Novartis Pharmaceuticals; December 2010.
19. Ritalin LA® [package insert]. East Hanover, NJ: Novartis Pharmaceuticals; December 2010.
20. Provigil® [package insert]. Fraser, PA: Cephalon, Inc.; October 2010.
21. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th ed., text revision (DSM-IV-TR). Washington, DC: American Psychiatric Association; 2000:356.
22. Searight HR, Burke JM, Rottneck F. Adult ADHD: Evaluation and treatment in family medicine. Am Fam Physician 2000;62:2077-86,2091-2.
23. Krull K. Attention deficit hyperactivity disorder in children and adolescents: Treatment with medications. In: UpToDate, Torchia, M (Ed), UpToDate, Waltham, MA, 2012.
24. American Academy of Child and Adolescent Psychiatry. Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 2007;46:894-921.
25. Institute for Clinical Systems Improvement. Health care guideline: diagnosis and management of attention deficit hyperactivity disorder in primary care for school-age children and adolescents [guideline on the Internet]. 9th ed. Bloomington (MN): Institute for Clinical Systems Improvement; March 2012. Available at: http://www.icsi.org/adhd/adhd_2300.html. Accessed May 2012.
26. American Academy of Pediatrics. ADHD: Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents. Pediatrics 2011;128:1-16.
27. National Institute for Health and Clinical Excellence. Attention deficit hyperactivity disorder: Diagnosis and management of ADHD in children, young people, and adults [guideline on the Internet]. London (UK). September 2008. Available at: http://guidance.nice.org.uk/CG72. Accessed May 2012.
28. British Association for Psychopharmacology. Evidence-based guidelines for management of attention-deficit/hyperactivity disorder in adolescents in transition to adult services and in adults: recommendations from the British Association for Psychopharmacology. J Psychopharmacol 2006;21:10-41.
29. American Academy of Sleep Medicine. Practice parameters for the treatment of narcolepsy and other hypersomnias of central origin. Sleep 2007;30:1705-1711.
30. European Federation of Neurological Sciences. Guidelines on management of narcolepsy. Eur J Neurol 2006;13:1035-48.
31. American Academy of Sleep Medicine. Practice Parameters for the Clinical Evaluation and Treatment of Circadian Rhythm Sleep Disorders. Sleep 2007;30:1445-1459.
32. American Academy of Sleep Medicine. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. J Clin Sleep Med 2009;5:263-276.
33. Black JE, Hirshkowitz M. Modafinil for treatment of residual excessive sleepiness in nasal continuous positive airway pressure-treated obstructive sleep apnea/hypopnea syndrome. Sleep 2005;28(4):464-71.

34. Huss M, Lehmkuhl U. Methylphenidate and substance abuse: a review of the pharmacology, animal, and clinical studies. J Atten Disord. 2002;6(1):S65-71.
35. Barkley RA, Fisher M, Smallish L et al. Does the treatment of attention deficit/hyperactivity disorder with stimulants contribute to drug use/abuse? A 13-year prospective study. Pediatrics. 2003;111:97-109.
36. Czeisler CA, Walsh JK, Roth T, Hughes RJ, Wright KP, et al. Modafinil for excessive sleepiness associated with Shift-Work Sleep disorder. N Engl J Med 2005;353:476-86.
37. Lage M, Hwang P. Effect of methylphenidate formulation for attention deficit hyperactivity disorder on patterns and outcomes of treatment. J Child Adol Psychopharmacol. 2004;14(4):575-81.
38. Sallee FR, Ambrosini PJ, Lopez FA, et al. Health-related quality of life and treatment satisfaction and preference in a community assessment study of extended-release mixed amphetamine salts for children with attention-deficit/hyperactivity disorder. J Outcomes Res. 2004;8:27-49.
39. Kollins SH. Comparing the abuse potential of methylphenidate versus other stimulants: A review of available evidence and relevance to the ADHD patient. J Clin Psychiatry 2003;64 (Suppl 11):14-18.
40. Czeisler CA, Walsh JK, Wesnes KA, et al. Armodafinil for treatment of excessive sleepiness associated with shift work disorder: a randomized controlled study. Mayo Clin Proc 2009;84:958-72.
41. Hirshkowitz M, Black JE, Wesnes K, et al. Adjunct armodafinil improves wakefulness and memory in obstructive sleep apnea/hypopnea syndrome. Respir Med 2007;101:616-27.
42. Newcorn JH, Kratochvil CJ, Allen AJ, et al. Atomoxetine and osmotically released methylphenidate for the treatment of attention deficit hyperactivity disorder: acute comparison and differential response. Am J Psychiatry 2008;165:721-30.
43. Faraone SV, Glatt SJ, Bukstein OG, et al. Effects of once-daily oral and transdermal methylphenidate on sleep behavior of children with ADHD. J Atten Disord 2009; 12:308-15.
44. Roth T, White D, Schmidt-Nowara W, et al. Effects of armodafinil in the treatment of residual excessive sleepiness associated with obstructive sleep apnea/hypopnea syndrome: a 12-week, multicenter, double-blind, randomized, placebo-controlled study in nCPAP-adherent adults. Clin Ther 2006;28:689-706.
45. Harsh JR, Hayduk R, Rosenberg R, et al. The efficacy and safety of armodafinil as treatment for adults with excessive sleepiness associated with narcolepsy. Curr Med Res Opin 2006;22:761-74.
46. Adler LA, Spencer TJ, Williams DW, et al. Long-term, open-label safety and efficacy of atomoxetine in adults with ADHD: final report of a 4-year study. J Atten Disord 2008;12:248-53.
47. Biederman J, Lopez FA, Boellner SW, et al. A randomized, double blind, placebo controlled parallel group study of SLI381 (Adderall XR) in children with attention-deficit/hyperactivity disorder. Pediatrics. 2002;110:258-66.
48. Goodman DW, Ginsberg L, Weisler, RH, Cutler AJ, Hodgkins P. An Interim Analysis of the Quality of Life, Effectiveness, Safety, and Tolerability (QU.E.S.T.) Evaluation of Mixed Amphetamine Salts Extended Release in Adults With ADHD. CNS Spectr. 2005;10(Suppl 20):26-34.
49. Greenhill LL, Muniz R, Ball RR, Levine A, Pestreich L, et al. Efficacy and safety of dexmethylphenidate extended-release capsules in children with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 2006;45(7):817-23.
50. Spencer TJ, Adler LA, McGough JJ, Muniz R, Jiang H, et al. Efficacy and safety of dexmethylphenidate extended-release capsules in adults with attention-deficit/hyperactivity disorder. Biol Psychiatry 2007;61:1380-7.
51. Biederman J, Krishnan S, Zhang Y, et al. Efficacy and tolerability of lisdexamfetamine dimesylate (NRP-104) in children with attention-deficit/hyperactivity disorder: A phase III, randomized, multicenter, double-blind, parallel-group study. Clin Ther. 2007;29:450–63.
52. Biederman J, Boellner SW, Childress A, et al. Lisdexamfetamine dimesylate and mixed amphetamine salts extended-release in children with ADHD: A double-blind, placebo-controlled, crossover analog classroom study. Biol Psychiatry 2007 ;62(9):970-976.
53. Wilens TE. Biederman J. Lerner M. Concerta Study Group. Effects of once-daily osmotic-release methylphenidate on blood pressure and heart rate in children with attention-deficit/hyperactivity disorder: results from a one-year follow-up study. Journal of Clinical Psychopharmacology. 2004; 24(1):36-41.
54. Greenhill LL, Findling RL, Swanson JM et al. A double-blind, placebo-controlled study of modified-release methylphenidate in children with attention-deficit/hyperactivity disorder. Pediatrics. 2002;109:e39.
55. McGough JJ, Wigal SB, Abikoff H, Turnbow JM, et al. A randomized, double-blind, placebo-controlled, laboratory classroom assessment of methylphenidate transdermal system. J of Att Dis. 2006;9(3):476-85.
56. Pelham WE, Manos MJ, Ezzell CE, Tresco KE, et al. A dose-ranging study of methylphenidate transdermal system in children with ADHD. J Am Acad Adolesc. 2005;44(6):522-9.

57. Pelham WE, Burrows-MacLean L, Gnagy EM, Fabiano GA, et al. Transdermal methylphenidate, behavioral, and combined treatment for children with ADHD. Exp Clin Psychopharmacology. 2005;13:111-26.
58. Biederman J, Heiligenstein JH, Faries DE et al. Atomoxetine ADHD Study Group. Efficacy of atomoxetine versus placebo in school-age girls with attention-deficit/hyperactivity disorder. Pediatrics. 2002;110(6):e75.
59. Michelson D, Adler L, Spencer T et al. Atomoxetine in the treatment of children and adolescents with attention deficit, hyperactivity disorder: A randomized, placebo controlled, dose response study. Pediatrics. 2001;108(5):e83.
60. Spencer T, Heiligenstein JH, Biederman J et al. Results from 2 proof-of-concept, placebo-controlled studies of atomoxetine in children with attention-deficit/hyperactivity disorder. J Clin Psychiatry 2002;63:1140-7.
61. Cheng JYW, Chen RYL, Ko JSN, Ng EML. Efficacy and safety of atomoxetine for attention-deficit/hyperactivity disorder in children and adolescents-meta-analysis and meta-regression analysis. Psychopharmacology 2007;194:197-209.
62. Prasad S, Harpin V, Poole L, Zeitlin H, Jamdar S, Puvanendran K; The SUNBEAM Study Group. A multi-centre, randomised, open-label study of atomoxetine compared with standard current therapy in UK children and adolescents with attention-deficit/hyperactivity disorder (ADHD). Curr Med Res Opin. 2007 Feb;23(2):379-94.
63. Faraone SV, Bierderman J, Spencer TJ, Aleardi M. Comparing the Efficacy of Medications for ADHD Using Meta-analysis. MedGenMed. 2006;8(4):4.
64. Pliszka SR, Browne RG, Olvera RL et al. A double-blind, placebo controlled study of Adderall and methylphenidate in the treatment of attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2000; 39(5):619-26.
65. McCracken JT, Biederman J, Greenhill LL et al. Analog classroom assessment of a once-daily mixed amphetamine formulation, SLL381 (Adderall XR) in children with ADHD. J Am Acad Child Adolesc Psychology. 2003;426(6):673-83.
66. Pelham WE, Aronof HR, Midlam JL et al. A comparison of Ritalin and Adderall; efficacy and time course in children with attention hyperactivity deficit disorder. Pediatrics. 1999;103:e43.
67. Wigal S, Swanson JM, Feifel D, Sangal RB, Elia J, et al. A double-blind, placebo-controlled trial of dexmethylphenidate hydrochloride and d,l-threo-methylphenidate hydrochloride in children with attention-deficit/hyperactivity disorder. J Am Acad Adolesc Psychiatry 2004;43(11):1406-14
68. Faraone SV, Biederman J, Roe C. Comparative efficacy of Adderall and methylphenidate in attention-deficit/hyperactivity disorder: a meta-analysis. J Clin Psychopharmacol. 2002;22(5):468-73.
69. Efron D, Jarman F, Barker M. Efficacy of methylphenidate and dextroamphetamine in children with attention hyperactivity disorder: a double blind crossover trial. Pediatrics. 1997;100:662-8.
70. Gau SS, Shen HY, Soong WT, Gau CS. An open-label, randomized, active-controlled equivalent trial of osmotic release oral system methylphenidate in children with attention-deficit/hyperactivity disorder in Taiwan. J Child Adolesc Psychopharmacol. 2006 Aug;16(4):441-55.
71. Biederman J, Wigal SB, Spencer TJ, McGough JJ, Mays DA. A post hoc subgroup analysis of an 18-day randomized controlled trial comparing the tolerability and efficacy of mixed amphetamine salts extended release and atomoxetine in school-age girls with attention-deficit/hyperactivity disorder. Clin Ther 2006; 28(2):280–293.
72. Wang Y, Zheng Y, Du Y, Song DH, Shin YJ, Cho SC, et al. Atomoxetine versus methylphenidate in paediatric outpatients with attention deficit hyperactivity disorder: a randomized, double-blind comparison trial. Aust N Z J Psychiatry. 2007 Mar;41(3):222-30.Clin Ther. 2006 Feb;28(2):280-93.
73. Wolraich ML, Greenhill LL, Pelham W et al. Randomized, controlled trial of OROS methylphenidate once a day in children with attention-deficit/hyperactivity disorder. Pediatrics. 2001;108:883-92.
74. Cox DJ, Merkel RL, Moore M, Thorndike F, Muller C, Kovatchev B. Relative benefits of stimulant therapy with OROS methylphenidate versus mixed amphetamine salts extended release in improving the driving performance of adolescent drivers with attention-deficit/hyperactivity disorder. Pediatrics. 2006 Sep;118(3):e704-10.
75. Pelham WE, Gnagy EM, Burrows-Maclean L et al. Once-a-day Concerta - methylphenidate versus three times daily methylphenidate in laboratory and natural settings. Pediatrics. 2001;107:e105.
76. Lopez F, Silva R, Pestreich L et al. Comparative efficacy of two once daily methylphenidate formulations (Ritalin LA and Concerta) and placebo in children with attention deficit hyperactivity disorder across the school day. Paediatr Drugs. 2003;5(8):545-55.
77. Swanson JM, Wigal SB, Wigal T et al. A comparison of one-daily extended-release methylphenidate formulations in children with attention-deficit/hyperactivity disorder in the laboratory school (the Comacs study). Pediatrics. 2004;113:e206-16.

78. Pelham WE, Greenslade KE, Vodde-Hamilton M, et al. Relative efficacy of long-acting stimulants on children with attention deficit-hyperactivity disorder: a comparison of standard methylphenidate, sustained-release methylphenidate, sustained-release dextroamphetamine, and pemoline. Pediatrics. 1990; 86:226-37.
79. Silva R, Muniz R, Pestreich LK, Brams M, Childress A, Lopez FA. Efficacy of two long-acting methylphenidate formulations in children with attention- deficit/hyperactivity disorder in a laboratory classroom setting. J Child Adolesc Psychopharmacol. 2005 Aug;15(4):637-54.
80. Kratochvil CJ, Heiligenstein JH, Dittmann R. et al. Atomoxetine and methylphenidate treatment in children with ADHD: a prospective, randomized, open-label trial. J Am Acad Child Adolesc Psychiatry. 2002;41(7):776-84.
81. Kemner JE, Starr HL, Ciccone PE, Hooper-Wood CG, Crockett RS. Outcomes of OROS methylphenidate compared with atomoxetine in children with ADHD: a multicenter, randomized prospective study. Adv Ther. 2005 Sep-Oct;22(5):498-512.
82. Starr HL, Kemner J. Multicenter, randomized, open-label study of OROS methylphenidate versus atomoxetine: treatment outcomes in African-American children with ADHD. J Natl Med Assoc. 2005 Oct;97(10 Suppl):11S-16S.
83. Randomized trial of modafinil for the treatment of pathological somnolence in narcolepsy. US Modafinil in Narcolepsy Multicenter Study Group. Ann Neurol. 1998 Jan;43(1):88-97.
84. Randomized trial of modafinil as a treatment for the excessive daytime somnolence of narcolepsy: US Modafinil in Narcolepsy Multicenter Study Group. Neurology. 2000 Mar 14;54(5):1166-75.
85. Broughton RJ, Felming JAE, George CFP, et al. Randomized, double blind, placebo controlled crossover trial of modafinil in the treatment of excessive daytime sleepiness in narcolepsy. Neurology. 1997;49:444-51.
86. Billiard M, Besset A, Montplaisir J, et al. Modafinil: A double-blind multicenter study. Sleep. 1994;17(8):S107-112.
87. Boivin DB, Montplasir J, Petit D, et al. Effects of modafinil on symptomatology of human narcolepsy. Clin Neuropharmaco. 1993;16:46-53.
88. Thorpy MJ, Schwartz JR, Kovacevic-Ristanovic R, Hayduk R. Initiating treatment with modafinil for control of excessive daytime sleepiness in patients switching from methylphenidate: an open label safety study. Psychopharmacology. 2003;167:380-5.
89. Biederman J, Melmed RD, Patel A, et al. A randomized, double-blind, placebo-controlled study of guanfacine extended release in children and adolescents with attention-deficit/hyperactivity disorder. Pediatrics 2008;121:e73-84.
90. Biederman J, Melmed RD, Patel A, et al. Long-term, open-label extension study of guanfacine extended release in children and adolescents with ADHD. CNS Spectr 2008;13:1047-55.
91. Faraone SV, Glatt SJ. Effects of extended-release guanfacine on ADHD symptoms and sedation-related adverse events in children with ADHD. J Atten Disord 2010;13:532-8.
92. Spencer TJ, Greenbaum M, Ginsberg LD, et al. Safety and effectiveness of coadministration of guanfacine extended release and psychostimulants in children and adolescents with attention-deficit/hyperactivity disorder. J Child Adolesc Psychopharmacol 2009;19:501-10.
93. Sallee FR, McGough J, Wigal T, et al. Guanfacine extended release in children and adolescents with attention-deficit/hyperactivity disorder: a placebo-controlled trial. J Am Acad Child Adolesc Psychiatry 2009;48:155-65.
94. Sallee FR, Lyne A, Wigal T, et al. Long-term safety and efficacy of guanfacine extended release in children and adolescents with attention-deficit/hyperactivity disorder. J Child Adolesc Psychopharmacol 2009;19:215-26.
95. Connor DF, Findling RL, Kollins SH, et al. Effects of guanfacine extended release on oppositional symptoms in children aged 6-12 years with attention-deficit hyperactivity disorder and oppositional symptoms: a randomized, double-blind, placebo-controlled trial. CNS Drugs 2010;24:755-68.
96. Jahromi LB, Kasari CL, McCracken JT, Lee LS, Aman MG, McDougle CJ, Scahill L, Tierney E, Arnold LE, Vitiello B, Ritz L, Witwer A, Kustan E, Ghuman J, Posey DJ. Positive effects of methylphenidate on social communication and self-regulation in children with pervasive developmental disorders and hyperactivity. J Autism Dev Disord 2009;39:395-404.
97. Findling RL, Bukstein OG, Melmed RD, López FA, Sallee FR, Arnold LE, Pratt RD. A randomized, double-blind, placebo-controlled, parallel-group study of methylphenidate transdermal system in pediatric patients with attention-deficit/hyperactivity disorder. J Clin Psychiatry 2008;69:149-59.
98. Findling RL, Childress AC, Krishnan S, et al. Long-term effectiveness and safety of lisdexamfetamine dimesylate in school-aged children with attention-deficit/hyperactivity disorder. CNS Spect 2008;13:614-20.

99. Weisler R, Young J, Mattingly G et al. Long-term safety and effectiveness of lisdexamfetamine dimesylate in adults with attention-deficit/ hyperactivity disorder. CNS Spectr 2009;14:573-85.
100. Krystal AD, Harsh JR, Yang RR et al. A double-blind, placebo-controlled study of armodafinil for excessive sleepiness in patients with treated obstructive sleep apnea and comorbid depression. J Clin Psychiatry 2010;71:32-40.
101. Spencer TJ, Mick E, Surman CB, et al. A randomized, single-blind, substitution study of OROS methylphenidate (Concerta) in ADHD adults receiving immediate release methylphenidate. J Atten Disord 2011;15:286-94.
102. Orlikowski D, Chevret S, Quera-Salva MA, et al. Modafinil for the treatment of hypersomnia associated with myotonic muscular dystrophy in adults: a multicenter, prospective, randomized double-blind, placebo-controlled, 4-week trial. Clin Ther 2009;31:1795-73.
103. Hammerness P, Doyle R, Kotarski M, et al. Atomoxetine in children with attention-deficit hyperactivity disorder with prior stimulant therapy: a prospective open-label study. Eur Child Adolesc Psychiatry 2009;18:493-8.
104. Kratochvil CJ, Vaughan BS, Stoner JA, et al. A double-blind, placebo-controlled study of atomoxetine in young children with ADHD. Pediatrics 2011;127:e862-8.
105. Dittmann RW, Schacht A, Helsberg K, et al. Atomoxetine versus placebo in children and adolescents with attention-deficit/hyperactivity disorder and comorbid oppositional defiant disorder: a double-blind, randomized, multicenter trial in Germany. J Child Adolesc Psychopharmacol 2011;21:97-110.
106. Wigal SB, Wigal T, Schuck S, et al. Academic, behavioral, and cognitive effects of OROS® methylphenidate on older children with attention-deficit/hyperactivity disorder. J Child Adolesc Psychopharmacol 2011;21:121-31.
107. Jean-Pierre P, Morrow GR, Roscoe JA, et al. A phase 3 randomized, placebo-controlled, double-blind, clinical trial of the effect of modafinil on cancer-related fatigue among 631 patients receiving chemotherapy: a University of Rochester Cancer Center Community Clinical Oncology Program Research base study. Cancer 2010;116:3513-20.
108. Jain R, Segal S, Kollins SH, et al. Clonidine extended-release tablets for pediatric patients with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 2011;50:171-9.
109. Palumbo DR, Sallee FR, Pelham WE, et al. Clonidine for attention-deficit/hyperactivity disorder: 1. Efficacy and tolerability of outcomes. J Am Acad Child Adolesc Psychiatry 2008;47: 180-8.
110. Hazell PL, Stuart JE. A randomized controlled trial of clonidine added to psychostimulant medication for hyperactive and aggressive children. J Am Acad Child Adolesc Psychiatry 2003;42:886-94.
111. Scahill L, Chappell PB, Kim YS, et al. A placebo-controlled study of guanfacine in the treatment of children with tic disorders and attention deficit hyperactivity disorder. Am J Psychiatry 2001;158:1067-74.
112. Muniz R, Brams M, Mao A, McCague K, Pestreich L, Silva R. Efficacy and safety of extended-release dexmethylphenidate compared with d,l-methylphenidate and placebo in the treatment of children with attention-deficit/hyperactivity disorder: a 12-hour laboratory classroom study. J Child Adolesc Psychopharmacol 2008;18:248-56.
113. Adler LA, Spencer T, McGough JJ, et al. Long-term effectiveness and safety of dexmethylphenidate extended-release capsules in adult ADHD. J Atten Disord 2009;12:449-59.
114. Czeisler CA, Walsh JK, Wesnes KA et al. Armodafinil for treatment of excessive sleepiness associated with shift work disorder: a randomized controlled study. Mayo Clin Proc 2009;84:958-72.
115. Schelleman H, Bilker WB, Kimmel SE, et al. Methylphenidate and risk of serious cardiovascular events in adults. Am J Psychiatry 2012;169:178-85.
116. Sutherland SM, Adler LA, Chen C, Smith MD, Feltner DE. An 8-week, randomized controlled trial of atomoxetine, atomoxetine plus buspirone, or placebo in adults with ADHD. J Clin Psychiatry 2012 Jan 10.
117. Hanwella R, Senanayake M, de Silva V. Comparative efficacy and acceptability of methylphenidate and atomoxetine in treatment of attention deficit hyperactivity disorder in children and adolescents: a meta-analysis. BMC Psychiatry 2011;11:176.
118. Yang L, Cao Q, Shuai L, Li H, Chan RC, Wang Y. Comparative study of OROS-MPH and atomoxetine on executive function improvement in ADHD: a randomized controlled trial. Int J Neuropsychopharmacol. 2011 Oct 21:1-12. [Epub ahead of print].
119. Pringsheim T, Steeves T. Pharmacological treatment for Attention Deficit Hyperactivity Disorder (ADHD) in children with comorbid tic disorders. Cochrane Database Syst Rev. 2011 Apr 13;(4):CD007990.
120. Wilens TE, Bukstein O, Brams M, et al. A controlled trial of extended-release guanfacine and psychostimulants for attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 2012;51:74-85.

121. Connor DF, Findling RL, Kollins SH, et al. Effects of guanfacine extended release on oppositional symptoms in children aged 6-12 years with attention-deficit hyperactivity disorder and oppositional symptoms: a randomized, double-blind, placebo-controlled trial. CNS Drugs 2010;24:755-68.
122. Kollins SH, Jain R, Brams M, et al. Clonidine extended-release tablets as add-on therapy to psychostimulants in children and adolescents with ADHD. Pediatrics 2011;127:e1406-13.
123. Tembe DV, Dhavale A, Desai H et al. Armodafinil versus Modafinil in Patients of Excessive Sleepiness Associated with Shift Work Sleep Disorder: A Randomized Double Blind Multicentric Clinical Trial. Neurol Res Int 2011;2011:514351. Epub 2011 Jun 1.
124. Findling RL, Childress AC, Cutler AJ, et al. Efficacy and safety of lisdexamfetamine dimesylate in adolescents with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 2011;50:395-405.
125. Olfson M, Huang C, Gerhard T, et al. Stimulants and cardiovascular events in youth with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 2012;51:147-56.
126. Casas M, Rösler M, Sandra Kooij JJ, et al. Efficacy and safety of prolonged-release OROS methylphenidate in adults with attention deficit/hyperactivity disorder: A 13-week, randomized, double-blind, placebo-controlled, fixed-dose study. World J Biol Psychiatry 2011 Nov 22. [Epub ahead of print].
127. Schelleman H, Bilker WB, Strom BL, et al. Cardiovascular events and death in children exposed and unexposed to ADHD agents. Pediatrics 2011;127:1102-10.
128. Stein MA, Waldman ID, Charney E, et al. Dose effects and comparative effectiveness of extended release dexmethylphenidate and mixed amphetamine salts. J Child Adolesc Psychopharmacol 2011;21:581-8.
129. Mattos P, Louzã MR, Palmini AL, et al. A Multicenter, Open-Label Trial to Evaluate the Quality of Life in Adults With ADHD Treated With Long-Acting Methylphenidate (OROS MPH): Concerta Quality of Life (CONQoL) Study. J Atten Disord. 2012 Feb 14. [Epub ahead of print].
130. Kollins SH, López FA, Vince BD, et al. Psychomotor functioning and alertness with guanfacine extended release in subjects with attention-deficit/hyperactivity disorder. J Child Adolesc Psychopharmacol 2011;21:111-20.
131. Bloch MH, Panza KE, Landeros-Weisenberger A, et al. Meta-analysis: treatment of attention-deficit/hyperactivity disorder in children with comorbid tic disorders. J Am Acad Child Adolesc Psychiatry 2009;48:884-93.
132. Xyrem International Study Group. A double-blind, placebo-controlled study demonstrates sodium oxybate is effective for the treatment of excessive daytime sleepiness in narcolepsy. J Clin Sleep Med 2005;1:391-7.
133. Weaver TE, Cuellar N. A randomized trial evaluating the effectiveness of sodium oxybate therapy on quality of life in narcolepsy. Sleep 2006;29:1189-94.
134. Xyrem International Study Group. Further evidence supporting the use of sodium oxybate for the treatment of cataplexy: a double-blind, placebo-controlled study in 228 patients. Sleep Med 2005;6:415-21.
135. Alshaikh MK, Gacuan D, George S, et al. Long-term follow-up of patients with narcolepsy-cataplexy treated with sodium oxybate (Xyrem). Clin Neuropharmacol 2011;34:1-4.
136. Wang YG, Swick TJ, Carter LP, et al. Safety overview of postmarketing and clinical experience of sodium oxybate (Xyrem): abuse, misuse, dependence, and diversion. J Clin Sleep Med 2009;5:365-71.
137. U.S. Xyrem Multicenter Study Group. Sodium oxybate demonstrates long-term efficacy for the treatment of cataplexy in patients with narcolepsy. Sleep Med 2004;5:119-23.
138. Black J, Houghton WC. Sodium oxybate improves excessive daytime sleepiness in narcolepsy. Sleep 2006;29:939-46.
139. Black J, Pardi D, Hornfeldt CS, et al. The nightly administration of sodium oxybate results in significant reduction in the nocturnal sleep disruption of patients with narcolepsy. Sleep Med 2009;10:829-35.
140. Black J, Pardi D, Hornfeldt CS, et al. The nightly use of sodium oxybate is associated with a reduction in nocturnal sleep disruption: a double-blind, placebo-controlled study in patients with narcolepsy. J Clin Sleep Med 2010;6:596-602.
141. Williams SC, Marshall NS, Kennerson M, et al. Modafinil effects during acute continuous positive airway pressure withdrawal: a randomized crossover double-blind placebo-controlled trial. Am J Respir Crit Care Med 2010;181:825-31.
142. Weaver TE, Chasens ER, Arora S. Modafinil improves functional outcomes in patients with residual excessive sleepiness associated with CPAP treatment. J Clin Sleep Med 2009;5:499-505.
143. Black JE, Hull SG, Tiller J, et al. The long-term tolerability and efficacy of armodafinil in patients with excessive sleepiness associated with treated obstructive sleep apnea, shift work disorder, or narcolepsy: an open-label extension study. J Clin Sleep Med 2010;6:458-66.

144. Schwartz JR, Khan A, McCall WV, et al. Tolerability and efficacy of armodafinil in naïve patients with excessive sleepiness associated with obstructive sleep apnea, shift work disorder, or narcolepsy: a 12-month, open-label, flexible-dose study with an extension period. J Clin Sleep Med 2010;6:450-7.
145. Strattera® [package insert]. Indianapolis, IN: Eli Lilly and Company; August 2011.
146. Intuniv® [package insert]. Wayne, PA: Shire US, Inc.; June 2011.
147. Xyrem® [package insert]. Palo Alto, CA: Jazz Pharmaceuticals, Inc.; November 2005.

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Pharmacotherapy Review of Anxiolytics, Sedatives and Hypnotics – Barbiturates
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I. Overview

The barbiturates are approved for the treatment of insomnia and for the induction of sedation.[1-5] 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 (GABA) system and cause reversible depression of all excitable tissues, especially the central nervous system.[1-6] 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.[1-6]

The use of barbiturates is associated with abuse and psychological/physical dependence.[1-5] 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 2 weeks.[1-6] 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.[1-4] 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 February 2010.

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	elixir, tablet	Butisol Sodium®	none
Pentobarbital	injection	Nembutal Sodium®	none
Phenobarbital	elixir, injection, tablet	Luminal Sodium®	phenobarbital
Secobarbital	capsule	Seconal Sodium®	none

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 (AASM): **Clinical Guideline for the Evaluation and Management of Chronic Insomnia in Adults[12] (2008)**	• 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 (BZD or newer BzRAs) or ramelteon.
	  o Alternate short-intermediate acting BzRAs or ramelteon if the

Clinical Guideline	Recommendation(s)
	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 BzRA 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 (OTC "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 CBT-I. • 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 (NIH): **Manifestations and Management of Chronic Insomnia in Adults[13] (2005)**	Behavioral and Cognitive Therapies • 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 (CBT) has been found to be as effective as prescription medications for short-term treatment of chronic insomnia. The beneficial effects of CBT may last well beyond the termination of active treatment. Benzodiazepine Receptor Agonists • 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

Clinical Guideline	Recommendation(s)
	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 OTC 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.
European Federation of Neurological Societies (EFNS): **Guideline on the Management of Status Epilepticus[14] (2006)**	<u>General Recommendations for the Management of Generalized Convulsive Status Epilepticus (GCSE), Non-convulsive Status Epilepticus (NCSE), and Subtle Status Epilepticus</u> • Assessment/control of the airways and of ventilation, arterial blood gas monitoring, ECG, blood pressure monitoring, intravenous glucose and thiamine as required, emergency measurement of antiepileptic drug levels, electrolytes and magnesium, a full hematological screen, and measures of hepatic and renal function. • The cause of the status should be identified urgently. <u>Initial Pharmacological Treatment Recommendations for GCSE and NCSE</u> • The preferred treatment is intravenous administration of lorazepam 4 mg, to be repeated if seizures continue for more than 10 minutes after first injections. If necessary, additional phenytoin (15-18 mg/kg) or equivalent fosphenytoin is recommended. • Alternatively, diazepam 10 mg directly (route of administration not specified) followed by phenytoin (15-18 mg/kg) or equivalent fosphenytoin. If seizures continue for more than 10 minutes after injection an additional 10 mg of diazepam is recommended. If necessary, additional lorazepam (4-8 mg) should be administered.

Clinical Guideline	Recommendation(s)
	• Refractory status epilepticus, or GCSE that does not respond to initial anticonvulsant agents, needs to be treated on an intensive care unit. Pharmacological Treatment Recommendations for Refractory GCSE and Subtle Status Epilepticus • Anesthetic doses of midazolam, propofol or barbiturates are recommended (pentobarbital given as a bolus dose of 10-20 mg/kg followed by an infusion of 0.5-1 mg/kg/hour increasing to 1-3 mg/kg/hour). Pharmacological Treatment Recommendations for Refractory NCSE • Phenobarbital 20 mg/kg intravenously. • Valproic acid 25-45 mg/kg as intravenous bolus followed by maximum rates up to 6 mg/kg/min. • If treatment regimen includes the administration of anesthetics, the same protocol as refractory GCSE applies.
Journal of Child Neurology: **Treatment of Pediatric Epilepsy: Expert Opinion[7] (2005)**	• 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.

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[1-5]

Indication	Amobarbital	Butabarbital	Pentobarbital	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				✔ †	

Indication	Amobarbital	Butabarbital	Pentobarbital	Phenobarbital	Secobarbital
Sedative-Hypnotic					
Short-term treatment of insomnia	✔	✔	✔	✔ §	✔
Sedation	✔	✔	✔	✔ †	

†Oral formulations
§Parenteral formulation

IV. Pharmacokinetics

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

Table 4. Pharmacokinetic Parameters of the Barbiturates[1-5]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Amobarbital	Not reported	Not reported	Liver	Renal Feces (4-5)	8-42
Butabarbital	Not reported	Not reported	Liver	Renal	34-100
Pentobarbital	95	5	Liver	Renal	15-48
Phenobarbital	80-100	20-60	Liver	Renal (21)	1.5-4.9 days
Secobarbital	90	52-57	Liver	Renal	19-34

V. Drug Interactions

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

Table 5. Significant Drug Interactions with the Barbiturates[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Barbiturates (amobarbital, butabarbital, pentobarbital, phenobarbital, secobarbital)	1	Anticoagulants	Barbiturates reduce the effects of anticoagulants through increased metabolic clearance of anticoagulants, probably caused by induction of hepatic microsomal enzymes.
Barbiturates (phenobarbital)	1	Axitinib	Plasma concentrations and pharmacologic effects of axitinib may be decreased by phenobarbital. Induction of CYP3A4/5 by phenobarbital may increase the metabolic elimination of axitinib.
Barbiturates (phenobarbital)	1	Bortezomib	Plasma concentrations and pharmacologic effects of bortezomib may be decreased by phenobarbital. Induction of CYP3A4 by phenobarbital may increase the metabolic elimination of bortezomib.
Barbiturates (phenobarbital)	1	Brentuximab	Plasma concentrations and pharmacologic effects of brentuximab may be decreased by phenobarbital. Induction of CYP3A4 by phenobarbital may decrease the plasma concentrations of monomethyl

Generic Name(s)	Significance Level	Interaction	Mechanism
			auristatin E (MMAE), the microtubule disrupting agent in brentuximab.
Barbiturates (phenobarbital)	1	Crizotinib	Plasma concentrations and pharmacologic effects of crizotinib may be decreased by phenobarbital. Induction of CYP3A4 by phenobarbital may increase the metabolic elimination of crizotinib.
Barbiturates (amobarbital, butabarbital, pentobarbital, phenobarbital, secobarbital)	1	Dienogest	Barbiturates may increase hepatic metabolism and decrease the pharmacologic effects of dienogest. Menstrual irregularities (spotting, breakthrough bleeding, and amenorrhea) and pregnancy may occur.
Barbiturates (phenobarbital)	1	Direct factor Xa inhibitors	Plasma concentrations and pharmacologic effects of direct factor Xa inhibitors may be decreased by phenobarbital.
Barbiturates (butabarbital)	1	Disulfiram	Coadministration of butabarbital and disulfiram may produce acute and severe alcohol intolerance. Induction of P-glycoprotein and CYP3A4 by phenobarbital may increase the metabolic elimination of direct factor Xa inhibitors.
Barbiturates (amobarbital, butabarbital, pentobarbital, phenobarbital, secobarbital)	1	Estrogens	Induction of hepatic microsomal enzymes by barbiturates increases elimination of estrogenic substances, decreasing plasma concentrations. Oral contraceptive-induced water retention may exacerbate seizures. Contraceptive failure has been reported.
Barbiturates (phenobarbital)	1	HCV protease inhibitors	Plasma concentrations and pharmacologic effects of HCV protease inhibitors may be decreased by phenobarbital. Induction of CYP3A4 by phenobarbital may increase the metabolic elimination of HCV protease inhibitors.
Barbiturates (amobarbital, butabarbital, pentobarbital, phenobarbital, secobarbital)	1	Hormonal contraceptives	Barbiturate induction of contraceptive-steroid hepatic metabolism and sex hormone-binding globulin synthesis combine to reduce effective concentrations of oral contraceptives and loss of oral contraceptive efficacy, possibly

Generic Name(s)	Significance Level	Interaction	Mechanism
			leading to unintended pregnancy.
Barbiturates (phenobarbital)	1	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)	1	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)	1	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)	1	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 (amobarbital, butabarbital, pentobarbital, phenobarbital, secobarbital)	1	Sodium oxybate	Concurrent use of sodium oxybate and barbiturates may result in an increase in sleep duration and central nervous system depression.
Barbiturates (phenobarbital)	1	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 (phenobarbital)	2	Aromatase inhibitors	Plasma concentrations and pharmacologic effects of aromatase inhibitors may be decreased by phenobarbital. Induction of cytochrome P450

Generic Name(s)	Significance Level	Interaction	Mechanism
			3A4 isoenzymes by phenobarbital may increase the metabolic elimination of aromatase inhibitors.
Barbiturates (amobarbital, butabarbital, pentobarbital, phenobarbital, secobarbital)	2	Cabazitaxel	Plasma concentrations and pharmacologic effects cabazitaxel may be decreased by barbiturates.
Barbiturates (butabarbital)	2	Cephalosporins	The combination of butabarbital and cephalosporins may produce acute alcohol intolerance.
Barbiturates (amobarbital, butabarbital, pentobarbital, phenobarbital, secobarbital)	2	Clozapine	Clozapine plasma concentrations may be reduced, possibly through induction of hepatic metabolism of clozapine, decreasing the pharmacologic effects.
Barbiturates (amobarbital, butabarbital, pentobarbital, phenobarbital, secobarbital)	2	Corticosteroids	Decreased pharmacologic effects of the corticosteroid may be observed, with possible exacerbation of the disease being treated, due to stimulation of corticosteroid metabolism secondary to barbiturate induction of liver enzymes.
Barbiturates (phenobarbital)	2	Deferasirox	Plasma concentrations and pharmacologic effects of deferasirox may be decreased by phenobarbital. Induction of UDP-glucuronosyltransferase (UGT) by phenobarbital may increase the metabolic elimination of deferasirox.
Barbiturates (amobarbital, butabarbital, pentobarbital, phenobarbital, secobarbital)	2	Doxycycline	Barbiturates may increase the hepatic metabolism of doxycycline via stimulation of microsomal enzymes. The coadministration of a barbiturate with doxycycline may decrease the half-life and serum levels of doxycycline, possibly resulting in a decreased therapeutic effect.
Barbiturates (phenobarbital)	2	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)	2	Epothilones	The pharmacologic effects of epothilones may be decreased by strong CYP3A4 inducers, such as phenobarbital. Induction of

Generic Name(s)	Significance Level	Interaction	Mechanism
			cytochrome P450 3A4 isoenzymes by phenobarbital may increase the metabolic elimination of epothilones.
Barbiturates (phenobarbital)	2	Erlotinib	Plasma concentrations of Erlotinib may be decreased by coadministration of phenobarbital. The potential for reduced therapeutic effects of erlotinib should be considered. Induction of cytochrome P450 3A4 isoenzymes by phenobarbital may increase the metabolic elimination of erlotinib.
Barbiturates (amobarbital, butabarbital, pentobarbital, phenobarbital, secobarbital)	2	Estradiol valerate	Plasma concentrations and pharmacologic effects of estradiol valerate may be decreased by barbiturates. Induction of CYP3A4 isoenzymes by barbiturates may increase the metabolic elimination of estradiol valerate.
Barbiturates (butabarbital)	2	Furazolidone	The combination of butabarbital and furazolidone may produce acute alcohol intolerance.
Barbiturates (phenobarbital)	2	HIV protease inhibitors	Plasma concentrations and pharmacologic effects of HIV protease inhibitors may be decreased by phenobarbital. Induction of CYP3A4 isoenzymes by barbiturates may increase the metabolic elimination of HIV protease inhibitors.
Barbiturates (phenobarbital)	2	Imatinib	Plasma concentrations and pharmacologic effects of imatinib may be decreased by phenobarbital. Induction of CYP3A4 isoenzymes by barbiturates may increase the metabolic elimination of imatinib.
Barbiturates (phenobarbital)	2	Ivacaftor	Plasma concentrations and pharmacologic effects of ivacaftor may be decreased by phenobarbital. Induction of CYP3A4 isoenzymes by barbiturates may increase the metabolic elimination of ivacaftor.
Barbiturates (phenobarbital)	2	Maraviroc	Induction of CYP3A4 isoenzymes by long-acting barbiturates may increase the metabolic elimination of maraviroc and decrease its

Generic Name(s)	Significance Level	Interaction	Mechanism
			pharmacologic effects.
Barbiturates (amobarbital, butabarbital, pentobarbital, phenobarbital, secobarbital)	2	Methoxyflurane	Barbiturates appear to stimulate degradation of methoxyflurane, perhaps to nephrotoxic metabolites. Enhanced renal toxicity may occur.
Barbiturates (amobarbital, butabarbital, pentobarbital, phenobarbital, secobarbital)	2	Metronidazole	Barbiturate induction of metronidazole metabolism resulting in more rapid elimination and lower serum concentrations may cause therapeutic failure of metronidazole.
Barbiturates (phenobarbital)	2	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)	2	MTOR inhibitors	Induction of CYP34A isoenzymes by phenobarbital may increase the metabolic elimination and decrease pharmacological of MTOR inhibitors.
Barbiturates (phenobarbital)	2	NNRT inhibitors	Induction of CYP34A isoenzymes by phenobarbital may increase the metabolic elimination and decrease pharmacological of NNRT inhibitors.
Barbiturates (amobarbital, butabarbital, pentobarbital, phenobarbital, secobarbital)	2	Quinidine	Barbiturates appear to produce decreased quinidine serum concentrations and a decreased quinidine elimination half-life, possibly because of an increased metabolic clearance of quinidine.
Barbiturates (phenobarbital)	2	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 (amobarbital, butabarbital, pentobarbital, phenobarbital, secobarbital)	2	Tacrolimus	Plasma concentrations and pharmacologic effects of tacrolimus may be decreased, due to increased hepatic metabolism of tacrolimus via CYP3A4.
Barbiturates	2	Theophylline	Decreased theophylline levels

Generic Name(s)	Significance Level	Interaction	Mechanism
(amobarbital, butabarbital, pentobarbital, phenobarbital, secobarbital)			may possibly result in reduced therapeutic effects. Barbiturates may induce cytochrome P450, stimulating theophylline metabolism and increasing clearance.
Barbiturates (phenobarbital)	2	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)	2	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, pentobarbital, phenobarbital, secobarbital)	2	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)	2	Valproic acid	Valproic acid may decrease the hepatic metabolism of barbiturates. Plasma barbiturate concentrations may be elevated, increasing the pharmacologic and adverse effects.
Barbiturates (phenobarbital)	2	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.
Barbiturates (phenobarbital)	2	Vasopressin receptor antagonists	Plasma concentrations and pharmacologic effects of vasopressin receptor antagonists may be decreased by phenobarbital. Induction of CYP3A4 isoenzymes by barbiturates may increase the metabolic elimination of vasopressin receptor antagonists.

Significance Level 1 = major severity
Significance Level 2 = moderate severity

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[1-5]

Adverse Events	Amobarbital	Butabarbital	Pentobarbital	Phenobarbital	Secobarbital
Cardiovascular					
Bradycardia	✔	✔	✔	✔	-
Hypotension	✔	✔	✔	✔	✔
Syncope	✔	✔	✔	✔	-
Central Nervous System					
Abnormal thinking	✔	✔	✔	-	-
Agitation	✔	✔	✔	✔	-
Anxiety	✔	✔	✔	✔	-
Ataxia	✔	✔	✔	✔	-
Confusion	✔	✔	✔	✔	✔
CNS depression	✔	-	-	✔	✔
CNS 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	✔	1-3	✔	✔	-
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	Pentobarbital	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

VII. Dosing and Administration

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

Table 7. Usual Dosing Regimens for the Barbiturates[1-5]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Amobarbital	Hypnotic: 65-200 mg at bedtime Sedative: 30-50 mg administered 2 to 3 times daily	Sedative/Hypnotic: 6-12 years: 65-500 mg IV	Injection: 500 mg
Butabarbital	Hypnotic: 50-100 mg at bedtime Preoperative Sedative: 50-100 mg administered 60-90 minutes before surgery Sedative: 15-30 mg administered 3 to 4 times daily	Preoperative Sedative: 2-6 mg/kg administered 60-90 minutes before surgery	Elixir: 30 mg/5 ml Tablet: 30 mg 50 mg
Pentobarbital	Anticonvulsant: The dosage should be kept to a minimum to avoid compounding the depression which may follow convulsions. Sedative/Hypnotic: IM: 150-200 mg as a single dose IV: 100 mg; may repeat every 1-3 minutes up to 200-500 mg total dose	Anticonvulsant: The dosage should be kept to a minimum to avoid compounding the depression which may follow convulsions. Sedative/Hypnotic: 2-6 mg/kg as a single IM injection; maximum, 100 mg	Injection: 50 mg/ml
Phenobarbital	Acute Convulsions: Injection: 20-320 mg IM/IV, repeated in 6 hours as	Anticonvulsant: Elixir: 3-6 mg/day	Elixir: 20 mg/5 ml

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	necessary Anticonvulsant: Elixir: 60-200 mg/day Tablet: 50-100 mg 2 or 3 times daily Hypnotic: Elixir: 100-200 mg at bedtime Injection/Tablet: 100-320 mg at bedtime Preoperative Sedative: Injection: 100-200 mg IM 60 to 90 minutes before surgery Sedative: Elixir/Injection/Tablet: 30-120 mg/day in 2-3 divided doses	Injection: 4-6 mg/kg/day for 7 to 10 days to blood level of 10 to 15 mcg/ml or 10-15 mg/kg/day IM/IV Tablet: 15-50 mg 2 or 3 times daily Preoperative Sedation: Injection: 1-3 mg/kg IM/IV 60-90 minutes prior to procedure Sedative: Tablet: 6 mg/kg in 3 divided doses Status Epilepticus: Injection: 15-20 mg/kg IV	Injection: 60 mg/ml 65 mg/ml 130 mg/ml Tablet: 15 mg 16.2 mg 30 mg 32.4 mg 60 mg 64.8 mg 97.2 mg 100 mg
Secobarbital	Hypnotic: 100 at bedtime Preoperative Sedative: 200-300 mg 1 to 2 hours before surgery	Preoperative Sedative: 2-6 mg/kg 1 to 2 hours before surgery	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.[15] (2006) Phenobarbital 60 mg QID for 1 day, 60 mg TID for 1 day, 60 mg BID for 1 day then 60 mg QD for 1 day vs gabapentin 2,400 mg on day 1 (titrated), 600 mg TID for 1 day, 600 mg BID for 1 day, then 600 mg QD for 1 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	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.
Insomnia				
Mello de Paula et al.[16] (1983) Pentobarbital 100 mg vs zopiclone 7.5 mg	DB, RCT Patients with insomnia and ≥3 of the following occurring regularly for at least 1 month: sleep onset exceeding 30 minutes, duration of	N=60 16 days	Primary: Efficacy (sleep onset, duration, frequency of awakenings, feeling of restfulness, alcohol, coffee and cigarette consumption,	Primary: Both pentobarbital and zopiclone showed significant improvement compared to placebo in therapeutic effect (P<0.001), sleep duration (P<0.001), sleep quality (P<0.001) and sleep onset (P<0.001). Zopiclone showed significant improvement compared to pentobarbital in sleep quality (P<0.05), therapeutic effect (P<0.05) and condition in the morning (P<0.01). Sleep onset and duration of sleep did not differ significantly among the 2 active treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	sleep per night <7 hours, ≥2 awakenings per night, total time awake exceeding 30 minutes, awakening ≥2 hours prior to expected time, and non-restful sleep		patient judgment of therapeutic effect), side effects	Fewer side effects were experienced in the zopiclone group (P<0.05).
Okawa et al.[17] (1978) Secobarbital 100 mg vs triazolam 0.5 mg vs placebo	DB, RCT, XO (2 trials) Patients 18 to 60 years of age with a history of insomnia and 2 of the following: onset of sleep longer than 30 minutes, duration of sleep 6 hours or less, or experiencing 3 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 6 hours or more), adverse effects	Primary: One trial compared triazolam to placebo and involved 19 patients. Sixteen patients preferred triazolam over placebo and 3 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 2 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, 3 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 6 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.
Seizures				
Painter et al.[11] (1999)	RCT, SB	N=59	Primary: Complete seizure	Primary: Phenobarbital controlled seizures completely in 43% of patients, while

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Phenobarbital 25 mcg/ml vs phenytoin 3 mcg/ml	Neonates with seizures	5 years	control determined by electro-encephalography	phenytoin controlled seizures in 45% of patients (P=1.00).
Smith et al.[8] (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	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.
Treiman et al.[9] (1998) Phenobarbital 15 mg/kg vs diazepam 0.15 mg/kg, followed by phenytoin 18 mg/kg vs lorazepam 0.1	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	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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/kg vs phenytoin 18 mg/kg				
Miscellaneous				
Gerhardt et al.[10] (2011) Secobarbital 100 mg for 1 to 2 doses post-discharge vs placebo	RCT, DB, PC Patients 18 to 65 years of age who presented to the Emergency Department (ED) with a migraine (with or without aura). Patients underwent standard treatment in the ED (IV 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 (VAS) 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 ED discharge. In the secobarbital group, the average change in reported headache pain was a decrease of 25 mm (95% CI, −13 to −38 mm; P=0.01 vs placebo). Secondary: A total of 94% of patients receiving secobarbital self-reported partial or complete headache resolution (95 CI, 81%-100%) compared to 50% of patients receiving placebo (95% CI, 24%-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, PRN=as needed, 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, PR=peer-reviewed, R=randomized, RCT=randomized controlled trial, SB=single-blind, XO=crossover

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®	$$$$$	N/A
Butabarbital	elixir, tablet	Butisol Sodium®	$$$-$$$$$	N/A
Pentobarbital	injection	Nembutal Sodium®	$$$-$$$$	N/A
Phenobarbital	elixir, injection, tablet	Luminal Sodium®	$$$	$
Secobarbital	capsule	Seconal Sodium®	$$$$	N/A

N/A=Not available

X. Conclusions

The barbiturates are approved for the treatment of insomnia and for the induction of sedation.[1-5] 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.

Currently, there are no clinical guidelines that recommend the use of a barbiturate as first-line therapy for any condition in an outpatient setting.[7,12-14] 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.

The use of barbiturates is associated with abuse and psychological/physical dependence.[1-5] 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 2 weeks.[1-6] 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 generics and OTC 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.

XII. References

1. Drug Facts and Comparisons. Drug Facts and Comparisons 4.0 [online]. 2012. Available from Wolters Kluwer Health, Inc. Accessed May 2012.
2. Lexi-Comp Online, Lexi-Drugs Online, Hudson, Ohio: Lexi-Comp, Inc.; 2012; May 2012.
3. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed May 2012.
4. Butisol Sodium® [package insert]. Somerset, NJ: Meda Pharmaceuticals, Inc.; January 2009.
5. Nembutal Sodium® [package insert]. Deerfield, IL: Lundbeck, Inc.; May 2009.
6. DuPont R, Greene W, Lydiard R. Sedatives and hypnotics abuse and dependence: Pharmacology and epidemiology. In: UpToDate, Oslin, D (Ed), UpToDate, Waltham, MA, 2012.
7. Wheless JW, Clarke DF, Carpenter D. Treatment of pediatric epilepsy: expert opinion. J Child Neurol 2005;20 (Suppl 1):S1-56.
8. Smith CT, Marson AG, Williamson PR. Carbamazepine versus phenobarbitone monotherapy for epilepsy. Cochrane Database of Systematic Reviews. 2003;1.
9. Treiman D, Meyers P, Walton N, Collins J, Colling C, Rowan AJ, et al. A comparison of four treatments for generalized convulsive status epilepticus. Veterans Affairs Status Epilepticus Cooperative Study Group. N Engl J Med 1998;339:792-8.
10. Gerhardt RT, Hermstad E, Crawford DM, et al. Postdischarge secobarbital after ED migraine treatment decreases pain and improves resolution. Am J Emerg Med 2011;29:86-90.
11. Painter M, Scher M, Stein A, Armatti S, Wang Z, Gardiner J, et al. Phenobarbital compared with phenytoin for the treatment of neonatal seizures. N Engl J Med 1999;341:485-9.
12. Schutte-Rodin S, Broch L, Buysse D, et al. Clinical guideline for the evaluation and management of chronic insomnia in adults. American Academy of Sleep Medicine (AASM). J Clin Sleep Med 2008;4:487-504.
13. NIH State-of-the-Science Conference statement on manifestations and management of chronic insomnia in adults. NIH Consens Sci Statements 2005;22(2) 1-30. Available from: http://consensus.nih.gov/2005/insomniastatement.pdf. Accessed May 2012.
14. Meierkord H, Boon P, Engelsen B, Göcke K, Shorvon S, Tinuper P, et al. EFNS guideline on the management of status epilepticus. Eur J Neurol 2006;13:445-50.
15. Mariani JJ, Rosenthal RN, Tross S, Singh P, Anand OP. A randomized, open-label, controlled trial of gabapentin and phenobarbital in the treatment of alcohol withdrawal. Am J Addict. 2006 Jan-Feb;15:76-84.
16. Mello de Paula A. Comparative study of zopiclone and pentobarbitone as hypnotics. Pharmacology 1983;27 Suppl 2:188-95.
17. Okawa KK, Allens G. A clinical comparison of triazolam with placebo and with secobarbital in insomniac patients. J Int Med Res 1978;6:343-7.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Anxiolytics, Sedatives and Hypnotics – Benzodiazepines
AHFS Class 282408
August 8, 2012

I. Overview

The benzodiazepines are approved for the treatment of anxiety disorders and insomnia.[1-16] Anxiety disorders include generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder and social phobia.[17] 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, quazepam, temazepam and triazolam. The key diagnostic feature of primary insomnia is difficulty initiating or maintaining sleep for at least one month, which causes marked distress or impairment in social, occupational, or other important areas of functioning.[17] 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. 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).

Benzodiazepines potentiate the effects of gamma-aminobutyric acid (GABA) and other inhibitory neurotransmitters.[1-16] Within the body, there are 3 major benzodiazepine receptor subtypes. Benzodiazepine receptor subtype-1 is located throughout the central nervous system (CNS) 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, CNS depression, as well as psychomotor impairment. Depression of the CNS may range from mild impairment of task performance to hypnosis.[1-3] Benzodiazepine receptor subtype-3 is located throughout the body and glial cells, and is believed to contribute to tolerance and withdrawal when activated.[1-3] The benzodiazepines are mechanistically similar; however, they differ with regards to their pharmacokinetic properties.[18-19] 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.

Clobazam was approved by the FDA in October 2011 for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients ≥2 years of age.[7] However, it has been available internationally for many years for the treatment of anxiety and epilepsy. LGS is characterized by a triad of signs, including multiple seizure types, slow spike waves on EEG recordings, and cognitive function deterioration.[68] It is one of the most difficult epilepsies to treat and most patients require combination therapy to control their seizures.

The benzodiazepines that are included in this review are listed in Table 1. Benzodiazepines are an excludable/optional drug class in accordance with the Omnibus Budget Reconciliation Act of 1990 (OBRA 90). There are several brand and generic products that are not covered by Alabama Medicaid. However, 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 and quazepam. This class was last reviewed in February 2010.

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	Niravam®*‡, Xanax®*‡, Xanax XR®*‡	alprazolam, alprazolam ER, alprazolam ODT
Chlordiazepoxide	capsule	N/A	chlordiazepoxide

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Clobazam	tablet	Onfi®‡	none
Clonazepam	orally disintegrating tablet, tablet	Klonopin®*‡	clonazepam
Clorazepate	tablet	Tranxene T-Tab®*‡	clorazepate
Diazepam	injection, oral concentrate, rectal gel, solution, tablet	Diastat®*, Diastat AcuDial®*, Valium®*‡	diazepam, Diastat®*, Diastat AcuDial®*
Estazolam	tablet‡	N/A	none
Flurazepam	capsule	N/A	flurazepam
Lorazepam	injection, oral concentrate, tablet	Ativan®*‡	lorazepam
Midazolam	injection, syrup‡	N/A	midazolam
Oxazepam	capsule	N/A	oxazepam
Quazepam	tablet	Doral®‡	none
Temazepam	capsule	Restoril®*‡	temazepam
Triazolam	tablet	Halcion®*‡	triazolam

*Generic is available in at least one dosage form or strength.
‡Product is currently not covered by Alabama Medicaid.
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 (NICE): **Generalized Anxiety Disorder and Panic Disorder (With or Without Agoraphobia) in Adults[28] (2011)**	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)
	  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.
	Panic Disorder General Considerations
	• 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

Clinical Guideline	Recommendation(s)
	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 selective serotonin-reuptake inhibitors (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 6 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 (APA): **Practice Guideline for the Treatment of Patients with Panic Disorder, Second Edition**[27] **(2009)**	• Selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (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 favorable safety and side effect profile of SSRIs and SNRIs makes them the best initial choice for many patients with panic disorder. • Selective serotonin reuptake inhibitors, 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. Several studies suggest that the short-term (4–6 week) addition of benzodiazepines to antidepressants produces a more rapid therapeutic response. Benzodiazepines may be used along with antidepressants to help control symptoms until the antidepressant takes effect, followed by slow tapering of the benzodiazepine. • With ongoing use, all benzodiazepines will produce physiological dependence in most patients. • Other medications with less empirical data (e.g., mirtazapine, anticonvulsants such as gabapentin) 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	• A multimodal treatment approach for children and adolescents with

Clinical Guideline	Recommendation(s)

Adolescent Psychiatry (AACAP): **Practice Parameter for the Assessment and Treatment of Children and Adolescents with Anxiety Disorders**[29] **(2007)**	anxiety disorders should consider education of the parents and the child about the anxiety disorder, consultation with school personnel and primary care physicians, cognitive-behavioral interventions, psychodynamic psychotherapy, family therapy, and pharmacotherapy.
	• Treatment of childhood anxiety disorders of mild severity should begin with psychotherapy.
	• Valid reasons for combining medication and treatment with psychotherapy include the following:
	  o Need for acute symptom reduction in a moderately to severely anxious child
	  o A comorbid disorder that requires concurrent treatment
	  o Partial response to psychotherapy and potential for improved outcome with combined treatment.
	• Selective serotonin-reuptake inhibitors (SSRIs) have emerged as the medication of choice in the treatment of childhood anxiety disorders.
	• When anxiety disorder symptoms are moderate or severe or impairment makes participation in psychotherapy difficult, or psychotherapy results in a partial response, treatment with medication is recommended.
	• No controlled studies are available for medication treatment of childhood-onset panic disorder. The use of a SSRI in adolescents with panic disorder has shown significant improvement in panic symptoms.
	• Controlled trials have established the safety and efficacy of short-term treatment with SSRIs for childhood anxiety disorders; however, the benefits and risks of long-term use of SSRIs have not been studied. It is recommended that clinicians consider a medication-free trial for children who have a significant reduction in anxiety or depressive symptoms on an SSRI and maintain stability in these symptoms for 1 year.
	• There is no empirical evidence that a particular SSRI is more effective than another for treatment of childhood anxiety disorders. The choice is often based on side effects, duration of action, or positive response to a particular SSRI in a first-degree relative with anxiety.
	• The risk-benefit ratio for a medication trial needs to be carefully assessed because cognitive-behavioral therapy (CBT) has been shown to be effective and long-term side effects of medications have not been studied in youths.
	• The safety and efficacy of medications other than SSRIs for the treatment of childhood anxiety disorders have not been established.
	• Noradrenergic antidepressants (venlafaxine and tricyclic antidepressants), buspirone, and benzodiazepines have been suggested as alternatives to be used alone or in combination with the SSRIs.
	• Data are limited in childhood anxiety disorders to guide treatment with combinations of medications when a single medication is not effective in managing anxiety symptoms. Comorbid diagnoses are strongly considered in selection of medication.
	• Preliminary findings from controlled trials of extended-release venlafaxine in the treatment of youths with generalized anxiety disorder (GAD) and social phobia suggest it may be well tolerated and effective relative to placebo.
	• Controlled trials with tricyclic antidepressants for pediatric anxiety disorders have shown conflicting results and have not established efficacy for this use.
	• Buspirone may be an alternative to SSRIs for GAD in youths, but there are no published controlled trials.

Clinical Guideline	Recommendation(s)
	• Benzodiazepines have not shown efficacy in controlled trials in childhood anxiety disorders despite established benefit in adult trials. They are used as an adjunct short-term treatment with SSRIs to achieve rapid reduction in severe anxiety symptoms that may permit initiation of the exposure phase of CBT. Clinicians should use benzodiazepines cautiously because of the possibility of developing dependency.
American Psychiatric Association (APA): **Practice Guideline for the Treatment of Patients with Obsessive-Compulsive Disorder[22] (2007)**	General Considerations • Obsessive-compulsive disorder (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 (CBT), serotonin-reuptake inhibitors (SRIs), or a combination of the two. The choice depends on past treatment history, comorbid psychiatric conditions, severity of symptoms, and functional limitations. • CBT 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 4-6 after treatment initiation, and some may ultimately respond after as many as 10-12 weeks. • Patients not responding after 10-12 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 CBT or augmentation of CBT 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.

Clinical Guideline	Recommendation(s)
	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 Psychiatric Association (APA): **Practice Guideline for the Treatment of Patients with Acute Stress Disorder and Posttraumatic Stress Disorder (PTSD)[23] (2004)**	• 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.

American Academy of Sleep Medicine (AASM): **Clinical Guideline for the Evaluation and Management of Chronic Insomnia in Adults[24] (2008)**	• 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, the 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 sequence of medication trials is as follows:
	• Short-intermediate acting benzodiazepine receptor agonists (BzRAs) or ramelteon
	  o No specific agent is preferable to the others. Each has been shown to have positive effects on sleep latency, total sleep time, and wake after sleep onset in placebo-controlled trials.
	  o Individual patients may respond differentially to medications within this class. Symptom pattern, past response and patient preference should be considered in selecting a specific agent.
	  o Zaleplon and ramelteon have very short half-lives and are likely to reduce sleep latency but have little effect on waking after sleep onset. They are unlikely to result in residual sedation.
	  o Eszopiclone and temazepam have relatively longer half-lives, are more likely to improve sleep maintenance, and are more

Clinical Guideline	Recommendation(s)
	likely to produce residual sedation (residual activity is limited to a minority of patients). o Triazolam has been associated with rebound anxiety and is not considered a first-line hypnotic. o Patients who prefer not to use a DEA-scheduled drug, and patients with a history of substance use disorders, may be candidates for ramelteon, particularly if the complaint is that of sleep initiation difficulty. • Alternate short-intermediate acting BzRAs or ramelteon o If a patient does not respond to the initial agent, a different agent within the same class is appropriate. o Selection of the alternative drug should be based on the patient's response to the first. For a patient who continues to complain of wake after sleep onset might be prescribed a drug with a longer half-life; a patient who complains of residual sedation might be prescribed a shorter-acting drug. o Flurazepam is rarely used because of its extended half-life. • Sedating low-dose antidepressants o May be used next when accompanied with comorbid depression or treatment failures. o Examples of these include trazodone, amitriptyline, doxepin, and mirtazapine. No specific agent is recommended as preferable to the others in this group. o Treatment history, coexisting medical conditions, side effects, and pharmacokinetics may guide the selection of a specific agent. • Combined BzRA or ramelteon and sedating antidepressants o A combination of medications from two different classes may improve efficacy by targeting multiple sleep-wake mechanisms while minimizing the toxicity that could occur with higher doses of a single agent. • Other sedating agents o Examples include anti-epilepsy medications (gabapentin, tiagabine) and atypical antipsychotics (quetiapine and olanzapine). o 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. • Prescription drugs – not recommended: o Older approved drugs for insomnia including barbiturates, barbiturate-type drugs and chloral hydrate are not recommended for the treatment of insomnia. • Over-the-counter drugs – not recommended: o Antihistamine or antihistamine/analgesic type drugs (OTC "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. • 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.

Clinical Guideline	Recommendation(s)
	• 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 CBT-I. • 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 follow-up, ongoing assessment of effectiveness, monitoring for adverse effects, and evaluation for new onset or exacerbation of comorbid disorders. • Long-term administration may be nightly, intermittent (e.g., three nights per week), or as needed.
National Institutes of Health (NIH): **Manifestations and Management of Chronic Insomnia in Adults[26] (2005)**	<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 (CBT) has been found to be as effective as prescription medications for short-term treatment of chronic insomnia. The beneficial effects of CBT may last well beyond the termination of active treatment. <u>Benzodiazepine Receptor Agonists</u> • Benzodiazepine receptor agonists include benzodiazepines (e.g., estazolam, flurazepam, quazepam, temazepam and triazolam) and newer agents that act at benzodiazepine receptors but have a nonbenzodiazepine structure (e.g., eszopiclone, zaleplon and zolpidem). • Results from moderate to high-quality studies indicate that these eight agents are effective in the short-term management of insomnia. With the exception of eszopiclone, the benefits of these agents for long-term use have not been studied using randomized, controlled trials. • 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

Clinical Guideline	Recommendation(s)
	individuals with chronic insomnia are lacking. Nonprescription Medications • Antihistamines are the most commonly used OTC treatments for chronic insomnia, but there is no systematic evidence for efficacy and there are significant concerns about risks of these medications.
American Academy of Neurology (AAN)/American Epilepsy Society (AES): **Efficacy and Tolerability of the New Antiepileptic Drugs, II: Treatment of Refractory Epilepsy[21] (2004)**	Lennox-Gastaut Syndrome • Patients with Lennox-Gastaut syndrome are difficult to treat and require drugs that are broad spectrum. They are also prone to exacerbation by AEDs. Carbamazepine has been reported to cause seizure worsening. • Topiramate and lamotrigine may be used to treat drop attacks associated with the Lennox Gastaut syndrome in adults and children. • Lamotrigine at doses adjusted for weight and valproic acid use, ranging from 50 to 400 mg/day, reduces seizures associated with the Lennox-Gastaut syndrome. • Topiramate 6 mg/kg/day is effective in reducing drop attacks (tonic and atonic seizures) in patients with the Lennox-Gastaut syndrome. • There is no evidence that gabapentin, tiagabine, oxcarbazepine, levetiracetam, or zonisamide are effective. • In case reports lamotrigine and gabapentin both worsened myoclonic seizures in some patients.
European Federation of Neurological Societies (EFNS): **Guideline on the Management of Status Epilepticus[31] (2006)**	General Recommendations for the Management of Generalized Convulsive Status Epilepticus (GCSE), Non-convulsive Status Epilepticus (NCSE), and Subtle Status Epilepticus • Assessment/control of the airways and of ventilation, arterial blood gas monitoring, ECG, blood pressure monitoring, intravenous glucose and thiamine as required, emergency measurement of antiepileptic drug levels, electrolytes and magnesium, a full hematological screen, and measures of hepatic and renal function. • The cause of the status should be identified urgently. Initial Pharmacological Treatment Recommendations for GCSE and NCSE • The preferred treatment is intravenous administration of lorazepam 4 mg, to be repeated if seizures continue for more than 10 minutes after first injections. If necessary, additional phenytoin (15-18 mg/kg) or equivalent fosphenytoin is recommended. • Alternatively, diazepam 10 mg directly (route of administration not specified) followed by phenytoin (15-18 mg/kg) or equivalent fosphenytoin. If seizures continue for more than 10 minutes after injection an additional 10 mg of diazepam is recommended. If necessary, additional lorazepam (4-8 mg) should be administered. • Refractory status epilepticus, or GCSE that does not respond to initial anticonvulsant agents, needs to be treated on an intensive care unit. Pharmacological Treatment Recommendations for Refractory GCSE and Subtle Status Epilepticus • Anesthetic doses of midazolam, propofol or barbiturates are recommended (pentobarbital given as a bolus dose of 10-20 mg/kg followed by an infusion of 0.5-1 mg/kg/hour increasing to 1-3 mg/kg/hour). Pharmacological Treatment Recommendations for Refractory NCSE • Phenobarbital 20 mg/kg intravenously. • Valproic acid 25-45 mg/kg as intravenous bolus followed by maximum rates up to 6 mg/kg/min.
Journal of Child Neurology: **Treatment of Pediatric Epilepsy: Expert Opinion[25]**	• 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

Clinical Guideline	Recommendation(s)
(2005)	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.
National Institute for Health and Clinical Excellence (NICE): **Alcohol-Use Disorders. Diagnosis, Assessment and Management of Harmful Drinking and Alcohol Dependence[20] (2011)**	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 (APA): **Treatment of Patients with Substance Use Disorders, Second Edition[30] (2007)**	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 3-4. 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-E)[1-16]

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			✔				
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 myoclonic seizures				✔			

Indication	Alprazolam	Chlordiazepoxide	Clobazam	Clonazepam	Clorazepate	Diazepam	Estazolam
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)
‡Extended-release formulation
‖Injection formulation
§Orally disintegrating tablet formulation
†Rectal formulation

Table 4. FDA-Approved Indications for the Benzodiazepines (Drugs F-T)[1-16]

Indication	Flurazepam	Lorazepam	Midazolam	Oxazepam	Quazepam	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[1-16]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Alprazolam	ER: 90	80	Liver	Renal (80)	ER: 10.7-15.8 IR: 6.3-26.9 ODT: 7.9-19.2
Chlordiazepoxide	Not reported	90-98	Liver	Renal (1-2)	10-48
Clobazam	87	80-90	Liver	Renal (82) Feces (11)	36-42
Clonazepam	90	85	Liver	Renal (<1)	30-40
Clorazepate	91	97-98	Liver	Renal (62-67) Feces (15-19)	2.29
Diazepam	98	94-99	Liver	Renal (75)	0.83-2.25 days
Estazolam	Not reported	93	Not reported	Renal Feces (4)	10-24
Flurazepam	Not reported	97	Liver	Renal	2.3
Lorazepam	90-93	85-91	Liver (75)	Renal (88) Feces (7)	12
Midazolam	36	95	Liver	Renal (45-57)	1.8-6.4
Oxazepam	93	86-99	Liver	Renal (50)	2.8-8.6
Quazepam	Not reported	95	Liver	Renal (31) Feces (23)	25-41
Temazepam	Well absorbed	96	Not reported	Renal (80-90)	3.5-18.4
Triazolam	Well absorbed	89-94	Liver	Renal (80) Feces (9)	2.3

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

V. Drug Interactions

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

Table 6. Significant Drug Interactions with the Benzodiazepines[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Benzodiazepines (diazepam, midazolam)	1	Azole antifungals	Increased and prolonged serum levels, CNS depression, and psychomotor impairment have been reported with benzodiazepines undergoing oxidative metabolism.
Benzodiazepines (clobazam, clonazepam, clorazepate, diazepam, estazolam, flurazepam, lorazepam, midazolam, oxazepam, quazepam, temazepam, triazolam)	1	Clozapine	Delirium, sedation, sialorrhea, and ataxia may occur when certain benzodiazepines and clozapine are coadministered. Severe orthostatic hypotension and respiratory depression may occur.
Benzodiazepines (diazepam)	1	Disulfiram	Coadministration of diazepam and disulfiram may produce acute and severe alcohol intolerance. Symptoms include flushing, headache, palpitations,

Generic Name(s)	Significance Level	Interaction	Mechanism
			tachycardia, dyspnea, hyperventilation, nausea, and vomiting. Hypotension and cardiovascular collapse may also occur.
Benzodiazepines (clorazepate, diazepam, estazolam, flurazepam, midazolam, quazepam)	1	Protease inhibitors	Concurrent use may lead to severe sedation and respiratory depression due to inhibition of hepatic metabolism.
Benzodiazepines (clobazam, clonazepam, clorazepate, diazepam, estazolam, flurazepam, lorazepam, midazolam, oxazepam, quazepam, temazepam, triazolam)	1	Sodium oxybate	Concurrent use of sodium oxybate and benzodiazepines may result in an increase in sleep duration and central nervous system depression.
Benzodiazepines (clobazam, estazolam, midazolam)	2	Carbamazepine	The pharmacologic effects of certain benzodiazepines may be decreased due to CYP3A4 induction by carbamazepine.
Benzodiazepines (diazepam)	2	Cephalosporins	The combination of cephalosporins and diazepam may produce acute alcohol intolerance. Symptoms include flushing, headache, palpitations, tachycardia, dyspnea, hyperventilation and nausea and vomiting. Hypotensive episodes also have been reported.
Benzodiazepines (midazolam)	2	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 (diazepam, midazolam)	2	Diltiazem	Increased CNS depression and prolonged effects have been observed with the use of diltiazem and certain benzodiazepines. Diltiazem may increase plasma concentrations of midazolam due to CYP3A4 inhibition.
Benzodiazepines (clonazepam, clorazepate, diazepam, estazolam, flurazepam, quazepam, temazepam, triazolam)	2	Disulfiram	Pharmacologic effects of certain benzodiazepines may be increased by disulfiram due to inhibition of benzodiazepine hepatic metabolism.
Benzodiazepines (midazolam)	2	Efavirenz	Pharmacologic and toxic effects of midazolam may be increased

Generic Name(s)	Significance Level	Interaction	Mechanism
			by efavirenz due to inhibition of CYP2C9, 2C19 and 3A4 by efavirenz.
Benzodiazepines (diazepam)	2	Furazolidone	This combination may produce acute alcohol intolerance in some patients. Symptoms include flushing, palpitations, tachycardia, dyspnea, hyperventilation, as well as nausea and vomiting.
Benzodiazepines (clobazam)	2	Hormonal contraceptives	Plasma concentrations and pharmacologic effects of hormonal contraceptives may be decreased by clobazam. Menstrual irregularities and/or contraceptive failure may occur
Benzodiazepines (clobazam, clorazepate, diazepam, estazolam, flurazepam, lorazepam, midazolam, oxazepam, quazepam, temazepam, triazolam)	2	Hydantoins	Serum hydantoin concentrations may be increased and phenytoin may increase the clearance of certain benzodiazepines.
Benzodiazepines (diazepam, estazolam, midazolam)	2	Macrolides and ketolides	CNS depression and prolonged sedation have been reported with the concurrent use of benzodiazepines and macrolides/ketolides.
Benzodiazepines (diazepam)	2	Metronidazole	This combination may produce alcohol intolerance reactions.
Benzodiazepines (lorazepam)	2	Narcotic analgesics	This combination may interact synergistically thus reducing the dosages needed for amnesia and analgesia. The hemodynamic status of some patients may deteriorate unexpectedly when these agents are coadministered.
Benzodiazepines (clonazepam, clorazepate, diazepam, estazolam, flurazepam, midazolam, quazepam)	2	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 (clobazam, clonazepam, clorazepate, diazepam, estazolam, flurazepam, midazolam, quazepam)	2	Omeprazole	Pharmacologic effects of certain benzodiazepines may be increased by omeprazole due to decreased hepatic oxidative metabolism. Toxicity may occur.
Benzodiazepines (clonazepam, clorazepate, diazepam, estazolam, flurazepam, midazolam, quazepam)	2	Rifamycins	Pharmacologic effects of certain benzodiazepines may be decreased by rifamycins due to CYP3A4 induction and increased metabolic elimination.

Generic Name(s)	Significance Level	Interaction	Mechanism
Benzodiazepines (clonazepam, diazepam, midazolam)	2	St. John's Wort	Plasma concentrations and pharmacologic effects of certain benzodiazepines may be decreased by St. John's wort. Reductions in the therapeutic efficacy of benzodiazepines may occur due to induction of CYP3A4 by St. John's wort and increased elimination of the benzodiazepine.
Benzodiazepines (clonazepam)	2	Valproic acid	Toxicity of clonazepam may be increased, while the therapeutic effects of both drugs may be reduced (increased seizure risk).
Benzodiazepines (midazolam)	2	Vasopressin receptor antagonists	Plasma concentrations of midazolam may be increased by vasopressin receptor antagonists.
Benzodiazepines (diazepam, midazolam)	2	Voriconazole	Plasma concentrations and pharmacologic effects of diazepam may be increased by voriconazole, leading to prolonged sedative effects. Inhibition of cytochrome CYP3A4 isoenzymes by voriconazole may decrease the metabolic elimination of diazepam.

Significance Level 1 = major severity
Significance Level 2 = moderate severity

VI. Adverse Drug Events

The most common adverse drug events reported with the benzodiazepines are listed in Tables 7-8. The boxed warnings for midazolam are listed in Tables 9-10. The benzodiazepines share a number of similar adverse drug events. The most common adverse events are CNS-related, including ataxia, confusion, drowsiness, dizziness and lightheadedness.[1-16] 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.[1-3]

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.[48-49] 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 1-2 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.[48,50]

Table 7. Adverse Drug Events (%) Reported with the Benzodiazepines (Drugs A-E)[1-16]

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

Adverse Events	Alprazolam	Chlordiazepoxide	Clobazam	Clonazepam	Clorazepate	Diazepam	Estazolam
Coordination abnormal	>10	-	-	✔	-	-	1-10
Delirium	-	-	✔	-	-	-	-
Delusions	-	-	✔	-	-	-	-
Depersonalization	1-10	-	-	-	-	-	-
Depression	>10	-	✔	✔	✔	✔	-
Derealization	1-10	-	-	-	-	-	-
Disinhibition	1-10	-	-	-	-	-	-
Disorientation	1-10	-	-	-	-	-	-
Dizziness	1-10	1-10	-	✔	✔	-	1-10
Dream abnormalities	1-10	-	-	-	-	-	-
Drowsiness	>10	>10	-	✔	✔	✔	-
Dysdiadochokinesia	-	-	-	✔	-	-	-
Emotional lability	-	-	-	✔	-	-	1-10
Euphoria	-	-	-	-	-	-	1-10
Fatigue	>10	>10	5	✔	✔	✔	-
Fear	1-10	-	-	-	-	-	-
Fever	-	-	13	✔	-	-	<1
Hallucinations	1-10	-	✔	✔	-	-	-
Hangover effect	-	-	-	-	-	-	1-10
Headache	1-10	-	-	✔	✔	✔	-
Hemiparesis	-	-	-	✔	-	-	-
Homicidal ideation	<1	-	-	-	-	-	-
Hostility	-	-	-	-	-	-	1-10
Hypersomnia	1-10	-	-	-	-	-	-
Hypoesthesia	1-10	-	-	-	-	-	-
Hypokinesia	-	-	-	-	-	-	1-10
Hypomania	<1	-	-	-	-	-	-
Hypotonia	-	-	-	✔	-	-	-
Hysteria	-	-	-	✔	-	-	-
Insomnia	1-10	-	5	✔	✔	-	-
Intellectual ability reduced	-	-	-	✔	-	-	-
Irritability	>10	>10	7	-	✔	-	-
Lethargy	1-10	-	10	-	-	-	-
Lightheadedness	>10	>10	-	-	✔	-	-
Malaise	1-10	-	-	-	-	-	-
Mania	<1	-	-	-	-	-	-
Memory impairment	>10	-	-	✔	✔	-	-

Adverse Events	Alprazolam	Chlordiazepoxide	Clobazam	Clonazepam	Clorazepate	Diazepam	Estazolam
Mental impairment	1-10	>10	-	-	-	-	-
Mood changes	-	-	✔	-	-	-	-
Nervousness	1-10	-	-	✔	✔	-	-
Nightmares	1-10	-	-	-	-	-	-
Paradoxical reactions	-	-	-	✔	-	✔	-
Paresthesia	1-10	-	-	-	-	-	1-10
Psychomotor hyperactivity	-	-	4	-	-	-	-
Psychosis	-	-	-	✔	-	-	-
Restlessness	1-10	-	-	-	-	-	-
Sedation	>10	-	5	-	-	-	-
Seizure	1-10	-	-	✔	-	-	1-10
Sleep disturbances	-	-	-	-	-	-	1-10
Slurred speech	-	-	-	✔	✔	✔	-
Somnolence	>10	-	22	✔	-	-	>10
Stupor	-	-	-	-	-	-	1-10
Suicidal ideation/attempts	<1	-	✔	✔	-	-	-
Talkativeness	1-10	-	-	-	-	-	-
Tremor	1-10	1-10	-	✔	✔	✔	1-10
Vasomotor disturbances	2	-	-	-	-	-	-
Vertigo	1-10	-	-	✔	-	✔	-
Dermatological							
Alopecia	-	-	-	✔	-	-	-
Dermatitis	1-10	1-10	-	-	-	-	1-10
Hirsutism	-	-	-	✔	-	-	-
Photosensitivity	-	1-10	-	-	-	-	-
Pruritus	-	-	-	-	-	-	1-10
Rash	1-10	>10	-	✔	✔	✔	1-10
Stevens-Johnson Syndrome	<1	-	✔	-	-	-	-
Toxic epidermal necrolysis	-	-	✔	-	-	-	-
Urticaria	-	-	-	-	-	-	1-10
Gastrointestinal							
Abdominal pain	1-10	-	-	✔	-	-	-
Anorexia	1-10	-	-	✔	-	-	-
Appetite increased/decreased	>10	>10	3	✔	✔	-	-
Change in appetite	-	-	-	-	-	-	1-10
Constipation	>10	-	5	✔	✔	✔	1-10
Dehydration	-	-	-	✔	-	-	-

Adverse Events	Alprazolam	Chlordiazepoxide	Clobazam	Clonazepam	Clorazepate	Diazepam	Estazolam
Diarrhea	1-10	-	-	✔	✔	✔	-
Dyspepsia	1-10	-	-	-	-	-	-
Dysphagia	-	-	2	-	-	-	-
Encopresis	-	-	-	✔	-	-	-
Flatulence	-	-	-	-	-	-	1-10
Gastritis	-	-	-	✔	-	-	1-10
Gingival soreness	-	-	-	✔	-	-	-
Nausea	1-10	-	-	✔	✔	✔	-
Salivation decreased	-	>10	-	-	✔	-	-
Salivation increased	1-10	1-10	9	-	-	✔	-
Taste alteration	-	-	-	-	-	-	1-10
Tongue coated	-	-	-	✔	-	-	-
Vomiting	1-10	-	7	-	✔	-	-
Xerostomia	>10	>10	-	✔	✔	✔	1-10
Genitourinary							
Colpitis	-	-	-	✔	-	-	-
Dysmenorrhea	1-10	-	-	✔	-	-	-
Dysuria	-	-	-	✔	-	-	-
Ejaculation delayed	-	-	-	✔	-	-	-
Enuresis	-	-	-	✔	-	-	-
Impotence	-	-	-	✔	-	-	-
Incontinence	1-10	1-10	-	-	-	✔	-
Libido decreased	>10	>10	-	✔	✔	✔	-
Libido increased	1-10	1-10	-	✔	-	✔	-
Menstrual disorders	1-10	>10	-	-	-	-	1-10
Micturition difficulty	>10	>10	-	-	-	-	1-10
Micturition frequency	-	-	-	✔	-	-	1-10
Nocturia	-	-	-	✔	-	-	-
Sexual dysfunction	1-10	1-10	-	-	-	-	-
Urinary retention	-	-	-	✔	-	✔	-
Urinary tract infection	-	-	4	✔	-	-	-
Vaginal discharge/itching	-	-	-	-	-	-	1-10
Hematologic							
Anemia	-	-	-	✔	-	-	-
Eosinophilia	-	-	✔	✔	-	-	-
Leukopenia	-	-	✔	✔	-	-	-
Neutropenia	-	-	-	-	-	✔	-

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

Adverse Events	Alprazolam	Chlordiazepoxide	Clobazam	Clonazepam	Clorazepate	Diazepam	Estazolam
Pharyngitis	-	-	-	✔	-	-	-
Pneumonia	-	-	4	-	-	-	-
Respiratory depression	-	-	✔	✔	-	✔	-
Respiratory tract infection	-	-	-	✔	-	-	-
Rhinitis	-	-	-	✔	-	-	1-10
Rhinorrhea	-	-	-	✔	-	-	-
Shortness of breath	-	-	-	✔	-	-	-
Sinusitis	-	-	-	✔	-	-	1-10
Upper respiratory infection	1-10	-	12	-	-	-	-
Special Senses							
Blurred vision	1-10	-	✔	✔	✔	✔	-
Diplopia	-	-	✔	-	✔	✔	-
Eye movements abnormal	-	-	-	✔	-	-	-
Eye pain/swelling	-	-	-	-	-	-	1-10
Nystagmus	-	-	-	✔	-	-	-
Other							
Allergic reaction	-	-	-	✔	-	-	<1
Anaphylaxis	-	-	-	-	-	-	<1
Angioedema	<1	-	-	-	-	-	<1
Aphonia	-	-	-	✔	-	-	-
Chills	-	-	-	-	-	-	<1
Diaphoresis	1-10	-	-	-	-	-	1-10
Drug dependence	-	-	-	-	-	-	<1
Edema	-	-	-	✔	-	-	-
Falls	<1	-	-	-	-	-	-
Galactorrhea	<1	-	-	-	-	-	-
Gynecomastia	<1	-	-	-	-	-	-
Hyperprolactinemia	<1	-	-	-	-	-	-
Lymphadenopathy	-	-	-	✔	-	-	-
Pain with injection	-	-	-	-	-	✔	-
Peripheral edema	<1	-	-	-	-	-	-
Phlebitis	-	-	-	-	-	✔	-
Sleep apnea syndrome	<1	-	-	-	-	-	-
Tinnitus	<1	1-10	-	-	-	-	-
Weight changes	>10	>10	-	✔	-	-	-

✔ Percent not specified
- Event not reported

Table 8. Adverse Drug Events (%) Reported with the Benzodiazepines (Drugs F-T)[1-16]

Adverse Events	Flurazepam	Lorazepam	Midazolam	Oxazepam	Quazepam	Temazepam	Triazolam
Cardiovascular							
Bigeminy	-	-	<1	-	-	-	-
Chest pain	✔	-	-	-	-	-	<1
Hypotension	✔	1-10	1-10	-	-	-	-
Palpitations	✔	-	-	-	✔	-	-
Syncope	-	-	-	✔	-	-	-
Tachycardia	-	-	-	-	-	-	<1
Central Nervous System							
Abnormal thinking	-	-	-	-	✔	-	-
Agitation	-	-	<1	-	✔	-	-
Akathisia	-	1-10	-	-	-	-	-
Amnesia	-	1-10	<1	-	✔	<1	<1
Anxiety	-	-	-	-	✔	1-10	-
Apathy	-	-	-	-	✔	-	-
Apprehension	✔	-	-	-	-	-	-
Ataxia	✔	1-10	-	✔	✔	<1	5
Coma	✔	-	-	-	-	-	-
Complex sleep-related behavior	-	-	-	-	✔	<1	<1
Confusion	✔	1-10	-	-	✔	1-10	<1
Delirium	-	-	<1	-	-	-	-
Depression	✔	1-10	-	-	✔	-	<1
Disinhibition	-	<1	-	-	-	-	-
Disorientation	-	1-10	-	-	-	-	-
Dizziness	✔	1-10	-	✔	2	1-10	8
Dream abnormalities	-	-	-	-	-	-	<1
Drowsiness	✔	-	1-10	✔	12	1-10	14
Dysesthesia	-	-	-	-	-	-	<1
Dystonia	-	-	-	-	✔	-	-
Euphoria	✔	<1	<1	-	✔	1-10	<1
Faintness	✔	-	-	-	-	-	-
Fatigue	-	<1	-	-	2	1-10	<1
Hallucinations	✔	-	<1	-	✔	-	-
Hangover effect	✔	-	-	-	-	1-10	-
Headache	✔	1-10	1-10	✔	5	1-10	10
Hyperkinesia	-	-	-	-	✔	-	-
Hypokinesia	-	-	-	-	✔	-	-
Incoordination	-	-	-	-	✔	-	-

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

Adverse Events	Flurazepam	Lorazepam	Midazolam	Oxazepam	Quazepam	Temazepam	Triazolam
Gastrointestinal pain	✔	-	-	-	-	-	-
Heartburn	✔	-	-	-	-	-	-
Hiccups	-	-	1-10	-	-	-	-
Nausea	✔	1-10	1-10	-	✔	-	5
Salivation increased	✔	<1	-	-	-	-	-
Taste alteration	-	-	-	-	✔	-	-
Upset stomach	✔	-	-	-	-	-	-
Vomiting	✔	-	1-10	-	-	<1	5
Weight changes	✔	1-10	-	-	-	-	-
Xerostomia	✔	-	-	-	2	-	<1
Genitourinary							
Impotence	-	-	-	-	✔	-	-
Incontinence	-	-	-	✔	✔	-	-
Libido changes	-	-	-	✔	✔	1-10	<1
Decreased libido	-	-	-	-	✔	-	-
Menstrual irregularities	-	<1	-	✔	✔	-	-
Urinary retention	-	-	-	-	✔	-	-
Hematologic							
Blood dyscrasias	-	<1	-	✔	-	<1	-
Granulocytopenia	✔	-	-	-	-	-	-
Leukopenia	✔	-	-	✔	-	-	-
Hepatic							
AST increased	✔	-	-	-	-	-	-
Alkaline phosphatase increased	✔	-	-	-	-	-	-
ALT increased	✔	-	-	-	-	-	-
Bilirubin increased	✔	-	-	-	-	-	-
Hepatic dysfunction	-	-	-	✔	-	-	-
Jaundice	✔	-	-	✔	✔	-	-
Musculoskeletal							
Asthenia	-	<1	-	-	-	-	-
Dysarthria	✔	-	-	✔	✔	1-10	<1
Joint pain	✔	-	-	-	-	-	-
Muscle spasticity	-	-	-	-	✔	-	-
Myoclonic jerks	-	-	1-10	-	-	-	-
Weakness	✔	1-10	-	-	✔	1-10	<1
Respiratory							
Apnea	✔	1-10	-	-	-	-	-

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

✔ Percent not specified
- Event not reported

Table 9. Boxed Warning for Midazolam Injection[1]

WARNING
Adults and pediatrics: IV 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. IV 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 CNS depressants. The initial dose and all subsequent doses should always be titrated slowly; administer over at least 2 minutes and allow an additional 2 or more minutes to fully evaluate the sedative effect. The use of the 1 mg/mL formulation or dilution of the 1 mg/mL 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 IV injection (less than 2 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 IV injection of fentanyl. Seizures have been reported in several neonates following rapid IV 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 CNS 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 (see Warnings). 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[1-16]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Alprazolam	Anxiety Disorders: Initial (IR): 0.25 to 0.5 mg	Safety and efficacy in children have not been	Oral concentrate (IR):

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	orally three times daily; may be increased to achieve a maximum therapeutic effect at every 3-4 days; maximum, 4 mg/day Panic Disorder: Initial (IR): 0.5 mg orally three times daily; may increase dosage up to 1 mg every 3-4 days; usual dosage range is 1 to 10 mg/day Initial (ER): 0.5 to 1 mg orally in the morning; may increase dosage by up to 1 mg/day every 3-4 days; usual dosage range is 3 to 6 mg/day; maximum, 10 mg/day	established.	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	Alcohol Withdrawal Syndrome: Initial, 50-100 mg, followed by repeated doses as needed; maximum, 300 mg/day Anxiety Disorders: Mild-to-moderate symptoms: 5 or 10 mg 3-4 times daily Severe symptoms: 20 or 25 mg 3-4 times daily Anxiety (Preoperative): 5 to 10 mg 3-4 times daily on days preceding surgery	Anxiety Disorders: ≥6 years of age: 5 mg 2-4 times daily; may be increased to 10 mg 2-3 times daily	Capsule: 5 mg 10 mg 25 mg
Clobazam	Seizures: Initial, 10 mg/day in two divided doses. Starting day 7, 20 mg/day in two divided doses. Starting day 14, 40 mg/day in two divided doses. Dosing should be individualized based on efficacy and tolerability.	Seizures: ≥2 years of age: ≤30 kg: Initial, 5 mg/day as a single dose. Starting day 7, 20 mg/day in two divided doses. Starting day 14, 40 mg/day in two divided doses. Dosing should be individualized based on efficacy and tolerability. >30 kg: Initial, 10 mg/day in two divided doses. Starting day 7, 20 mg/day in two divided doses. Starting day 14, 40 mg/day in two divided doses. Dosing should be individualized based on efficacy and	Tablet: 5 mg 10 mg 20 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
		tolerability.	
Clonazepam	Panic Disorder: Initial, 0.25 mg twice daily; increase by 0.125 to 0.25 mg twice daily every 3 days; maximum, 4 mg/day Seizures: Initial, 1.5 mg/day divided into 3 doses; increase daily by 0.5 to 1 mg/day every 3 days; maximum, 20 mg/day	Seizures: ≤10 years of age (≤30 kg): 0.01 to 0.03 mg/kg/day divided 2-3 times daily; increase by 0.25 to 0.5 mg/day every 3 days; maximum, 0.2 mg/kg/day >10 years of age (>30 kg): Initial, 1.5 mg/day divided into 3 doses; increase by 0.5 to 1 mg/day every 3 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	Alcohol Withdrawal Syndrome: Day 1: 30 mg initially, then 30 to 60 mg in divided doses for the remainder of the day Day 2: 45 to 90 mg/day in divided doses Day 3: 22.5 to 45 mg/day in divided doses Day 4: 15-30 mg/day in divided doses Day 5 and thereafter: 7.5 to 15 mg/day in divided doses until the patient's condition is stable; maximum, 90 mg/day Anxiety Disorders: 15 to 60 mg/day in divided doses; usual daily dose is 30 mg/day. May be administered in a single dose at bedtime. Seizures (Adjunct): 7.5 mg 3 times daily; may increase dose by 7.5 mg/week; maximum, 90 mg/day	Seizures (Adjunct): 9 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 3 times daily; increase by 7.5 mg/week; maximum, 90 mg/day	Tablet 3.75 mg 7.5 mg 15 mg
Diazepam	Alcohol Withdrawal Syndrome: Injection: Initial, 10 mg IM/IV, then 5 to 10 mg in 3-4 hours, if necessary Oral: 10 mg 3-4 times during the first 24 hours, reducing to 5 mg 3-4 times daily as needed Anxiety Disorders: Injection: Moderate symptoms: Initial, 2 to 5 mg IM/IV; repeat in 3-4 hours, if necessary	Anxiety Disorders: Oral: ≥6 months of age: 1 to 2.5 mg 3-4 times daily; increase gradually as needed and tolerated Muscle Spasm: Injection: 30 days to 5 years of age: 1 to 2 mg IM/IV, repeated every 3-4 hours, if necessary ≥5 years of age: 5 to 10 mg IM/IV, repeated every 3-4 hours, if necessary	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 Solution: 5 mg/5 ml Tablet:

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Severe symptoms: Initial, 5 to 10 mg IM/IV; repeat in 3-4 hours, if necessary Oral: 2 to 10 mg 2-4 times daily Anxiety (Cardioversion): Injection: 5 to 15 mg IV 5-10 minutes prior to the procedure Anxiety (Endoscopic Procedure): Injection: 10 to 20 mg IV immediately prior to procedure or 5 to 10 mg IM 30 minutes prior to procedure Anxiety (Preoperative Medication): Injection: 10 mg IM (preferred route) before surgery Muscle Spasm: Injection: Initial, 5 to 10 mg IM/IV, then 5 to 10 mg in 3-4 hours, if necessary. Oral: 2 to 10 mg 3-4 times daily Seizures (Adjunct): Oral: 2 to 10 mg 2-4 times daily Rectal: 0.2 mg/kg; may repeat in 4-12 hours Status Epilepticus and Severe Recurrent Convulsive Seizures: Injection: Initial, 5 to 10 mg (IV preferred); may be repeated at 10-15 minute intervals; maximum, 30 mg	Oral: ≥6 months of age: 1 to 2.5 mg 3-4 times daily; increase gradually as needed and tolerated Seizures (Adjunct): Oral: ≥6 months of age: 1 to 2.5 mg 3-4 times daily; increase gradually as needed and tolerated Rectal: 2 to 5 years of age: 0.5 mg/kg; may repeat in 4-12 hours 6 to 11 years of age: 0.3 mg/kg; may repeat in 4-12 hours ≥12 years of age: 0.2 mg/kg; may repeat in 4-12 hours Status Epilepticus and Severe Recurrent Convulsive Seizures: Injection: 30 days to 5 years of age: 0.2 to 0.5 mg (IV preferred) every 2-5 minutes; maximum, 5 mg ≥5 years of age: 1 mg (IV preferred) every 2-5 minutes; maximum, 10 mg	2 mg 5 mg 10 mg
Estazolam	Insomnia: 1 to 2 mg at bedtime	Safety and efficacy in children have not been established.	Tablet: 1 mg 2 mg
Flurazepam	Insomnia: 15 to 30 mg at bedtime	Safety and efficacy in children have not been established.	Capsule: 15 mg 30 mg
Lorazepam	Anxiety: Oral: 2 to 3 mg/day divided into 2-3 daily doses Insomnia:	Safety and efficacy in children have not been established.	Injection: 2 mg/ml 4 mg/ml 50 mg/50 ml 60 mg/60 ml

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Oral: 2 to 4 mg at bedtime Preanesthetic: Injection: 0.05 mg/kg IM 2-3 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 Status Epilepticus: Injection: 4 mg IV; may repeat dose in 10-15 minutes if needed		100 mg/100 ml Oral concentrate: 2 mg/ml Tablet: 0.5 mg 1 mg 2 mg
Midazolam	Anesthesia (Induction): Injection: Unpremedicated patients: 0.3-0.35 mg/kg IV Premedicated patients: 0.15-0.35 mg/kg IV Anesthesia (Maintenance): Incremental injections of approximately 25% of the induction dose should be given in response to signs of lightening of anesthesia and repeated as necessary. Sedation, Anxiolysis, Amnesia (Preoperative and Pre-procedural): Injection: 0.07 to 0.08 mg/kg IM administered up to 1 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 2 minutes. Sedation (Continuous Infusion): 0.01-0.05 mg/kg IV loading dose, followed by a continuous IV infusion at a rate of 0.02-0.10 mg/kg/hr	Sedation, Anxiolysis, Amnesia (Preoperative and Pre-procedural): Injection: Non-neonatal: 0.1-0.15 mg/kg IM 6 months to 5 years of age: 0.05-0.1 mg/kg IV 6 to 12 years of age: 0.025-0.05 mg/kg IV 12 to 16 years of age: refer to adult dosing Oral: 0.25 to 1 mg/kg; maximum, 20 mg Sedation, Anxiolysis, Amnesia (Critical Care Settings): 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	Injection: 1 mg/ml 2 mg/2 ml 3 mg/3 ml 5 mg/ml 5 mg/5 ml 15 mg/30 ml 25 mg/25 ml 50 mg/50 ml Syrup: 2 mg/ml 10 mg/5 ml
Oxazepam	Alcohol Withdrawal Syndrome: 15 to 30 mg 3-4 times daily Anxiety Disorders: Mild-to-moderate symptoms: 10 to 15 mg 3-4 times daily	Safety and efficacy in children <6 years of age have not been established. Absolute dosage for patients 6 to 12 years of age is not established.	Capsule: 10 mg 15 mg 30 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Severe symptoms: 15 to 30 mg 3-4 times daily	Anxiety Disorders: Mild-to-moderate symptoms: 10 to 15 mg 3-4 times daily Severe symptoms: 15 to 30 mg 3-4 times daily	
Quazepam	Insomnia: 7.5 to 15 mg at bedtime	Safety and efficacy in children have not been established.	Tablet: 15 mg
Temazepam	Insomnia: 7.5 to 30 mg at bedtime	Safety and efficacy in children have not been established.	Capsule: 7.5 mg 15 mg 22.5 mg 30 mg
Triazolam	Insomnia: 0.25 mg at bedtime	Safety and efficacy in children have not been established.	Tablet: 0.125 mg 0.25 mg

ER=extended-release, IR=immediate-release

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.[32] (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	Primary: In 3 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 2 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 9 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 5 trials and indicated that fewer patients in the benzodiazepines group compared to the alternative treatment group dropped out within the first 7 days of treatment (OR 0.68, 95% CI: 0.47 to 0.97).
Ntais et al.[33] (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 5 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 not significant.
Kumar et al.[53] (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	RCT, DB Male inpatients in a state of moderately severe, uncomplicated alcohol withdrawal	N=100 12 days	Primary: Withdrawal severity and changes in the Clinical Institute Withdrawal Assessment for Alcohol-Revised (CIWA-Ar) scale	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 the last 4 days of the study, nor were there impairing adverse events

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.				reported during this period.
Anxiety Disorders				
Martin et al.[55] (2007) Alprazolam, diazepam, lorazepam vs placebo	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 relative risk of withdrawal for any reason was 0.78 (95% CI 0.62–1.00; P=0.05) in favor of benzodiazepines. The relative risk of withdrawal due to adverse events was 1.54 (95% CI 1.17–2.03; P=0.002) indicating an increased risk for the benzodiazepine group. Secondary: The relative risk of withdrawal due to lack of efficacy was 0.29 (95% CI 0.18–0.45; P<0.00001) in favor of benzodiazepines.
Moylan et al.[56] (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: Panic attack frequency (PAF), Hamilton Anxiety Scale (HAM-A), proportion of panic attack-free patients, adverse events	Primary: There was no significant difference in mean PAF improvement between alprazolam and other benzodiazepines (weighted mean difference 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 (weighted mean difference, 0.8 points; 95% CI, -0.5 to 2.1). There was no significant difference between alprazolam and other

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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.
Mitte et al.[34] (2005) Benzodiazepines vs azaspirones vs placebo	MA Patients with generalized anxiety disorder	N=12,053 (48 trials) Variable duration	Primary: Anxiety (Hamilton Rating Scale for Anxiety [HAM-A]), depression (Hamilton Rating Scale for Depression [HAM-D])	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).
Blanco et al.[35] (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 Liebowitz Social Anxiety Scale (LSAS) or a categorical measure of status Secondary: Clinical Global Impression of Change (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.
van Balkom et al.[36] (1997) Benzodiazepines	MA Patients with panic disorder (with or	N=5,011 (106 trials) Variable	Primary: Panic, agoraphobia, depression, and	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs antidepressants vs psychological panic management vs exposure in vivo vs placebo	without agoraphobia)	duration	general anxiety	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.
Chessick et al.[37] (2006) Benzodiazepines vs azaspirones The meta-analysis also compared the azaspirones to hydroxyzine, kava kava, placebo, venlafaxine and psychotherapy, but only the results from studies comparing the azaspirones to the	MA Patients with generalized anxiety disorder	N=5,908 (36 trials) 4 to 14 weeks	Primary: HAM-A, Clinical Global Impression [CGI]), patient acceptability	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). 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 6 or 12 weeks, neither group had worsening symptoms of anxiety but those on diazepam did show withdrawal symptoms at 6 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
benzodiazepines are reported in this review.				40% of patients on lorazepam (P<0.001).
Insomnia				
Holbrook et al.[38] (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	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 3 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 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 9-week follow-up.
Smith et al.[39] (2002) Benzodiazepines or benzodiazepine	MA Patients with primary insomnia for ≥1 month	N=470 (21 trials) 1 to 10 weeks	Primary: Sleep latency, total sleep time, number of awakenings, wake time after	Primary: Sleep latency was reduced by 30% with pharmacological treatment compared with 43% with behavioral interventions. Pharmacotherapy increased total sleep time by 12% compared to 6% with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
receptor agonists vs behavioral treatment vs placebo			sleep onset, and sleep quality before and after treatment	behavior therapy. Both pharmacotherapy and behavior therapy reduced number of awakenings per night by 1. 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 total sleep time, 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 0.17-1.04).
Nowell et al.[40] (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: Sleep latency, TST, number of awakenings, sleep quality	Primary: Zolpidem and benzodiazepines were significantly more effective than placebo with regards to sleep latency, TST, number of awakenings and sleep quality (P<0.001).
Buscemi et al.[41] (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	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Meta-analyses 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 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.
Glass et al.[54] (2008) Temazepam 15 mg for 2 weeks vs diphenhydramine 50 mg for 2 weeks vs	RCT, DB, PC, 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 digit symbol substitution task	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 total sleep time 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo for 2 weeks			[DSST] and the manual tracking task [MTT]); morning-after memory impairment (using free-recall)	treatment. No treatment effects could be detected on the memory assessment performed.
Piccione et al.[51] (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 sleep latency, total sleep time [TST], number of awakenings, overall quality of sleep), side effects	Primary: The patients' global evaluation of effectiveness indicated that triazolam 0.25 mg and 0.50 mg improved sleep more than placebo (both P<0.05), while chloral hydrate 250 mg 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. 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 mg or 500 mg (both P<0.05). There were no significant differences in reported side effects between the active treatments and placebo.
Okawa et al.[43] (1978) Triazolam 0.5 mg vs secobarbital 100	DB, RCT, XO (2 trials) Patients 18 to 60 years of age with a history of insomnia and 2 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 6 hours or more),	Primary: One trial compared triazolam to placebo and involved 19 patients. Sixteen patients preferred triazolam over placebo and 3 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 2 study groups. Seven patients

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg vs placebo	sleep longer than 30 minutes, duration of sleep 6 hours or less, or experiencing 3 or more awakenings		adverse effects	receiving active treatment experienced mild-to-moderate adverse effects, with dizziness, drowsiness and headache as the most frequently reported. In comparison, 3 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 6 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.
Seizures				
Canadian Study Group for Childhood Epilepsy[66] (1998) Clobazam (CLB) vs carbamazepine (CBZ) vs phenytoin (PHT)	RCT, DB, MC Patients 6 months to 17 years of age with newly diagnosed epilepsy or previous failure of one drug	N=235 12 months	Primary: One-year retention rates, seizure control and adverse events	Primary: Overall, 131 (56%) patients were retained on their initial medication for 12 months. A total of 39% of the patients retained for 12 months were seizure-free; 23% on CLB, 25% on CBZ, and 11% on PHT. A total of 17% had seizure(s) after randomization, but became seizure free for at least the last 6 months in the study. A total of 17% of patients experienced a seizure during the last 6 months of the study, but continued to receive study medication. The retention rate for patients receiving CLB versus standard therapy (CBZ or PHT) was similar at 12 months (54.6% vs 56.9%; P=0.7). There was no significant difference in retention rate between drug naïve and previously treated patients (59.1% vs 52.5%; P=0.6). The retention rate in the group previously treated with CBZ was significantly less than the retention for the "other" pretreatment failure group (44.7% vs 65.9%; P=0.02). For those previously treated with CBZ, there was no significant difference in 12- month retention rate between CLB and PHT (48.7% vs

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				40.5%; P=0.5). There was no difference between the retention rate for CLB and CBZ in the "other" group (70.6% vs 68.0%; P=0.6). Overall, 44% of patients discontinued treatment before 12 months due to side effects, poor seizure control, and other reasons. Only six patients discontinued the study because of noncompliance. Tolerance was noted in 7.5% of patients receiving CLB, 4.2% of patients receiving CBZ, and 6.7% of patients receiving PHT (P=NS).
Mehndiratta et al.[62] (2003) Clobazam 20 to 80 mg/day	OL Patients ≥12 years of age with newly diagnosed epilepsy who were drug naïve and who had a seizure frequency of ≥2 seizures per 4 weeks in the last 12 weeks	N=26 24 weeks	Primary: Change in seizure severity, dose of clobazam required, adverse events	Primary: A total of 64% of patients became seizure free and 20% of patients had >50% reduction in their seizure frequency. The average dose of clobazam used was 26.86 mg (range 20–80 mg). The most common adverse event was sedation (16%).Weight gain, gait ataxia and loss of short-term memory were noted in one patient each.
Conry et al.[61] (2009) Clobazam low-dosage (target 0.25 mg/kg/day) vs clobazam high-dosage (target 1.0 mg/kg/day)	RCT, DB, MC Patients 2 to 26 years of age with Lennox-Gastaut syndrome (LGS)	N=68 7 weeks	Primary: Percent reduction in drop seizure rates (average per week) Secondary: Responder rates, percent reduction in weekly nondrop seizures, physicians' and caregivers' global evaluations	Primary: The mean drop seizure rate was reduced in the low-dose from 141 to 91 drop seizures per week and in the high-dose group from 207 to 32 drop seizures per week. The percent change from baseline was significant in the low-dose group (12%; P=0.0162) and the high-dose group (85%; P<0.0001). The reduction in drop seizure rates was significantly greater in the high-dose group compared with the low-dose group (P=0.0001). Secondary: Significantly more patients in the high-dose group compared to the low-dose group had a reduction in weekly drop seizure rates of ≥25% (89% vs 56%, P=0.0025), ≥50% (83% vs 38%, P=0.0001), and ≥75% (67% vs 25%, P=0.0006). In the low-dose group, the percent change from baseline in nondrop seizures was not significant (9%; P=0.1466). In the high-dose group, the percent change from baseline in nondrop seizures was significant (59%;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				P<0.0001). The reduction in nondrop seizure rates was significantly greater in the high-dose group compared with the low-dose group (P=0.0222). In the parent/caregiver global evaluations, patients in the high-dose group were more likely to show significant improvements in overall symptoms compared with the low-dose group. A total of 94% of patients in the high-dose group compared to 55% of patients in the low-dose group were much improved or very much improved at week 3 compared to baseline. At week 7, the percentage of patients considered to be much improved or very much improved increased in the high-dose group (93%), but decreased in the low-dose group (43%). The high-dose group showed significantly lower scores than the low-dose group at 3 weeks (1.7 vs 2.4, P=0.0024) and at 7 weeks (1.6 vs 2.6, P=0.0002). In the investigator global evaluations, patients in the high-dose group were more likely to show significant improvements in overall symptoms compared with the low-dose group. At week 3, 94% of patients in the high-dose group compared to 45% of patients in the low-dose group were much improved or very much improved. At week 7, 90% of patients in the high dose group and 41% of patients in the low-dose group were much improved or very much improved. The high-dose group showed significantly lower scores than the low-dose group at 3 weeks (1.8 vs 2.7, P=0.0001) and at 7 weeks (1.8 vs 2.8, P<0.0001). The most common adverse events with clobazam were somnolence, lethargy, sedation, salivary hypersecretion, constipation, aggression, hypomania, and insomnia. The incidence of treatment-emergent AEs, regardless of relation to therapy, was similar between the low-dose group (84%) and the high-dose group (86%). The low dose group and high dose group were also similar in incidence of mild (47% vs 44%), moderate (34% vs 36%), and severe (3% vs 6%) adverse events.
Ng et al.[60] (2011) Clobazam low-dosage (target 0.25	RCT, DB, MC PC Patients 2 to 60 years of age weighing ≥12.5 kg	N=238 15 weeks	Primary: Percentage decrease in mean weekly drop seizure rates	Primary: The mean percentage decrease in average weekly rate of drop seizures was 12.1% for placebo compared to 41.2% for the clobazam 0.25 mg/kg/day (P=0.0120), 49.4% for clobazam 0.5 mg/kg/day (P=0.0015), and 68.3% for clobazam 1.0 mg/kg/day (P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/kg/day) vs clobazam medium-dosage (target 0.5 mg/kg/day) vs clobazam high-dosage (target 1 mg/kg/day) vs placebo	with an onset of Lennox-Gastaut syndrome (LGS) before age 11		Secondary: Percentage decreases in average weekly rate of nondrop seizures and total (drop and nondrop) seizures; responder rates; and physicians' and caregivers' global evaluations of the patients' overall changes in symptoms over time	Secondary: The mean percentage decrease in average weekly rate of total seizures was 9.3% for placebo compared to 34.8% for clobazam 0.25 mg/kg/day (P=0.0414), 45.3% for clobazam 0.5 mg/kg/day (P=0.0044), and 65.3% for clobazam 1.0 mg/kg/day (P=0.0001). There was no significant difference in the average weekly rates of nondrop seizures. The percentage of patients with ≥50% decreases in average weekly rate of drop seizures was 31.6% for placebo compared to 43.4% for clobazam 0.25 mg/kg/day, 58.6% for clobazam 0.5 mg/kg/day, and 77.6% for clobazam 1.0 mg/kg/day. The likelihood of achieving ≥50% response was greater for the medium-dosage (OR, 2.8; 95% CI, 1.2– 6.5; P=0.0159) and high-dosage (OR, 7.5; 95% CI, 3.0– 18.5; P=0.0001) clobazam groups compared with the placebo group. The percentages of patients who were at least minimally improved ranged from 71.2% to 80.7% (physicians' assessments) and 79.2% to 81.6% (caregivers' assessments) for clobazam vs 47.3% (physicians' assessments) and 45.5% (caregivers' assessments) for placebo. The percentages of patients who were much improved or very much improved ranged from 46.2% to 64.9% (physicians' assessments) and 41.5% to 59.2% (caregivers' assessments) for clobazam vs 23.6% (physicians' assessments) and 25.5% (caregivers' assessments) for placebo. The percentages of patients with ≥1 adverse event were 67.8% for placebo, 72.4% for the low-dosage group, 88.7% for the medium-dosage group, and 76.3% for the high-dosage group. Adverse events with ≥10% difference between placebo and any clobazam group were somnolence, pyrexia, lethargy, drooling, and constipation.
Kalra et al.[67] (2010) Clobazam 0.3 to 2 mg/kg/day as add-	PRO Indian children with seizures who were refractory to first-	N=88 6 months to 3 years	Primary: Therapeutic response, tolerance, safety	Primary: Complete therapeutic response with 100% seizure control was seen in 60.2% of patients, good in 25% of patients, uncontrolled in 4.5% of patients, and the status was not known in 10% of patients.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
on therapy	line treatments (phenobarbitone, phenytoin, carbamazepine or sodium valproate)			Tolerance was seen in 5.7% of patients at 3 months and in 10.2% of patients after 6 months of follow-up. Adverse events occurred in 26% of patients, including sedation (11.3%), hyperactivity/behavioral problems (8%), irritability (5.6%), salivation (4.5%), ataxia (4.5%), fatigue (1%), weight gain (1%), and sleep disturbance (1%).
Shimizu et al.[57] (2003) Clobazam 5 to 20 mg/day as add-on therapy	OL Outpatients with intractable complex partial seizures (CPS) that occurred more often than monthly and remained intractable despite maximum drug therapy with all of the standard antiepileptic drugs available in Japan	N=183 6 months	Primary: Adverse events, change in seizure frequency, tolerance	Primary: A total of 21 patients dropped out of the study within 1 month of the initiation of clobazam. Somnolence was the most frequently reported adverse event (37.7%), followed by gait disturbance (12.0%) and irritability (4.9%). After 1 month, 44.3% of patients had an improvement in seizure frequency with clobazam. Complete seizure remission was achieved in 37.7% of patients. The number of patients who achieved improvement decreased during the observation period (44.3%, 1 month later; 37.2%, 3 months later; 30.1%, 6 months later). The responder rates decreased over the course of the study (50.3%, 1 month later; 40.4%, 3 months later; 32.8%, 6 months later). Once complete remission had been achieved for more than 3 months, seizure recurred in only 25.8% of the patients over the next 3 months. Among the seizure-free patients, development of tolerance decreased as the duration of remission extended (37.7%, 1 month later; 50.8%, 3 months later; 74.2%, 6 months later).
Jan et al.[65] (2000) Clobazam 5 to 40 mg/day as add-on therapy	PRO Patients 2 to 5 years of age with intractable epilepsy (recurrent seizures after ≥3 anti-	N=31 3 to 12 months	Primary: Therapeutic response	Primary: A total of 35.5% of patients became completely seizure-free after the addition of clobazam, 45% had >50% seizure reduction, 13% had <50% seizure reduction, and 6.5% had no response. None of the patients had worsening of seizures. The number of antiepileptic drugs decreased after the addition of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	epileptic medication trials)			clobazam (mean, 1.7). There were no adverse events reported in 77.5% of patients. The remaining patients reported excessive sedation, vomiting, irritability, behavioral change and ataxia. Clobazam was withdrawn in 3 patients.
Silva et al.[64] (2006) Clobazam 5 to 60 mg/day as add-on therapy	RETRO Patients 6 months to 18 years of age with epileptic encephalopathy and previous failure of ≥2 monotherapies	N=97 18 months	Primary: Seizure control	Primary: Nine patients (9.2%) were seizure-free after clobazam adjunctive therapy. Seizures improved >75% in 11.3% of patients, >50% in 16.5% of patients, <50% in 17.5% of patients, and in 45.5% of patients there was no modification in the seizure frequency. In 85% of the patients with seizure improvement, the results lasted for more than one year. A total of 41% of patients experienced an adverse event, most of which were mild and transitory. Clobazam was withdrawn in 11 patients.
da Silveira et al.[58] (2006) Clobazam 5 to 60 mg/day as add-on therapy	RETRO Patients 6 months to 18 years of age with refractory focal epilepsy who had previous failure of ≥2 monotherapies	N=100 Up to 78 months	Primary: Adverse events and therapeutic response	Primary: A total of 22 patients experienced adverse events: somnolence, irritability, headache, allergic reaction, vomiting and ataxia. In 11 patients the adverse events were mild or transitory; however, in 11 patients clobazam was withdrawn due to the severity of the adverse events, primarily irritability. A total of 26 patients became seizure-free, 11 had >75% of seizure reduction, and there was no modification in seizure frequency in 58 patients. Five patients had an increase in seizure frequency. In 42% of the seizure-free patients and 36% of the patients with >75% seizure reduction, clobazam efficacy lasted for more than one year. Patients with lower seizure frequency showed a sustained response to the treatment (P=0.021). Seizures were controlled for more than one year in 11 patients with weekly or monthly seizures, and only in one patient with daily seizures.
Khosroshahi et al.[59] (2011)	RCT Children 6 months	N=72 12 months	Primary: Occurrence of febrile seizures	Primary: During the 12 month follow-up period, 243 episodes of fever occurred (47.7% of episodes in the clobazam group and 52.3% of episodes in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Clobazam 5 mg QD (≤5 kg), 5 mg BID (6-10 kg), 7.5 mg BID (11-15 kg), or 10 mg BID (>15 kg) for 2 days vs diazepam 0.33 mg/kg/dose every 8 hours for 2 days Medications were administered for the first 48 hours of each febrile illness.	to 5 years of age with a history of simple febrile seizures			diazepam group). Two patients (1.7%) in the clobazam group and 4 patients (3.1%) in the diazepam group developed febrile convulsions in their febrile episodes (OR, 0.54; 95% CI, 0.01-3; P=0.474). The number needed to treat to prevent one febrile seizure with clobazam was 71.43.
Mills et al.[63] (2011) Clobazam (CLB) vs topiramate (TOP) vs lamotrigine (LAM)	RETRO Patients <18 years of age who were prescribed clobazam, topiramate or lamotrigine as adjunctive therapy for controlling difficult to treat focal or generalized epilepsies	N=194 8 years	Primary: Efficacy, tolerability and retention rate	Primary: Two patients on CLB, 3 patients on TOP and 1 patient on LAM achieved monotherapy. Both CLB patients and the patient on LAM had an improvement in seizure frequency by the last follow up. Two of the 3 patients on TOP had a significant improvement with the other patient demonstrating a lack of efficacy by the last follow up. The majority of these patients had at least 2 previous AEDs. Possibly and probably related adverse events were reported in 60% on CLB, 47% of patients on TOP, and 39% of patients on LAM. The most frequent adverse events involved excessive sleepiness (27% of CLB patients); behavioral problems (15%) and excessive weight loss (12%) were reported with TOP. Sleeping problems (12%) and rash (10%) were reported with LAM. A total of 42% of patients withdrew from CLB therapy, 48% withdrew from TOP therapy, and 38% withdrew from LAM.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Retention rates beyond 12 months were 51% for CLB, 37% for TOP, and 69% for LAM. The differences in time spent on each drug were not significant. Seizure response rates of >50% reduction were highest at 2 months for TOP and LAM with 37% and 47% improved, respectfully. Seizure response was highest at 6 months for CLB with 49% improved. Beyond 12 months seizure improvement was reported in 43%, 35% and 44% on CLB, TOP and LAM, including 5% and 8% remaining seizure free on CLB and LAM respectively.
Pavlidou et al.[44] (2006) Diazepam 0.33 mg/kg every 8 hours rectally for 1 day, followed by every 12 hours on day 2 vs no treatment	PRO, RCT Children 6 months to 3 years of age who experienced a first febrile seizure	N=139 3 years	Primary: Recurrence rates	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).
Treiman et al.[46] (1998) Diazepam 0.15 mg/kg, followed by phenytoin 18 mg/kg vs lorazepam 0.1 mg/kg	DB, MC, RCT Adults with overt or subtle generalized convulsive status epilepticus	N=518 5 years	Primary: Success (when all motor and electrical seizure activity stopped within 20 minutes of start of drug infusion and no recurrence of seizure activity within the next 40 minutes), side effects	Primary: For treatment success in overt status epilepticus, a significant difference in the rates was found: lorazepam, 64.9%; phenobarbital, 58.2%; diazepam/phenytoin, 55.8%; and phenytoin, 43.6% (P<0.02). For subtle status epilepticus, no significant differences were seen between treatment groups (P<0.18). Lorazepam showed significantly higher treatment success compared to phenytoin in pair wise comparison of overt status epilepticus (P<0.002). There were no significant differences among any of the treatment groups with respect to adverse effects or 30 day outcomes.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs phenobarbital 15 mg/kg vs phenytoin 18 mg/kg				
Appleton et al.[45] (2002) Lorazepam IV or rectally (dose not specified) vs diazepam IV 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)	Primary: Administration of 1-2 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 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).
Miscellaneous				
Leufkens et al.[47] (2007) Alprazolam XR 1 mg vs	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)	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 cm 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
alprazolam IR 1 mg vs placebo			measured by Standard Deviation of Lateral Position (SDLP in centimeters) Secondary: Comparison of effects on cognitive and psychomotor functioning related to driving in a controlled laboratory setting	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 1 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 noted for all times of measurement (P<0.05). Alprazolam XR did not differ significantly from placebo 1 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 1 hour after administration but not with alprazolam XR.
Hindmarch et al.[42] (2006) Flurazepam 30 mg vs zolpidem modified release (MR) 6.25 mg vs	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 MR	Primary: There were no significant differences in psychometric tests between the zolpidem MR 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 MR and with flurazepam (all P<0.05). Neither zolpidem MR, nor flurazepam, modified perception of well-being on awakening.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
zolpidem MR 12.5 mg vs placebo			only)	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 MR, which is consistent with dose linearity.
Johnson et al.[52] (2006) Triazolam 0.25 mg, 0.5 mg or 0.75 mg vs ramelteon 16 mg, 80 mg or 160 mg vs placebo	DB, XO Adults with a history of sedative abuse	N=14 18 days	Primary: Subject-rated measures (drug liking, street value, pharmacological classification), observer-rated measures (sedation, impairment), motor and cognitive performance (balance task, DSST, word recall)	Primary: Triazolam showed dose-related effects on subject-rated, observer-rated, and motor and cognitive performance measures. Compared with 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 with placebo, ramelteon had no effect at any dose on any observer-rated or motor and cognitive performance measure (all P>0.05).

Study abbreviations**:** CI=confidence interval, DB=double-blind, MA=meta-analysis, MC=multi-center, PC=placebo controlled, PRO=prospective trial, OR=odds ratio, RCT=randomized controlled trial, RR=relative risk, XO=crossover, WMD=weighted mean difference
Other abbreviations: CGI=Clinical Global Impression, CIWA-Ar=Clinical Institute Withdrawal Assessment of Alcohol Scale, DSM=Diagnostic and Statistical Manual of Mental Disorders, GAD=generalized anxiety disorder, HAM-A=Hamilton Rating Scale for Anxiety, HAM-D=Hamilton Rating Scale for Depression, IR=immediate-release, MAOI=monoamine oxidase inhibitor, RIMA=reversible inhibitor of monoamine-oxidase-A, SSRI=Selective serotonin reuptake inhibitor, XR=extended-release

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	Niravam®*‡, Xanax®*‡, Xanax XR®*‡	$$$-$$$$$	$-$$$
Chlordiazepoxide	capsule	N/A	N/A	$
Clobazam	tablet	Onfi®‡	$$$$$	N/A
Clonazepam	orally disintegrating tablet, tablet	Klonopin®*‡	$$$$	$-$$$
Clorazepate	tablet	Tranxene T-Tab®*‡	$$$$-$$$$$	$
Diazepam	injection, oral concentrate, rectal gel, solution, tablet	Diastat®*, Diastat AcuDial®*, Valium®*‡	$$$$-$$$$$	$-$$
Estazolam	tablet‡	N/A	N/A	$
Flurazepam	capsule	N/A	N/A	$
Lorazepam	injection, oral concentrate, tablet	Ativan®*‡	$$$$-$$$$$	$-$$
Midazolam	injection, syrup‡	N/A	N/A	$-$$
Oxazepam	capsule	N/A	N/A	$-$$$
Quazepam	tablet	Doral®‡	$$$$	N/A
Temazepam	capsule	Restoril®*‡	$$$$$	$
Triazolam	tablet	Halcion®*‡	$$$	$

*Generic is available in at least one dosage form or strength.
‡Product is currently not covered by Alabama Medicaid.
N/A=Not available

X. Conclusions

The benzodiazepines are approved for the treatment of anxiety disorders and for the short-term treatment of insomnia.[1-16] 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. The benzodiazepines are mechanistically similar; however, they differ with regards to their pharmacokinetic properties (e.g., onset and duration of action).[18-19] All of the benzodiazepines are available in a generic formulation, with the exception of clobazam and quazepam.

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.[27] 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.[27] 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.[28] Benzodiazepines should only be used as a short-term measure during crises.[28] 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.[27,34-37,55] 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.[27] Benzodiazepines are not recommended as monotherapy for the treatment of obsessive-compulsive disorder or posttraumatic stress disorder.[22-23]

Several benzodiazepines are approved for the short-term treatment of insomnia, including estazolam, flurazepam, quazepam, 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.[24,26] 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.[24,26,38,40-41]

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.[11] Clobazam was approved by the FDA in October 2011 for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS). Clobazam significantly decreased weekly drop seizure rates compared to placebo and has also been shown to be effective as add-on therapy in patients with refractory epilepsy.[57,60,65,67]

Currently, Alabama Medicaid does not cover several brand and generic benzodiazepines (refer to Table 1 for specific products) as this is an excludable/optional drug class in accordance with the Omnibus Budget Reconciliation Act of 1990 (OBRA 90). There is insufficient evidence to support that one benzodiazepine (brand or generic) is more efficacious than another.

Therefore, all benzodiazepines within the class reviewed, with the exception of diazepam rectal gel and clobazam, are comparable to each other 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. Clobazam is effective for the adjunctive treatment of seizures associated with LGS, which is one of the most difficult epilepsies to treat. Therefore, patients should be allowed approval for these agents through the medical justification portion of the prior authorization process.

XI. Recommendations

No brand benzodiazepine is recommended for preferred status. Alabama Medicaid should consider not covering brand benzodiazepines, with the exception of diazepam rectal gel (Diastat® and Diastat AcuDial®) and clobazam (Onfi®).

Alabama Medicaid should consider covering all generic benzodiazepines.

XII. References

1. Drug Facts and Comparisons. Drug Facts and Comparisons 4.0 [online]. 2012. Available from Wolters Kluwer Health, Inc. Accessed May 2012.
2. Lexi-Comp Online, Lexi-Drugs Online, Hudson, Ohio: Lexi-Comp, Inc.; 2012; May 2012.
3. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed May 2012.
4. Xanax® [package insert]. New York, NY: Pfizer, Inc.; August 2011.
5. Xanax® XR [package insert]. New York, NY: Pfizer, Inc.; August 2011.
6. Niravam® [package insert]. Philadelphia, PA: Azur Pharma, Inc.; June 2011.
7. Onfi® [package insert]. Deerfield, IL: Lundbeck, Inc.; October 2011.
8. Klonopin® [package insert]. South San Francisco: Genentech USA, Inc.; August 2010.
9. Tranxene T-Tab® [package insert]. Deerfield, IL: Lundbeck, Inc.; May 2010.
10. Valium® [package insert]. Nutley, NJ: Roche Laboratories, Inc.; January 2008.
11. Diastat® [package insert]. Aliso Viejo, CA: Valeant Pharmaceuticals International; November 2006.
12. Ativan® tablets [package insert]. Bridgewater, NJ: Biovail Pharmaceuticals, Inc.; March 2007.
13. Ativan® injection [package insert]. Deerfield, IL: Baxter Healthcare Corporation; November 2006.
14. Doral® [package insert]. Union City, CA: Questcor Pharmaceuticals; August 2011.
15. Restoril® [package insert].Hazelwood, MO: Mallinckrodt, Inc.; November 2010.
16. Halcion® [package insert]. New York, NY: Pfizer, Inc.; December 2008.
17. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th ed., text revision (DSM-IV-TR). Washington, DC: American Psychiatric Association; 2000.
18. DuPont R, Greene W, Lydiard R. Sedatives and hypnotics abuse and dependence: Pharmacology and epidemiology. In: UpToDate, Oslin, D (Ed), UpToDate, Waltham, MA, 2012.
19. Bonnet M and Arand D. Treatment of insomnia. In: UpToDate, Wilson, KC (Ed), UpToDate, Waltham, MA, 2012.
20. National Institute for Health and Clinical Excellence (NICE). Alcohol-use disorders. Diagnosis, assessment and management of harmful drinking and alcohol dependence. London (UK): National Institute for Health and Clinical Excellence (NICE); 2011 Feb. 54 p. (Clinical guideline; no. 115). Available at: http://www.nice.org.uk/nicemedia/live/12995/48991/48991.pdf. Accessed May 2012.
21. French JA, Kanner AM, Bautista J, et al. Efficacy and tolerability of the new antiepileptic drugs, II: Treatment of refractory epilepsy: report of the TTA and QSS Subcommittees of the American Academy of Neurology and the American Epilepsy Society. Epilepsia 2004;45:410-23.
22. Koran L, Hanna G, Hollander E, Nestadt G, Simpson H; American Psychiatric Association. Practice guideline for the treatment of patients with obsessive-compulsive disorder. Arlington (VA): American Psychiatric Association; July 2007. Available at: http://psychiatryonline.org/data/Books/prac/OCDPracticeGuidelineFinal05-04-07.pdf. Accessed May 2012.
23. Ursano RJ, Bell C, Eth S, et al. Practice guideline for the treatment of patients with acute stress disorder and posttraumatic stress disorder. American Psychiatric Association; November 2004. Available at: http://psychiatryonline.org/data/Books/prac/ASD_PTSD_Inactivated_04-16-09.pdf. Accessed May 2012.
24. Schutte-Rodin S, Broch L, Buysse D, et al. Clinical guideline for the evaluation and management of chronic insomnia in adults. American Academy of Sleep Medicine (AASM). J Clin Sleep Med 2008;4:487-504.
25. Wheless JW, Clarke DF, Carpenter D. Treatment of pediatric epilepsy: expert opinion. J Child Neurol 2005;20(Suppl 1):S1-56.
26. NIH State-of-the-Science Conference statement on manifestations and management of chronic insomnia in adults. NIH Consens Sci Statements 2005;22(2) 1-30. Available from: http://consensus.nih.gov/2005/insomniastatement.pdf. Accessed May 2012.
27. Stein M, Goin M, Pollack M, et al. Practice guideline for the treatment of patients with panic disorder, second edition. American Psychiatric Association; 2009. Available at: http://psychiatryonline.org/data/Books/prac/PanicDisorder_2e_PracticeGuideline.pdf. Accessed May 2012.
28. National Institute for Clinical Excellence. Generalized anxiety disorder and panic disorder (with or without agoraphobia) in adults. National Institute for Clinical Excellence (NICE); January 2011. Available at: http://www.nice.org.uk/nicemedia/live/13314/52599/52599.pdf. Accessed May 2012.
29. Connolly S, Bernstein G, AACAP Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with anxiety disorders. American Academy of Child and Adolescent Psychiatry (AACAP). J Am Acad Child Adolesc Psychiatry 2007;46(2):267-283.

30. Kleber HD, Weiss RD, Anton RF Jr, Treatment of patients with substance use disorders, second edition. American Psychiatric Association. Am J Psychiatry 2007;164(4 Suppl):5-123.
31. Meierkord H, Boon P, Engelsen B, Göcke K, Shorvon S, Tinuper P, et al. EFNS guideline on the management of status epilepticus. Eur J Neurol. 2006; 13:445-50.
32. Holbrook A, Crowther R, Lotter A, Cheng C, King D. Meta-analysis of benzodiazepine use in the treatment of acute alcohol withdrawal. CMAJ. 1999 Mar 9;160(5):649-55.
33. Ntais C, Pakos E, Kyzas P, Ioannidis JP. Benzodiazepines for alcohol withdrawal. Cochrane Database Syst Rev. 2005 Jul 20;(3):CD005063.
34. Mitte K, Noack P, Steil R, Hautzinger M. A meta-analytic review of the efficacy of drug treatment in generalized anxiety disorder. J Clin Psychopharmacol. 2005 Apr;25(2):141-50.
35. Blanco C, Schneier F, Schmidt A, Blanco-Jerez C, Marshall R, Sanchez-Lacay A et al. Pharmacological treatment of social anxiety disorder: a meta-analysis. Depress Anxiety. 2003;18(1):29-40.
36. van Balkom AJ, Bakker A, Spinhoven P, Blaauw BM, Smeenk S, Ruesink B. A meta-analysis of the treatment of panic disorder with or without agoraphobia: a comparison of psychopharmacological, cognitive-behavioral, and combination treatments. J Nerv Ment Dis. 1997 Aug;185(8):510-6.
37. Chessick CA, Allen MH, Thase M, Batista Miralha da Cunha AB, Kapczinski FF, de Lima MS, et al. Azaspirones for generalized anxiety disorder. Cochrane Database Syst Rev. 2006 Jul 19;3:CD006115.
38. Holbrook A, Crowther R, Lotter A, Cheng C, King D. Meta-analysis of benzodiazepine use in the treatment of insomnia. CMAJ. 2000 Jan 25;162(2):225-33.
39. Smith MT, Perlis ML, Park A, Smith MS, Pennington J, Giles DE, Buysse DJ. Comparative meta-analysis of pharmacotherapy and behavior therapy for persistent insomnia. Am J Psychiatry. 2002 Jan;159(1):5-11.
40. Nowell PD, Mazumdar S, Buysse DJ, Dew MA, Reynolds CF, Kupfer DJ. Benzodiazepines and zolpidem for chronic insomnia. A meta-analysis of treatment efficacy. JAMA. 1997 Dec 24/31;278(24):2170-7.
41. Buscemi N, Vandermeer B, Friesen C, Bialy L, Tubman M, Ospina M, Klassen TP, Witmans M. The efficacy and safety of drug treatments for chronic insomnia in adults: a meta-analysis of RCTs. J Gen Intern Med. 2007 Sep;22(9):1335-50.
42. Hindmarch I, Legangneux E, Stanley N, Emegbo S, Dawson J. A double-blind, placebo-controlled investigation of the residual psychomotor and cognitive effects of zolpidem-MR in healthy elderly volunteers. Br J Clin Pharmacol. 2006;62(5):538-45.
43. Okawa KK, Allens G. A clinical comparison of triazolam with placebo and with secobarbital in insomniac patients. J Int Med Res. 1978;6(4):343-7.
44. Pavlidou E, Tzitiridou M, Panteliadis. Effectiveness of intermittent diazepam prophylaxis in febrile seizures: Long-term prospective controlled study. J Child Neurol. 2006; 21:1036-40.
45. Appleton R, Martland T, Phillips B. Drug management for acute tonic-clonic convulsions including convulsive status epilepticus in children. Cochrane Database Syst Rev. 2002;(4):CD001905.
46. Treiman D, Meyers P, Walton N, Collins J, Colling C, Rowan AJ, et al. A comparison of four treatments for generalized convulsive status epilepticus. Veterans Affairs Status Epilepticus Cooperative Study Group. N Engl J Med. 1998 Sep 17;339(12):792-8.
47. Leufkens TR, Vermeeren A, Smink BE, van Ruitenbeek P, Ramaekers JG. Cognitive, psychomotor and actual driving performance in healthy volunteers after immediate and extended release formulations of alprazolam 1 mg. Psychopharmacology. 2007; 191:951-9.
48. Roth T, Roehrs TA. A review of the safety profiles of benzodiazepine hypnotics. J Clin Psychiatry. 1991 Sep;52 Suppl:38-41.
49. Moller HJ. Effectiveness and safety of benzodiazepines. J Clin Psychopharmacol 1999;19(Suppl 2):2S-11S.
50. Rickels K, DeMartinis N, Rynn M, Mandos L. Pharmacologic strategies for discontinuing benzodiazepine treatment. J Clin Psychopharmacol. 1999;19(Suppl 2):12S-6S.
51. Piccione P, Zorick F, Lutz T, Grissom T, Kramer M, Roth T. The efficacy of triazolam and chloral hydrate in geriatric insomniacs. J Int Med Res. 1980;8(5):361-7.
52. Johnson MW, Suess PE, Griffiths RR. Ramelteon: a novel hypnotic lacking abuse liability and sedative adverse effects. Arch Gen Psych. 2006 Oct;63:1149-57.
53. Kumar CN, Andrade C, Murthy P, et al. A randomized, double-blind comparison of lorazepam and chlordiazepoxide in patients with uncomplicated alcohol withdrawal. J Stud Alcohol Drugs 2009;70:467-74.
54. Glass JR, Sproule BA, Herrmann N, et al. Effects of 2-week treatment with temazepam and diphenhydramine in elderly insomniacs: a randomized, placebo-controlled trial. J Clin Psychopharmacol 2008;28:182-8.
55. Martin JL, Sainz-Pardo M, Furukawa TA, et al. Benzodiazepines in generalized anxiety disorder: heterogeneity of outcomes based on a systematic review and meta-analysis of clinical trials. J Psychopharmacol 2007;21:774-82.

56. Moylan S, Staples J, Ward SA, et al. The efficacy and safety of alprazolam versus other benzodiazepines in the treatment of panic disorder. J Clin Psychopharmacol 2011;31:647-52.
57. Shimizu H, Kawasaki J, Yuasa S, et al. Use of clobazam for the treatment of refractory complex partial seizures. Seizure 2003;12:282-6.
58. da Silveira MR, Montenegro MA, Franzon RC, et al. Effectiveness of clobazam as add-on therapy in children with refractory focal epilepsy. Arq Neuropsiquiatr 2006;64:705-10.
59. Khosroshahi N, Faramarzi F, Salamati P, et al. Diazepam vs clobazam for intermittent prophylaxis of febrile seizures. Indian J Pediatr 2011;78:38-40.
60. Ng YT, Conry JA, Drummond R, et al. Randomized, phase III study results of clobazam in Lennox-Gastaut syndrome. Neurology 2011;77:1473-81.
61. Conry JA, Ng YT, Paolicchi JM, et al. Clobazam in the treatment of Lennox-Gastaut syndrome. Epilepsia 2009;50:1158-66.
62. Mehndiratta MM, Krishnamurthy M, Rajesh KN, et al. Clobazam monotherapy in drug naïve adult patients with epilepsy. Seizure 2003;12:226-8.
63. Mills JK, Lewis TG, Mighal K, et al. Retention rate of clobazam, topiramate, and lamotrigine in children with intractable epilepsies at 1 year. Seizure 2011;20:402-5.
64. Silva RC, Montenegro MA, Guerreiro CA, et al. Clobazam as add-on therapy in children with epileptic encephalopathy. Can J Neurol Sci 2006;33:209-13.
65. Jan MM, Shaabat AO. Clobazam for the treatment of intractable childhood epilepsy. Saudi Med J 2000;21:622-4.
66. Canadian Study Group for Childhood Epilepsy. Clobazam has equivalent efficacy to carbamazepine and phenytoin as monotherapy for childhood epilepsy. Epilepsia 1998;39:952-9.
67. Kalra V, Seth R, Mishra D, et al. Clobazam in refractory childhood epilepsy. Indian J Pediatr 2010;77:263-6.
68. Arzimanoglou A, French J, Blume WT, et al. Lennox-Gastaut syndrome: a consensus approach on diagnosis, assessment, management, and trial methodology. Lancet Neurol 2009;8:82-93.

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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, obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder and social phobia.[13] The agents approved for the treatment of anxiety include buspirone, hydroxyzine and meprobamate.[1-3] 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.

The key diagnostic feature of primary insomnia is difficulty initiating or maintaining sleep for at least one month, which causes marked distress or impairment in social, occupational, or other important areas of functioning.[13] Insomnia may be classified as transient (1-3 nights), short-term (3 nights to 1 month) or chronic ($\geq$1 month) based upon the duration of symptoms.[14] Eszopiclone, zaleplon and zolpidem are approved for the treatment of insomnia.[5,8-12] 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.[5,8-12] Ramelteon is a melatonin receptor agonist, which is also approved for the treatment of insomnia.[8] 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.[7] 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.[7]

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. The mechanism of chloral hydrate is unknown. Dexmedetomidine is a selective $alpha_2$-adrenergic agonist with sedative properties.[4] Droperidol is a butyrophenone antipsychotic. The antiemetic effect is due to the blockade of dopamine stimulation of the chemoreceptor trigger zone.[1-3] Other effects include alpha-adrenergic blockade, peripheral vascular dilation, and reduction of the pressor effect of epinephrine.

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 dexmedetomidine, eszopiclone and ramelteon. This class was last reviewed in February 2010.

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
Chloral hydrate	capsule, syrup	N/A	chloral hydrate
Dexmedetomidine	injection	Precedex®	none
Droperidol	injection	N/A	droperidol
Eszopiclone	tablet	Lunesta®	none
Hydroxyzine	capsule, injection, syrup, tablet	Vistaril®*	hydroxyzine
Meprobamate	tablet	N/A	meprobamate

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Ramelteon	tablet	Rozerem®	none
Zaleplon	capsule	Sonata®*	zaleplon
Zolpidem	extended-release tablet, oral spray, sublingual tablet, tablet	Ambien®*, Ambien CR®*, Edluar®, ZolpiMist®	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 (NICE): **Generalized Anxiety Disorder and Panic Disorder (With or Without Agoraphobia) in Adults[15] (2011)**	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)
	  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.
	Panic Disorder General Considerations
	• 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

Clinical Guideline	Recommendation(s)
	selective serotonin-reuptake inhibitors (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 6 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 (APA): **Practice Guideline for the Treatment of Patients with Panic Disorder, Second Edition**[22] **(2009)**	• Selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (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 favorable safety and side effect profile of SSRIs and SNRIs makes them the best initial choice for many patients with panic disorder. • Venlafaxine ER has been shown to be effective for panic disorder. It is generally well tolerated and has a side effect profile similar to the SSRIs. • 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. • Selective serotonin reuptake inhibitors, SNRIs, and TCAs are all preferable to benzodiazepines as monotherapies for patients with comorbid depression or substance use disorders. • 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. • Monoamine oxidase inhibitors 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 (e.g., mirtazapine, anticonvulsants such as gabapentin) 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. • The available data suggest that buspirone monotherapy is not effective for panic disorder and does not enhance the efficacy of CBT. Although it is sometimes used clinically in individual circumstances as an

Clinical Guideline	Recommendation(s)
	augmentation strategy for patients with panic disorder, there are no published data except case reports to support this practice.

American Academy of Child and Adolescent Psychiatry (AACAP): **Practice Parameter for the Assessment and Treatment of Children and Adolescents with Anxiety Disorders**[16] **(2007)**	• A multimodal treatment approach for children and adolescents with anxiety disorders should consider education of the parents and the child about the anxiety disorder, consultation with school personnel and primary care physicians, cognitive-behavioral interventions, psychodynamic psychotherapy, family therapy, and pharmacotherapy.
	• Treatment of childhood anxiety disorders of mild severity should begin with psychotherapy.
	• Valid reasons for combining medication and treatment with psychotherapy include the following:
	  o Need for acute symptom reduction in a moderately to severely anxious child
	  o A comorbid disorder that requires concurrent treatment
	  o Partial response to psychotherapy and potential for improved outcome with combined treatment.
	• Selective serotonin-reuptake inhibitors (SSRIs) have emerged as the medication of choice in the treatment of childhood anxiety disorders.
	• When anxiety disorder symptoms are moderate or severe or impairment makes participation in psychotherapy difficult, or psychotherapy results in a partial response, treatment with medication is recommended.
	• No controlled studies are available for medication treatment of childhood-onset panic disorder. The use of a SSRI in adolescents with panic disorder has shown significant improvement in panic symptoms.
	• Controlled trials have established the safety and efficacy of short-term treatment with SSRIs for childhood anxiety disorders; however, the benefits and risks of long-term use of SSRIs have not been studied. It is recommended that clinicians consider a medication-free trial for children who have a significant reduction in anxiety or depressive symptoms on an SSRI and maintain stability in these symptoms for 1 year.
	• There is no empirical evidence that a particular SSRI is more effective than another for treatment of childhood anxiety disorders. The choice is often based on side effects, duration of action, or positive response to a particular SSRI in a first-degree relative with anxiety.
	• The risk-benefit ratio for a medication trial needs to be carefully assessed because cognitive-behavioral therapy (CBT) has been shown to be effective and long-term side effects of medications have not been studied in youths.
	• The safety and efficacy of medications other than SSRIs for the treatment of childhood anxiety disorders have not been established.
	• Noradrenergic antidepressants (venlafaxine and tricyclic antidepressants), buspirone, and benzodiazepines have been suggested as alternatives to be used alone or in combination with the SSRIs.
	• Data are limited in childhood anxiety disorders to guide treatment with combinations of medications when a single medication is not effective in managing anxiety symptoms. Comorbid diagnoses are strongly considered in selection of medication.
	• Preliminary findings from controlled trials of extended-release venlafaxine in the treatment of youths with generalized anxiety disorder (GAD) and social phobia suggest it may be well tolerated and effective relative to placebo.
	• Controlled trials with tricyclic antidepressants for pediatric anxiety disorders have shown conflicting results and have not established

Clinical Guideline	Recommendation(s)
	efficacy for this use. • Buspirone may be an alternative to SSRIs for GAD in youths, but there are no published controlled trials. • Benzodiazepines have not shown efficacy in controlled trials in childhood anxiety disorders despite established benefit in adult trials. They are used as an adjunct short-term treatment with SSRIs to achieve rapid reduction in severe anxiety symptoms that may permit initiation of the exposure phase of CBT. Clinicians should use benzodiazepines cautiously because of the possibility of developing dependency.
American Psychiatric Association (APA): **Practice Guideline for the Treatment of Patients with Obsessive-Compulsive Disorder[23] (2007)**	General Considerations • Obsessive-compulsive disorder (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 (CBT), serotonin-reuptake inhibitors (SRIs), or a combination of the two. The choice depends on past treatment history, comorbid psychiatric conditions, severity of symptoms, and functional limitations. • CBT 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. • Clomipramine, fluoxetine, fluvoxamine, paroxetine, and sertraline are Food and Drug Administration (FDA)-approved for the treatment of OCD. • Meta-analyses and placebo-controlled trials suggest better efficacy for clomipramine compared to fluoxetine, fluvoxamine, and sertraline though head-to-head trials do not support this claim. • 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 4-6 after treatment initiation, and some may ultimately respond after as many as 10-12 weeks. • Patients not responding after 10-12 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 CBT may be effective. • 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.

Clinical Guideline	Recommendation(s)
	• 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.
American Psychiatric Association (APA): **Practice Guideline for the Treatment of Patients with Acute Stress Disorder and Posttraumatic Stress Disorder (PTSD)[24] (2004)**	• 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. • Two small open-label trials showed promising results with the serotonergic anxiolytic buspirone, but the data are insufficient to recommend it for use at this time. • 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.

American Academy of Sleep Medicine (AASM): **Clinical Guideline for the Evaluation and Management of Chronic Insomnia in Adults[17] (2008)**	• 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, the 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 sequence of medication trials is as follows:
	• Short-intermediate acting benzodiazepine receptor agonists (BzRAs) or ramelteon
	  o No specific agent is preferable to the others. Each has been shown to have positive effects on sleep latency, total sleep time, and wake after sleep onset in placebo-controlled trials.
	  o Individual patients may respond differentially to medications within this class. Symptom pattern, past response and patient preference should be considered in selecting a specific agent.
	  o Zaleplon and ramelteon have very short half-lives and are likely to reduce sleep latency but have little effect on waking

Clinical Guideline	Recommendation(s)
	after sleep onset. They are unlikely to result in residual sedation. o Eszopiclone and temazepam have relatively longer half-lives, are more likely to improve sleep maintenance, and are more likely to produce residual sedation (residual activity is limited to a minority of patients). o Triazolam has been associated with rebound anxiety and is not considered a first-line hypnotic. o Patients who prefer not to use a DEA-scheduled drug, and patients with a history of substance use disorders, may be candidates for ramelteon, particularly if the complaint is that of sleep initiation difficulty. • Alternate short-intermediate acting BzRAs or ramelteon o If a patient does not respond to the initial agent, a different agent within the same class is appropriate. o Selection of the alternative drug should be based on the patient's response to the first. For a patient who continues to complain of wake after sleep onset might be prescribed a drug with a longer half-life; a patient who complains of residual sedation might be prescribed a shorter-acting drug. o Flurazepam is rarely used because of its extended half-life. • Sedating low-dose antidepressants o May be used next when accompanied with comorbid depression or treatment failures. o Examples of these include trazodone, amitriptyline, doxepin, and mirtazapine. No specific agent is recommended as preferable to the others in this group. o Treatment history, coexisting medical conditions, side effects, and pharmacokinetics may guide the selection of a specific agent. • Combined BzRA or ramelteon and sedating antidepressants o A combination of medications from two different classes may improve efficacy by targeting multiple sleep-wake mechanisms while minimizing the toxicity that could occur with higher doses of a single agent. • Other sedating agents o Examples include anti-epilepsy medications (gabapentin, tiagabine) and atypical antipsychotics (quetiapine and olanzapine). o 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. • Prescription drugs – not recommended: o Older approved drugs for insomnia including barbiturates, barbiturate-type drugs and chloral hydrate are not recommended for the treatment of insomnia. • Over-the-counter drugs – not recommended: o Antihistamine or antihistamine/analgesic type drugs (OTC "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. • 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

Clinical Guideline	Recommendation(s)
	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 CBT-I. • 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 follow-up, ongoing assessment of effectiveness, monitoring for adverse effects, and evaluation for new onset or exacerbation of comorbid disorders. • Long-term administration may be nightly, intermittent (e.g., three nights per week), or as needed.
National Institutes of Health (NIH): **Manifestations and Management of Chronic Insomnia in Adults[18] (2005)**	Behavioral and Cognitive Therapies • 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 (CBT) has been found to be as effective as prescription medications for short-term treatment of chronic insomnia. The beneficial effects of CBT may last well beyond the termination of active treatment. Benzodiazepine Receptor Agonists • Benzodiazepine receptor agonists include benzodiazepines (e.g., estazolam, flurazepam, quazepam, temazepam and triazolam) and newer agents that act at benzodiazepine receptors but have a nonbenzodiazepine structure (e.g., eszopiclone, zaleplon and zolpidem). • Results from moderate to high-quality studies indicate that these eight agents are effective in the short-term management of insomnia. With the exception of eszopiclone, the benefits of these agents for long-term use have not been studied using randomized, controlled trials. • 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. Other Prescription Medications • 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. Antidepressants • Antidepressants (especially trazodone) are often prescribed for

Clinical Guideline	Recommendation(s)
	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 OTC 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 (ASGE): **Sedation and Anesthesia in GI Endocscopy[19] (2008)**	• 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 ECG before procedure.
	  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 2-3 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 with 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.

International Anesthesia Research Society (IARS): **Consensus Guidelines for Managing Postoperative Nausea and Vomiting[20] (2003)**	• There is no evidence of any difference in the efficacy and safety profiles of the serotonin (5-HT3) receptor antagonists in the prophylaxis of PONV. • Because the 5-HT_3 antagonists as a group have greater efficacy in the prevention of vomiting than nausea, they are the drugs of first choice for prophylaxis in children. • If a patient has received no prophylaxis, therapy with small-dose 5-

Clinical Guideline	Recommendation(s)
	HT_3 receptor antagonists should be initiated on the first signs of PONV. • Dexamethasone effectively prevents nausea and vomiting. It appears to be most effective when administered before the induction of anesthesia rather than at the end. • Prophylactic doses of droperidol are effective for the prevention of PONV. The efficacy of droperidol is equivalent to that of ondansetron for PONV prophylaxis. It is most effective when administered at the end of surgery. It is also effective when given concomitantly with patient-controlled analgesia devices that deliver morphine. • When prophylaxis with dexamethasone fails to prevent PONV, treatment with a small-dose 5-HT_3 receptor antagonist has been recommended. • When prophylaxis with a 5-HT_3 antagonist is inadequate to prevent PONV, a 5-HT_3 antagonist should not be initiated as rescue therapy within the first 6 h after surgery because it confers no additional benefit. • When PONV occurs more than 6 h after surgery, repeat dosing of 5-HT_3 antagonists and droperidol can be considered. • Dimenhydrinate seems to be similar in efficacy to that of the 5-HT_3 receptor antagonists and droperidol. • The role of prochlorperazine in the treatment of PONV is still poorly understood. • Prochlorperazine 5–10 mg IV, administered at the end of surgery, has been shown to be effective. However, use of phenothiazines is limited in the ambulatory setting because of the resulting sedation.
American Gastroenterological Association (AGA): **Technical Review: Nausea and Vomiting**[21] **(2001)**	• 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. • For postoperative nausea and vomiting (PONV), the use of 5-HT_3 receptor antagonists and droperidol have proven most effective in comparisons both with 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. • Droperidol has been shown to be useful in the treatment of anticipatory and acute chemotherapy-related nausea and vomiting, and also in the therapy of PONV.
National Institute for Health and Clinical Excellence (NICE): **Alcohol-Use Disorders. Diagnosis, Assessment and Management of Harmful Drinking and Alcohol Dependence**[51] **(2011)**	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 (APA): **Treatment**	Alcohol Use Disorders: Treatment Principles and Alternatives • The treatment of patients in moderate to severe withdrawal includes

Clinical Guideline	Recommendation(s)
of Patients with Substance Use Disorders, Second Edition[52] (2007)	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 miscellaneous anxiolytics, sedatives, and hypnotics are noted in Tables 3-4. 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-E)[1-12]

Indication	Buspirone	Chloral Hydrate	Dexmedetomidine	Droperidol	Eszopiclone
Anxiety Disorders					
Management of anxiety disorders	✔				
Short-term relief of symptoms of anxiety	✔				
Sedative-Hypnotic					
Preoperatively or prior to EEG evaluation to allay anxiety and produce sedation and/or sleep		✔			
Sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting			✔		
Sedation of non-intubated patients prior to and/or during surgical and other procedures			✔		
Short-term treatment of simple insomnia		✔			
Treatment of insomnia					✔
Miscellaneous					
Prevention or suppression of alcohol withdrawal symptoms		✔			
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 H-Z)[1-12]

Indication	Hydroxyzine	Meprobamate	Ramelteon	Zaleplon	Zolpidem
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	✔				
Short-term treatment of insomnia				✔	
Short-term treatment of insomnia characterized by					✔ †

Indication	Hydroxyzine	Meprobamate	Ramelteon	Zaleplon	Zolpidem
difficulty with sleep onset					
Treatment of insomnia characterized by difficulty with sleep onset			✔		
Treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance					✔ ‡
Miscellaneous					
Management of pruritus due to allergic conditions	✔				

‡Extended-release formulation
†Immediate-release formulations (oral spray, sublingual tablet, and tablet)

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[1-12]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Buspirone	Low	86	Liver	Renal (29-63) Feces (18-38)	2.4-2.7
Chloral hydrate	Well absorbed	70-80	Liver	Not reported	4-12
Dexmedetomidine	Not reported	94	Liver	Renal (95) Feces (4)	2-2.67
Droperidol	Rapid	Extensive	Liver	Renal (75) Feces (22)	2
Eszopiclone	75	Not reported	Liver	Renal	5-6
Hydroxyzine	Not reported	Not reported	Liver	Not reported	3-20
Meprobamate	Not reported	0-30	Liver	Renal (10-20)	9-11
Ramelteon	1.8	82	Liver	Renal (84) Feces (4)	1-2.6
Zaleplon	30	60	Liver	Renal (71) Feces (17)	1
Zolpidem	70	93	Liver	Renal (<1)	2.5-3

V. Drug Interactions

Significant drug interactions with the miscellaneous anxiolytics, sedatives, and hypnotics are listed in Table 6.

Table 6. Significant Drug Interactions with the Miscellaneous Anxiolytics, Sedatives, and Hypnotics[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Buspirone	1	Monoamine oxidase inhibitors	Coadministration may increase the risk of adverse effects, including severe hypertension.
Buspirone, chloral hydrate, droperidol, hydroxyzine, meprobamate, ramelteon, zaleplon, zolpidem	1	Sodium oxybate	Coadministration may result in an increase in sleep duration and central nervous system depression. The pharmacologic effects are additive.
Droperidol	1	Class IA, IC, III antiarrhythmics	Droperidol in combination with Class IA, Class IC or Class III antiarrhythmics may cause additive QT interval prolongation and arrhythmias.
Droperidol	1	Nilotinib	Additive QT prolongation may occur during coadministration of nilotinib and droperidol.
Droperidol	1	Phenothiazines	Droperidol and phenothiazines may cause additive QT interval prolongation and possible arrhythmias.
Droperidol	1	Pimozide	Droperidol and pimozide may cause additive QT interval prolongation and possible arrhythmias.

Generic Name(s)	Significance Level	Interaction	Mechanism
Droperidol	1	Quinolones	Droperidol and quinolones may cause additive QT interval prolongation and possible arrhythmias.
Droperidol	1	Toremifene	Prolongation of the QT interval with possible development of cardiac arrhythmias, including torsades de pointes, should be considered when toremifene is coadministered with droperidol.
Droperidol	1	Tricyclic and tetracyclic antidepressants	Droperidol and tricyclic/ tetracyclic antidepressants may cause additive QT interval prolongation and possible arrhythmias.
Droperidol	1	Vandetanib	Additive QT prolongation may occur during coadministration of vandetanib and droperidol. QT interval effects of each agent may be additive. Other mechanisms may exist.
Droperidol	1	Ziprasidone	The combination of ziprasidone and droperidol may have cause additive prolongation of the QT interval.
Hydroxyzine	1	Disulfiram	Coadministration may produce acute alcohol intolerance. Symptoms include flushing, headache, palpitations, tachycardia, dyspnea, hyperventilation, nausea, and vomiting. Hypotension and cardiovascular collapse may also occur.
Ramelteon	1	Fluvoxamine	Plasma concentrations of ramelteon may be increased by coadministration of fluvoxamine. Inhibition of CYP1A2 by fluvoxamine may decrease the metabolic elimination of ramelteon.
Buspirone, eszopiclone, ramelteon	2	Azole antifungals	Inhibition of CYP3A4 by azole antifungals may decrease the metabolic elimination and increase plasma concentrations of eszopiclone.
Buspirone	2	Furazolidone	Use of furazolidone with buspirone may increase the risk of adverse effects, including severe hypertension.
Buspirone, eszopiclone	2	Macrolides and ketolides	Inhibition of CYP3A4 by macrolides and ketolides may decrease the metabolic elimination and increase plasma concentrations of buspirone or eszopiclone.

Generic Name(s)	Significance Level	Interaction	Mechanism
Buspirone	2	Serotonin modulators	Inhibition of CYP3A4 isoenzymes by serotonin modulators may decrease the metabolic elimination and increase plasma concentrations of buspirone.
Chloral hydrate	2	Anticoagulants	Chloral hydrate may displace oral anticoagulants from plasma protein binding sites. The hypoprothrombinemic effect of oral anticoagulants may be transiently increased.
Chloral hydrate	2	Loop diuretics	Combination of loop diuretics with chloral hydrate may produce unexpected diaphoresis, uneasiness, tachycardia and a variable change in blood pressure.
Droperidol	2	Metoclopramide	Coadministration may increase the risk of extrapyramidal reactions.
Eszopiclone, zolpidem	2	HIV protease inhibitors	Inhibition of CYP3A4 by protease inhibitors may decrease the metabolic elimination and increase plasma concentrations of eszopiclone and zolpidem.
Eszopiclone	2	Nefazodone	Inhibition of CYP3A4 by nefazodone may decrease the metabolic elimination and increase plasma concentrations of eszopiclone.
Eszopiclone, ramelteon	2	Rifampin	Induction of CYP3A4 isoenzymes by rifampin may increase the metabolic elimination of eszopiclone, ramelteon, zaleplon or zolpidem.
Hydroxyzine	2	Cephalosporins	Coadministration may produce acute alcohol intolerance.
Hydroxyzine	2	Furazolidone	Coadministration may produce acute alcohol intolerance in some patients. Symptoms include flushing, palpitations, tachycardia, dyspnea, hyperventilation, as well as nausea and vomiting.
Hydroxyzine	2	Metronidazole	Coadministration may produce acute alcohol intolerance.
Zaleplon	2	Cimetidine	Cimetidine may inhibit the metabolism (aldehyde oxidase and CYP3A4) of zaleplon resulting in a potentiation of zaleplon effects. Excessive sedation may occur.

Significance Level 1 = major severity
Significance Level 2 = moderate severity

VI. Adverse Drug Events

The most common adverse drug events reported with the miscellaneous anxiolytics, sedatives, and hypnotics are listed in Table 7. The boxed warning for droperidol is listed in Table 8. Chloral hydrate, meprobamate, eszopiclone, 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[1-12]

Adverse Events	Buspirone	Chloral Hydrate	Dexmede-tomidine	Droperidol	Eszopiclone	Hydroxyzine	Meprobamate	Ramelteon	Zaleplon	Zolpidem
Cardiovascular										
Angina	-	-	-	-	-	-	-	-	<1	-
Arrhythmia	-	-	✔	-	-	-	✔	-	-	-
Atrial fibrillation	-	-	4-5	-	-	-	-	-	-	-
Atrioventricular block	-	-	✔	-	-	-	-	-	-	-
Bigeminy	-	-	-	-	-	-	-	-	<1	-
Bradycardia	<1	-	5-14	-	-	-	-	-	-	-
Bundle branch block	-	-	-	-	-	-	-	-	<1	-
Cardiac arrest	-	-	✔	✔	-	-	-	-	-	-
Cardiomyopathy	<1	-	-	-	-	-	-	-	-	-
Cardiospasm	-	-	-	-	-	-	-	-	<1	-
Chest pain	≥1	-	-	-	1-10	-	-	-	≥1	1-10
ECG changes	-	-	-	-	-	-	✔	-	-	-
Extrasystoles	-	-	✔	-	-	-	-	-	-	-
Heart block	-	-	✔	-	-	-	-	-	-	-
Heart failure	<1	-	-	-	-	-	-	-	-	-
Hypertension	<1	-	✔	✔	<1	-	-	-	<1	<1
Hypotension	<1	-	24-54	✔	-	-	-	-	<1	<1
Hypotensive crisis	-	-	-	-	-	-	✔	-	-	-
Hypovolemia	-	-	3	-	-	-	-	-	-	-
Myocardial infarction	<1	-	✔	-	-	-	-	-	-	-
Palpitation	-	-	-	-	-	-	✔	-	<1	1-10
Pericardial effusion	-	-	-	-	-	-	-	-	<1	-
Peripheral edema	-	-	-	-	1-10	-	✔	-	≤1	-
QTc prolongation	-	-	-	✔	-	-	-	-	-	-
Supraventricular tachycardia	-	-	✔	-	-	-	-	-	-	-
Syncope	<1	-	-	-	-	-	✔	-	<1	<1
T-wave inversion	-	-	✔	-	-	-	-	-	-	-

Adverse Events	Buspirone	Chloral Hydrate	Dexmede-tomidine	Droperidol	Eszopiclone	Hydroxyzine	Meprobamate	Ramelteon	Zaleplon	Zolpidem
Tachycardia	-	-	-	✔	-	-	✔	-	-	<1
Torsades de pointes	-	-	-	✔	-	-	-	-	-	-
Vasodilation	-	-	-	-	-	-	-	-	<1	-
Ventricular arrhythmia	-	-	✔	-	-	-	-	-	-	-
Ventricular extrasystoles	-	-	-	-	-	-	-	-	<1	-
Ventricular tachycardia	-	-	✔	✔	-	-	-	-	<1	-
Central Nervous System										
Abnormal gait	-	-	-	-	<1	-	-	-	-	-
Abnormal thinking	-	-	-	-	-	-	-	-	≥1	-
Agitation	-	-	✔	-	<1	-	-	-	-	<1
Amnesia	-	-	-	-	-	-	-	-	2-4	1-10
Anger	2	-	-	-	-	-	-	-	-	-
Anxiety	-	-	-	✔	1-3	-	-	-	≤1	1-10
Apathy	-	-	-	-	-	-	-	-	-	1-10
Ataxia	<1	✔	-	-	<1	-	✔	-	<1	1-10
Attention disturbance	-	-	-	-	-	-	-	-	-	1-10
Burning sensation	-	-	-	-	-	-	-	-	-	1-10
Cerebrovascular attack	<1	-	-	-	-	-	-	-	<1	<1
Chills	-	-	-	✔	-	-	✔	-	-	-
CNS stimulation	-	-	-	-	-	-	-	-	<1	-
Cognition decreased	-	-	-	-	-	-	-	-	-	<1
Complex sleep-related activities	-	-	-	-	<1	-	-	✔	<1	<1
Concentration decreased	-	-	-	-	-	-	-	-	-	<1
Confusion	2	✔	✔	-	≤3	-	-	-	≤1	1-10
Delirium	-	-	✔	-	-	-	-	-	-	-
Delusions	-	-	-	-	-	-	-	-	<1	-
Depersonalization	-	-	-	-	-	-	-	-	<1-2	1-10
Depression	-	-	-	✔	1-4	-	-	2	≥1	1-10
Disinhibition	-	-	-	-	-	-	-	-	-	1-10
Disorientation	-	✔	-	-	-	-	-	-	-	1-10
Dizziness	12	✔	✔	✔	5-7	✔	✔	4-5	7-9	1-12
Dream disturbances	≥1	-	-	-	1-3	-	-	-	-	1-10
Drowsiness	10	✔	-	✔	-	✔	✔	-	-	1-10
Drugged feeling	-	-	-	-	-	-	-	-	-	1-10
Dysphoria	-	-	-	✔	-	-	-	-	-	-
Emotional lability	-	-	-	-	<1	-	-	-	-	<1

Adverse Events	Buspirone	Chloral Hydrate	Dexmede-tomidine	Droperidol	Eszopiclone	Hydroxyzine	Meprobamate	Ramelteon	Zaleplon	Zolpidem
Euphoria	-	-	-	-	<1	-	✔	-	-	1-10
Excitement	2	✔	-	-	-	-	✔	-	-	-
Extrapyramidal symptoms	<1	-	-	✔	-	-	-	-	-	-
Fatigue	-	-	-	-	-	✔	-	3-4	-	1-10
Fever	-	✔	✔	-	<1	-	✔	-	≥1	1-10
Hallucinations	<1	✔	✔	✔	1-3	✔	-	-	≤1	1-10
Hangover effect	-	✔	-	-	-	-	-	-	-	-
Headache	6	✔	✔	-	15-21	✔	✔	-	30-42	3-19
Hostility	-	-	-	-	<1	-	-	-	-	-
Hyperactivity	-	-	-	✔	-	-	-	-	-	-
Hypoesthesia	-	-	-	-	-	-	-	-	<1-2	1-10
Illusion	-	-	✔	-	-	-	-	-	-	<1
Incoordination	1	-	-	-	-	-	-	-	-	-
Insomnia	-	-	-	-	-	-	-	3	-	1-10
Involuntary movements	-	-	-	-	-	✔	-	-	-	-
Lethargy	-	-	-	-	-	-	-	-	-	1-10
Lightheadedness	3	✔	-	-	-	-	-	-	-	1-10
Memory impairment	-	-	-	-	<1	-	-	-	-	1-10
Malaise	-	-	-	-	<1	-	-	-	<1-2	-
Migraine	-	-	-	-	1-10	-	-	-	≥1	<1
Mood disorder	-	-	-	-	-	-	-	-	-	1-10
Nervousness	5	-	-	-	≤5	✔	-	-	≥1	-
Neuralgia	-	-	✔	-	≤3	-	-	-	-	-
Neuritis	-	-	✔	-	<1	-	-	-	-	-
Neuroleptic malignant syndrome	-	-	-	✔	-	-	-	-	-	-
Neuropathy	-	-	-	-	<1	-	-	-	-	-
Neurosis	-	-	-	-	<1	-	-	-	-	-
Nightmares	-	✔	-	-	-	-	-	-	-	-
Numbness	2	-	-	-	-	-	-	-	-	-
Overstimulation	-	-	-	-	-	-	✔	-	-	-
Paresthesia	1	-	-	-	<1	✔	✔	-	3	<1-10
Parkinsonism	<1	-	-	-	-	-	-	-	-	-
Personality disorders	<1	-	-	-	-	-	-	-	-	-
Psychosis	<1	-	-	-	-	-	-	-	-	-
Restlessness	-	-	-	✔	-	-	-	-	-	-
Sedation	-	✔	-	-	-	-	-	-	-	-

Adverse Events	Buspirone	Chloral Hydrate	Dexmede-tomidine	Droperidol	Eszopiclone	Hydroxyzine	Meprobamate	Ramelteon	Zaleplon	Zolpidem
Seizure	<1	-	✔	-	-	✔	-	-	-	-
Sleep disorder	-	-	-	-	-	-	-	-	-	1-10
Somnolence	-	-	-	-	8-10	-	-	3-5	5-6	6-15
Speech disorder	-	-	✔	-	-	-	✔	-	-	<1
Stress	-	-	-	-	-	-	-	-	-	1-10
Stupor	-	-	-	-	-	-	-	-	-	<1
Suicidal ideation	<1	-	-	-	-	-	-	-	-	-
Temperature regulation altered	-	-	-	-	-	-	-	-	-	1-10
Tremor	1	-	-	-	<1	✔	-	-	2	1-10
Vertigo	-	-	-	-	<1	-	✔	-	≤1	1-10
Dermatological										
Alopecia	-	-	-	-	<1	-	-	-	<1	-
Contact dermatitis	-	-	-	-	<1	-	✔	-	-	-
Ecchymosis	<1	-	-	-	-	-	✔	-	<1	-
Eczema	-	-	-	-	<1	-	-	-	-	-
Erythema multiforme	-	-	-	-	<1	-	✔	-	-	-
Maculopapular rash	-	-	-	-	<1	-	-	-	-	-
Petechiae	-	-	-	-	-	-	✔	-	-	-
Photosensitivity reaction	-	-	-	-	<1	-	-	-	≤1	-
Pruritus	-	-	-	-	1-4	✔	-	-	≥1	<1
Purpura	-	-	-	-	-	-	✔	-	<1	-
Rash	1	✔	-	-	3-4	✔	✔	-	≥1	1-10
Stevens-Johnson syndrome	-	-	-	-	-	-	✔	-	-	-
Urticaria	-	✔	-	-	<1	✔	-	-	-	1-10
Vesiculobullous rash	-	-	-	-	<1	-	-	-	-	-
Wrinkling	-	-	-	-	-	-	-	-	-	1-10
Endocrine and Metabolic										
Acidosis	-	-	✔	-	-	-	-	-	-	-
Breast enlargement	-	-	-	-	<1	-	-	-	-	-
Breast neoplasm	-	-	-	-	<1	-	-	-	-	-
Cholelithiasis	-	-	-	-	<1	-	-	-	<1	-
Cyanosis	-	-	-	-	-	-	-	-	<1	-
Diabetes mellitus	-	-	-	-	-	-	-	-	<1	-
Galactorrhea	<1	-	-	-	-	-	-	-	-	-
Goiter	-	-	-	-	-	-	-	-	<1	-
Gout	-	-	-	-	<1	-	-	-	-	-

Adverse Events	Buspirone	Chloral Hydrate	Dexmede-tomidine	Droperidol	Eszopiclone	Hydroxyzine	Meprobamate	Ramelteon	Zaleplon	Zolpidem
Gynecomastia	-	-	-	-	≤3	-	-	-	-	-
Ketosis	-	-	-	-	-	-	-	-	<1	-
Mastitis	-	-	-	-	<1	-	-	-	-	-
Thyroid abnormality	<1	-	-	-	-	-	-	-	-	-
Gastrointestinal										
Abdominal pain	-	-	✔	-	-	-	-	-	6	1-10
Anorexia	<1	-	-	-	<1	-	-	-	<1-2	-
Appetite disorder	-	-	-	-	-	-	-	-	-	1-10
Bleeding gums	-	-	-	-	-	-	-	-	<1	-
Colitis	-	-	-	-	<1	-	-	-	≤1	-
Constipation	-	-	-	-	-	-	-	-	≥1	1-10
Dehydration	-	-	-	-	<1	-	-	-	-	-
Diarrhea	2	✔	✔	-	2-4	-	✔	-	-	1-10
Dysgeusia	-	-	-	-	8-34	-	-	2	≥1	-
Dyspepsia	-	-	-	-	2-6	-	-	-	≥1	1-10
Dysphagia	-	-	-	-	<1	-	-	-	-	<1
Flatulence	-	✔	-	-	-	-	-	-	-	1-10
Gastric irritation	-	✔	-	-	-	-	-	-	-	-
Gastroenteritis	-	-	-	-	-	-	-	-	<1	1-10
Gastroesophageal reflux	-	-	-	-	-	-	-	-	-	1-10
Gastrointestinal ulcer	-	-	-	-	<1	-	-	-	<1	-
Hiccup	-	-	-	-	-	-	-	-	-	1-10
Intestinal obstruction	-	-	-	-	-	-	-	-	<1	-
Irritable colon	<1	-	-	-	-	-	-	-	-	-
Melena	-	-	-	-	<1	-	-	-	-	-
Nausea	8	✔	3-9	-	4-5	-	✔	3	6-8	1-10
Proctitis	-	-	-	-	-	-	✔	-	-	-
Rectal hemorrhage	<1	-	-	-	<1	-	-	-	<1	-
Stomatitis	-	-	-	-	-	-	✔	-	-	-
Thirst	-	-	✔	-	-	-	-	-	-	-
Tongue edema	-	-	-	-	<1	-	-	-	<1	-
Ulcerative stomatitis	-	-	-	-	<1	-	-	-	<1	-
Vomiting	-	✔	✔	-	≤3	-	✔	-	-	1-10
Xerostomia	-	-	3-4	-	3-7	✔	-	-	≥1	1-10
Genitourinary										
Amenorrhea	-	-	-	-	<1	-	-	-	-	-

Adverse Events	Buspirone	Chloral Hydrate	Dexmede-tomidine	Droperidol	Eszopiclone	Hydroxyzine	Meprobamate	Ramelteon	Zaleplon	Zolpidem
Anuria	-	-	-	-	-	-	✔	-	-	-
Cystitis	-	-	-	-	<1	-	-	-	-	<1
Dysmenorrhea	-	-	-	-	≤3	-	-	-	3-4	-
Dysuria	-	-	-	-	<1	-	-	-	<1	1-10
Enuresis	<1	-	-	-	-	-	-	-	-	-
Hematuria	-	-	-	-	<1	-	-	-	<1	-
Impotence	-	-	-	-	-	-	-	-	<1	-
Incontinence	-	-	-	-	-	-	-	-	<1	<1
Kidney calculus	-	-	-	-	<1	-	-	-	-	-
Kidney pain	-	-	-	-	<1	-	-	-	-	-
Libido decreased	-	-	-	-	≤3	-	-	-	-	-
Menorrhagia	-	-	-	-	<1	-	-	-	-	1-10
Menstrual irregularities	<1	-	-	-	-	-	-	-	-	-
Oliguria	-	-	✔	-	<1	-	✔	-	-	-
Pelvic inflammatory disease	<1	-	-	-	-	-	-	-	-	-
Pyelonephritis	-	-	-	-	<1	-	-	-	-	-
Renal failure	-	-	-	-	-	-	-	-	-	<1
Urethritis	-	-	-	-	<1	-	-	-	-	-
Urinary frequency	-	-	-	-	<1	-	-	-	-	-
Urinary incontinence	-	-	-	-	<1	-	-	-	-	-
Urinary retention	-	-	1	-	-	-	-	-	<1	-
Urinary tract infection	-	-	-	-	≤3	-	-	-	-	1-10
Vaginal hemorrhage	-	-	-	-	<1	-	-	-	-	-
Vaginitis	-	-	-	-	<1	-	-	-	-	<1
Vulvovaginal dryness	-	-	-	-	-	-	-	-	-	1-10
Hematologic										
Acute intermittent porphyria	-	✔	-	-	-	-	-	-	-	-
Agranulocytosis	-	-	-	-	-	-	✔	-	-	-
Anemia	-	-	✔	-	-	-	-	-	<1	<1
Aplastic anemia	-	-	-	-	-	-	✔	-	-	-
Eosinophilia	<1	✔	-	-	-	-	✔	-	<1	-
Leukocytosis	-	-	-	-	-	-	-	-	<1	-
Leukopenia	<1	✔	-	-	-	-	✔	-	-	<1
Lymphadenopathy	-	-	-	-	-	-	-	-	<1	<1
Lymphocytosis	-	-	-	-	-	-	-	-	<1	-
Porphyria exacerbation	-	-	-	-	-	-	✔	-	-	-

Adverse Events	Buspirone	Chloral Hydrate	Dexmede-tomidine	Droperidol	Eszopiclone	Hydroxyzine	Meprobamate	Ramelteon	Zaleplon	Zolpidem
Thrombocytopenia	<1	-	-	-	-	-	-	-	-	-
Thrombocytopenic purpura	-	-	-	-	-	-	✔	-	-	-
Thrombophlebitis	-	-	-	-	<1	-	-	-	<1	-
Hepatic										
Abnormal hepatic function	-	-	-	-	-	-	-	-	-	<1
Alkaline phosphatase increased	-	-	✔	-	-	-	-	-	-	-
ALT increased	-	-	✔	-	-	-	-	-	<1	-
AST increased	-	-	✔	-	-	-	-	-	<1	-
GGT increased	-	-	✔	-	-	-	-	-	-	-
Hepatic impairment	-	-	✔	-	-	-	-	-	-	-
Hepatitis	-	-	-	-	<1	-	-	-	-	-
Hepatomegaly	-	-	-	-	<1	-	-	-	-	-
Hyperbilirubinemia	-	-	✔	-	-	-	-	-	<1	-
Liver damage	-	-	-	-	<1	-	-	-	-	-
Liver function tests abnormal	-	-	-	-	-	-	-	-	<1	-
Transaminases increased	<1	-	-	-	-	-	-	-	-	-
Laboratory Test Abnormalities										
BUN increased	-	-	✔	-	-	-	-	-	-	-
Cortisol decreased	-	-	-	-	-	-	-	1	-	-
Hypercholesterolemia	-	-	-	-	<1	-	-	-	-	-
Hyperglycemia	-	-	-	-	-	-	-	-	<1	<1
Hyperkalemia	-	-	✔	-	-	-	-	-	-	-
Hyperuricemia	-	-	-	-	-	-	-	-	<1	-
Hypocalcemia	-	-	1	-	-	-	-	-	-	-
Hypoglycemia	-	-	✔	-	-	-	-	-	<1	-
Hypokalemia	-	-	-	-	<1	-	-	-	-	-
Hypothyroidism	-	-	-	-	-	-	-	-	<1	-
Prolactin increased	-	-	-	-	-	-	-	✔	-	-
Testosterone decreased	-	-	-	-	-	-	-	✔	-	-
Musculoskeletal										
Arthralgia	-	-	-	-	-	-	-	2	≥1	1-10
Arthritis	-	-	-	-	-	-	-	-	≥1	-
Back pain	-	-	-	-	-	-	-	-	≥1	1-10
Balance disorder	-	-	-	-	-	-	-	-	-	1-10
Cogwheel rigidity	<1	-	-	-	-	-	-	-	-	-
Dysarthria	-	-	-	-	-	-	-	-	<1	-

Adverse Events	Buspirone	Chloral Hydrate	Dexmede-tomidine	Droperidol	Eszopiclone	Hydroxyzine	Meprobamate	Ramelteon	Zaleplon	Zolpidem
Dyskinesia	<1	-	-	-	-	-	-	-	-	-
Dystonia	<1	-	-	-	-	-	-	-	<1	-
Hypertonia	-	-	-	-	-	-	-	-	1	-
Involuntary muscle contractions	-	-	-	-	-	-	-	-	-	1-10
Muscle spasms	<1	-	-	-	-	-	-	-	-	-
Myalgia	-	-	-	-	-	-	-	2	≥1	1-10
Myasthenia	-	-	-	-	<1	-	-	-	<1	-
Myopathy	-	-	-	-	<1	-	-	-	-	-
Myositis	-	-	-	-	-	-	-	-	<1	-
Neck pain	-	-	-	-	-	-	-	-	-	1-10
Neck rigidity	-	-	-	-	<1	-	-	-	-	-
Osteoporosis	-	-	-	-	-	-	-	-	<1	-
Psychomotor retardation	-	-	-	-	-	-	-	-	-	1-10
Restless leg syndrome	<1	-	-	-	-	-	-	-	-	-
Rigors	-	-	✔	-	-	-	-	-	-	-
Weakness	2	-	-	-	-	-	✔	-	5-7	1-10
Respiratory										
Apnea	-	-	✔	-	-	-	-	-	-	-
Asthma	-	-	-	-	<1	-	-	-	-	-
Bronchitis	-	-	-	-	<1	-	-	-	≥1	-
Bronchospasm	-	-	✔	✔	-	-	✔	-	-	-
Dyspnea	<1	-	✔	-	<1	-	-	-	-	<1
Epistaxis	<1	-	-	-	<1	-	-	-	≤1	-
Hypercapnia	-	-	✔	-	-	-	-	-	-	-
Hyperventilation	<1	-	-	-	-	-	-	-	-	-
Hypoventilation	-	-	✔	-	-	-	-	-	-	-
Hypoxia	-	-	✔	-	-	-	-	-	-	-
Laryngospasm	-	-	-	✔	-	-	-	-	-	-
Nasal congestion	≥1	-	-	-	-	-	-	-	-	-
Pharyngitis	-	-	-	-	-	-	-	-	-	1-10
Pleural effusion	-	-	2	-	-	-	-	-	-	-
Pulmonary congestion	-	-	✔	-	-	-	-	-	-	-
Pulmonary embolus	-	-	-	-	-	-	-	-	<1	-
Respiratory acidosis	-	-	✔	-	-	-	-	-	-	-
Respiratory depression	-	-	37	-	-	✔	-	-	-	-
Sinusitis	-	-	-	-	-	-	-	-	-	1-10

Adverse Events	Buspirone	Chloral Hydrate	Dexmede-tomidine	Droperidol	Eszopiclone	Hydroxyzine	Meprobamate	Ramelteon	Zaleplon	Zolpidem
Throat irritation	≥1	-	-	-	-	-	-	-	-	1-10
Upper respiratory tract infection	-	-	-	-	-	-	-	3	-	1-10
Wheezing	-	-	≤1	-	-	-	-	-	-	-
Special Senses										
Accommodation impaired	-	-	-	-	-	-	✔	-	-	-
Asthenopia	-	-	-	-	-	-	-	-	-	1-10
Blurred vision	2	-	-	-	-	✔	-	-	-	1-10
Conjunctivitis	<1	-	-	-	<1	-	-	-	≥1	-
Depth perception altered	-	-	-	-	-	-	-	-	-	1-10
Diplopia	-	-	-	-	-	-	-	-	-	1-10
Dry eyes	-	-	-	-	<1	-	-	-	-	-
Ear pain	-	-	-	-	-	-	-	-	≤1	-
Eye pain	-	-	-	-	-	-	-	-	3-4	-
Eye redness	-	-	-	-	-	-	-	-	-	1-10
Glaucoma	-	-	-	-	-	-	-	-	<1	-
Hyperacusis	-	-	-	-	-	-	-	-	1-2	-
Mydriasis	-	-	-	-	<1	-	-	-	-	-
Nystagmus	-	-	-	-	<1	-	-	-	-	-
Parosmia	-	-	-	-	-	-	-	-	1-2	-
Photophobia	-	-	-	-	<1	-	-	-	<1	-
Photopsia	-	-	✔	-	-	-	-	-	-	-
Ptosis	-	-	-	-	-	-	-	-	<1	-
Scleritis	-	-	-	-	-	-	-	-	-	<1
Tinnitus	≥1	-	-	-	<1	-	-	-	-	1-10
Vestibular disorder	-	-	-	-	<1	-	-	-	-	-
Visual disturbance	<1	-	✔	-	-	-	-	-	<1-2	1-10
Other										
Accidental injury	-	-	-	-	≤3	-	-	-	-	-
Allergic reaction	<1	-	-	-	<1	✔	-	-	-	1-10
Anaphylaxis	-	-	-	✔	<1	-	✔	✔	<1	<1
Angioedema	<1	-	-	-	<1	-	-	✔	<1	<1
Angioneurotic edema	-	-	-	-	-	-	✔	-	-	-
Binge eating	-	-	-	-	-	-	-	-	-	1-10
Diaphoresis	1	-	✔	-	<1	-	-	-	-	<1
Drug dependence	-	✔	-	-	-	-	-	-	-	-
Edema	<1	-	-	-	<1	-	-	-	-	<1

Adverse Events	Buspirone	Chloral Hydrate	Dexmede-tomidine	Droperidol	Eszopiclone	Hydroxyzine	Meprobamate	Ramelteon	Zaleplon	Zolpidem
Facial edema	-	-	-	-	<1	-	-	-	-	-
Facial paralysis	-	-	-	-	-	-	-	-	<1	-
Falling	-	-	-	-	-	-	-	-	-	<1
Flu-like syndrome	-	-	-	-	-	-	-	-	-	1-10
Heat stroke	-	-	-	-	<1	-	-	-	-	-
Hemorrhage	-	-	✔	-	-	-	-	-	-	-
Herpes zoster	-	-	-	-	<1	-	-	-	-	-
Hypersensitivity	-	-	-	-	-	-	✔	-	-	-
Infection	-	-	-	-	5-10	-	-	-	-	-
Influenza	-	-	-	-	-	-	-	1	-	-
Lactose intolerance	-	-	-	-	-	-	-	-	<1	-
Pain	1	-	✔	-	4-5	-	-	-	-	-
Serotonin syndrome	<1	-	-	-	-	-	-	-	-	-
Shivering	-	-	-	✔	-	-	-	-	-	-
Somnambulism	-	-	-	-	-	-	-	-	-	<1
Thrombosis	-	-	-	-	-	-	-	-	-	<1
Twitching	-	-	-	-	<1	-	-	-	-	-
Viral infection	-	-	-	-	3	-	-	-	-	-

✔ Percent not specified
- Event not reported

Table 8. Boxed Warning for Droperidol[1]

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 ECG 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 ECG monitoring prior to treatment and continue for 2 to 3 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 IV 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 9.

Table 9. Usual Dosing Regimens for the Miscellaneous Anxiolytics, Sedatives, and Hypnotics[1-12]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Buspirone	Anxiety Disorders: 7.5 mg twice daily; increase by 5 mg/day every 2-3 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
Chloral hydrate	Alcohol Withdrawal Syndrome: 500 mg to 1 g every 6 hours as needed Hypnotic: 500 mg to 1 g 15- 30 minutes before bedtime Sedation: 250 mg 3 times daily	Hypnotic: 50 mg/kg/dose at bedtime; maximum, 1 g/dose Sedation: 25 mg/kg/day in divided doses every 6-8 hours	Capsule: 500 mg Syrup: 500 mg/5 ml
Dexmedetomidine	Sedation (ICU): 1 mcg/kg IV over 10 minutes, then 0.2 to 0.7 mcg/kg/hour	Safety and efficacy in children have not been established.	Injection: 200 mcg/2 ml

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Sedation (Procedural): 1 mcg/kg IV over 10 minutes, then 0.2 to 1 mcg/kg/hour		
Droperidol	Nausea and Vomiting: 2.5 mg IM/IV; additional 1.25 mg doses may be given to achieve desired effect	Nausea and Vomiting: IM/IV: 2-12 years of age: 0.1 mg/kg >12 years of age: 2.5 mg	Injection: 2.5 mg/ml
Eszopiclone	Insomnia: 2 mg immediately before bedtime; maximum, 3 mg	Safety and efficacy in children have not been established.	Tablet: 1 mg 2 mg 3 mg
Hydroxyzine	Anxiety Disorders: Injection: 50 to 100 mg IM stat, then every 4-6 hours as needed Oral: 50 to 100 mg 4 times daily Nausea and Vomiting: Injection: 25 to 100 mg IM Pre-/Postpartum Adjunctive Therapy: Injection: 25 to 100 mg IM Pruritus: Oral: 25 mg 3-4 times per day Sedation (Premedication or Following Anesthesia): Injection: 25 to 100 mg IM Oral: 50 to 100 mg	Anxiety Disorders: Oral: ≥6 years of age: 50 to 100 mg daily in divided doses <6 years of age: 50 mg daily in divided doses Nausea and Vomiting: Injection: 0.5 mg/lb Pruritus: Oral: ≥6 years of age: 50 to 100 mg daily in divided doses <6 years of age: 50 mg daily in divided doses Sedation (Premedication or Following Anesthesia): Injection: 0.5 mg/lb Oral: 0.6 mg/kg	Capsule: 25 mg 50 mg 100 mg Injection: 25 mg/ml 50 mg/ml Syrup: 10 mg/5 ml Tablet: 10 mg 25 mg 50 mg
Meprobamate	Anxiety Disorders: 1,200 to 1,600 mg/day in 3-4 doses; maximum, 2,400 mg	Anxiety Disorders: 6-12 years: 200 to 600 mg/day in 2-3 divided doses	Tablet: 200 mg 400 mg
Ramelteon	Insomnia: 8 mg within 30 minutes of going to bed; maximum, 8 mg	Safety and efficacy in children have not been established.	Tablet: 8 mg
Zaleplon	Insomnia: 10 mg immediately before bedtime; maximum, 20 mg	Safety and efficacy in children have not been established.	Capsule: 5 mg 10 mg
Zolpidem	Insomnia: IR: 10 mg immediately before bedtime; maximum, 10 mg ER: 12.5 mg immediately before bedtime; maximum, 12.5 mg	Safety and efficacy in children have not been established.	Oral spray (IR): 5 mg/0.1 ml Sublingual tablet : 5 mg 10 mg Tablet (IR): 5 mg 10 mg Tablet (ER): 6.25 mg 12.5 mg

ER=extended-release, IR=immediate-release

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the miscellaneous anxiolytics, sedatives, and hypnotics are summarized in Table 10.

Table 10. 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				
Chessick et al.[28] (2006) Azaspirones (buspirone, gepirone*, ipsapirone*, lesopitron*) vs benzodiazepines, hydroxyzine, kava kava, placebo, venlafaxine XR or psychotherapy	MA Outpatients with generalized anxiety disorder	N=5,908 (36 trials) 4-14 weeks	Primary: Efficacy (HAM-A, CGI), acceptability (dropout rates, specific side effects)	Primary: Overall, azaspirones were more effective than placebo in treating GAD. Using the CGI scale in trials lasting 6 weeks, the calculated number needed to treat (NNT) for azaspirones was 4.4 (95% CI: 2.16 to 15.4). Using the HAM-A assessment, 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). Another small study reported comparable efficacy between buspirone and diazepam in treating GAD, but buspirone did not show equal efficacy until 6 weeks demonstrating a more rapid improvement on diazepam. Utilizing the CGI scale, buspirone was comparable in efficacy to venlafaxine XR 75 mg (N=182, RR: 0.74; 95% CI: 0.41 to 1.34) and venlafaxine XR 150 mg (N=184, RR; 1.24; 95% CI: 0.69 to 2.21) (P=0.47); but, venlafaxine XR 150 mg appeared to be more effective than venlafaxine XR 75 mg. The meta-analysis was not able to conclude if buspirone was more effective than kava kava (P=0.3) or psychotherapy. Significantly fewer patients dropped out who were on buspirone compared to placebo (RR: 0.68; 95% CI: 0.49 to 0.94, P=0.02). Significantly fewer patients dropped out on benzodiazepines compared to buspirone (RR: 1.24; 95% CI: 1.01 to 1.52, P=0.04). There was no difference in dropout rates between buspirone and venlafaxine XR 75 mg (P=0.92) or 150 mg (P=0.12), and kava kava

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(P=0.48). None of the studies reported significant side effects. Overall, side effects were more common in the drug treated groups than in the placebo treated groups. Patients on buspirone reported more dizziness (P=0.00005) and nausea (P=0.02) compared to those on placebo. 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, while those on 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 6 or 12 weeks, neither group had worsening symptoms of anxiety, but those on diazepam did show withdrawal symptoms at 6 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). Patients on buspirone reported less dry mouth (P=0.03) compared to venlafaxine XR while those on venlafaxine XR reported less dizziness (P<0.00001) compared to buspirone. No differences in side effects were reported between buspirone and kava kava (P=0.5).
Mitte et al.[29] (2005) Benzodiazepines vs azaspirones vs placebo	MA Patients with generalized anxiety disorder	N=12,053 (48 trials) Variable duration	Primary: Anxiety (HAM-A, HAM-D), clinical significance	Primary: Pharmacotherapy showed better results compared to placebo in reducing both anxiety and depression symptoms. There were no significant differences in efficacy, in terms of anxiety and depression, between the benzodiazepines and azaspirones. Significantly fewer patients in the benzodiazepine group dropped out of the study (20.5% vs 30.7%, P<0.05).
Blanco et al.[30] (2003)	MA	N=2,954 (23 trials)	Primary: Outcome data on	Primary: In terms of LSAS, effect sizes of each medication group were: clonazepam

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Benzodiazepines, SSRIs, MAOIs, RIMAs, β-blockers, gabapentin, buspirone vs placebo	Patients with social anxiety disorder	6-20 weeks	the Liebowitz Social Anxiety Scale (LSAS) or a categorical measure of status Secondary: Proportion of responders with CGI score change of 1 or 2	(0.97), gabapentin (0.78), phenelzine (0.66), brofaromine (0.66), SSRIs (0.65), moclobemide (0.25), atenolol (0.10), and buspirone (0.02). No statistical differences were detected between these 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.
Gammans et al.[27] (1992) Buspirone 10 to 60 mg/day vs placebo	MA Adult outpatients with generalized anxiety disorder	N=509 (8 trials) 4 weeks	Primary: Hamilton Rating Scale for Anxiety (HAM-A) score, Hamilton Rating Scale for Depression (HAM-D) score, Clinical Global Impression (CGI) score to determine responders	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 4-week double-blind treatment period in patients with GAD and coexisting depressive symptoms (P<0.05 at week 1 for HAM-D and P<0.05 at week 2 for HAM-A).
Lader et al.[31] (1998) Buspirone 20 mg/day vs	DB, MC, PC, RCT Adult outpatients with generalized anxiety disorder	N=244 6 weeks	Primary: HAM-A scores Secondary: CGI, Montgomery-Asberg Depression Rating 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
hydroxyzine 50 mg/day vs placebo			(MADRS), Hospital Anxiety and Depression (HAD) Scale, Ferreri Anxiety Rating Diagram (FARD), Tyrer Withdrawal Symptom Scale	than placebo. There was no significant difference between buspirone and 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 EDC (P<0.02 for both buspirone and hydroxyzine) and 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 with 4.9% in the buspirone and none in the placebo group.
Llorca et al.[32] (2002) Hydroxyzine 50 mg/day or bromazepam* 6 mg/day vs	DB, MC, PG, RCT Adult outpatients with generalized anxiety disorder	N=334 18 weeks	Primary: HAM-A scores Secondary: Responder and remission rates, change in Clinical Global Impressions-Severity (CGI-S) scale score and HAD scale score, maintenance of	Primary: Mean change in HAM-A scores from baseline was significantly greater for hydroxyzine (-12.16) compared with 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo			treatment efficacy, evaluation of rebound and withdrawal symptoms, safety	hydroxyzine and bromazepam; however, the study was not designed or powered to detect differences between these 2 active treatments. Efficacy was significantly maintained vs placebo in 86.5% of patients in 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 1 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).
Insomnia				
Buscemi et al.[38] (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	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). Meta-analyses 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. PSG results significantly favored antidepressants vs placebo. There were no significant differences between treatment for

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				WASO or TST (as measured using sleep diary results). 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 sleep diary for non-benzodiazepines. There was no significant difference in adverse events. All drug groups had a statistically significant higher risk of harm (more adverse events) compared to placebo, although the most commonly reported adverse events were minor. Risk differences were 0.15, 0.07 and 0.09 for the benzodiazepines, non-benzodiazepines and antidepressants, respectively, compared to placebo. The adverse events most commonly reported in these studies were headache, drowsiness, dizziness and nausea.
Smith et al.[50] (2002) Benzodiazepines or benzodiazepine receptor agonists vs behavioral treatment vs placebo	MA Patients with primary insomnia for 1 month or longer	N=470 (21 trials) Up to 10 weeks	Primary: Sleep latency, TST, number of awakenings, WASO, and sleep quality before and after treatment	Primary: Sleep latency was reduced by 30% with pharmacological treatment compared with 43% with behavioral interventions. Pharmacotherapy increased TST by 12% and behavior therapy by 6%. Both pharmacotherapy and behavior therapy reduced number of awakenings per night by 1. WASO was reduced by 46% with pharmacotherapy and by 56% with behavior therapy. Pharmacotherapy improved sleep quality by 20% and behavior therapy by 28%. Overall, there were no differences in TST, number of awakenings, WASO, and sleep quality between benzodiazepine receptor agonists and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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: 0.17-1.04).
Nowell et al.[43] (1997) Benzodiazepines or benzodiazepine receptor agonists vs placebo	MA Adults <65 years with chronic insomnia	N=1,894 (22 trials) 4 to 35 days	Primary: Sleep latency, TST, number of awakenings, sleep quality	Primary: Zolpidem and benzodiazepines were significantly more effective than placebo with regards to sleep latency, TST, number of awakenings and sleep quality (P<0.001).
Piccione et al.[33] (1980) Chloral hydrate 250 mg vs chloral hydrate 500 mg vs triazolam 0.25 mg vs triazolam 0.50 mg vs placebo	DB, XO Patients >60 years of age with primary insomnia	N=27 5 days	Primary: Efficacy (questionnaire with subjective estimates of sleep latency, total sleep time [TST], number of awakenings, overall quality of sleep), side effects	Primary: The patients' global evaluation of effectiveness indicated that triazolam 0.25 mg and 0.50 mg improved sleep more than placebo (both P<0.05), while chloral hydrate 250 mg and 500 mg were not better than placebo. Triazolam 0.50 mg but not 0.25 mg was felt to be 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. 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 mg or 500 mg (both P<0.05). There were no significant differences in reported side effects between the active treatments and placebo.
Zammit et al.[34] (2004)	DB, MC, PC, RCT	N=308	Primary: Efficacy	Primary: Eszopiclone 2 mg and 3 mg had significantly less time to sleep onset

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Eszopiclone 2 to 3 mg vs placebo	Adults 21-64 years of age with chronic primary insomnia	6 weeks	(polysomnography [PSG] and patient reports), next day residual effects (Digit-Symbol Substitution Test [DSST]), tolerance, rebound insomnia, safety	(P<0.001 and P<0.0001, respectively), more TST (P<0.01 and P<0.0001), better sleep efficiency (P<0.001 and P<0.0001), and enhanced quality and depth of sleep (both P<0.05) across the double-blind period compared with placebo. Eszopiclone 3 mg (P<0.01) but not 2 mg significantly improved sleep maintenance compared to placebo. 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.
Krystal et al.[36] (2003) Eszopiclone 3 mg vs placebo	DB, MC, PC, RCT Adults with chronic insomnia	N=788 6 months	Primary: Sleep latency, WASO, number of awakenings, TST, quality of sleep, next-day ratings of ability to function, daytime alertness, sense of physical well-being, safety	Primary: At the first week and each month for the study duration, eszopiclone produced significant and sustained improvements in sleep latency, WASO, number of awakenings, number of nights awakened per week, TST, and quality of sleep compared to placebo (all P<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<0.002). There was no evidence of tolerance and the most common adverse events were unpleasant taste and headache.
Walsh et al.[37] (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 (sleep latency, WASO, TST, number of awakenings, sleep quality, daytime alertness, ability to concentrate,	Primary: Patient-reported sleep and daytime function improved more with eszopiclone than with placebo at all months (P<0.001). Eszopiclone reduced Insomnia Severity Index scores to below clinically meaningful levels for 50% of patients (vs 19% with placebo; P<0.05) at 6 months. Lower mean scores on the Fatigue Severity Scale and the Epworth Sleepiness Scale were observed in the eszopiclone group relative to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			physical well-being, and ability to function), Insomnia Severity Index, Fatigue Severity Scale, Epworth Sleepiness Scale, Medical Outcomes Study Short-Form Health Survey (SF-36), Work Limitations Questionnaire, safety (assessments performed at baseline, treatment Months 1-6, and 2 weeks after discontinuation of treatment)	placebo for each month and the Month 1-6 average (P<0.05). SF-36 domains of Physical Functioning, Vitality, and Social Functioning were improved with eszopiclone vs placebo for the Month 1-6 average (P<0.05). Similarly, improvements were observed for all domains of the Work Limitations Questionnaire with eszopiclone vs placebo for the Month 1-6 average (P<0.05). There was no evidence of rebound insomnia after discontinuation of eszopiclone as sleep latency, 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 sleep latency 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). 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 placebo.
Erman et al.[40] (2008) Eszopiclone 1 mg for 2 nights vs eszopiclone 2 mg for 2 nights vs eszopiclone 2.5 mg for 2 nights	RCT, MC, XO Patients 21 to 64 years of age with primary insomnia	N=65 2 nights	Primary: Latency to persistent sleep (LPS) Secondary: Sleep efficiency (SE), wake time after sleep onset (WASO), wake time during sleep (WTDS), number of awakenings (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 min for eszopiclone 3 mg and zolpidem 10 mg. The median LPS was 29.0, 16.8, 15.5, and 13.8 min for the placebo, eszopiclone 1 mg, 2 mg, and 2.5 mg dose groups, respectively. The 2 highest doses of eszopiclone (2.5 mg and 3 mg) and zolpidem demonstrated significantly lower LPS when compared with 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 mg, 2.5 mg, and 3 mg, and zolpidem 10 mg demonstrated significantly higher SE when compared with eszopiclone 1 mg (P<0.05). Treatment with eszopiclone 3 mg resulted in significant differences

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs eszopiclone 3 mg for 2 nights vs zolpidem 10 mg for 2 nights vs placebo for 2 nights There was a 3-7 day washout between crossover treatments				compared 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 were 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 mg 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 mg and 3 mg and zolpidem 10 mg were significantly different from placebo for sNAW and sWASO (P<0.05). Morning sleepiness was significantly less with eszopiclone 3 mg compared with placebo (P<0.05). Evening ratings of daytime alertness were significantly increased with eszopiclone 2 mg and with zolpidem 10 mg compared with placebo (P<0.05), and daytime ability to function was significantly improved for eszopiclone 2 mg and 3 mg and zolpidem 10 mg compared with placebo (P<0.05). The most common adverse events were headache, unpleasant taste, somnolence, dizziness, and nausea. The overall rate of CNS adverse events was 7.9% for placebo, 6.2% to 12.5% for the eszopiclone groups, and 23.4% for zolpidem 10 mg.
Joffe et al.[59] (2009) Eszopiclone 3 mg for 4 weeks vs placebo for 4 weeks Each treatment	RCT, DB, PC, XO Perimenopausal and postmenopausal women 40 to 65 years of age with sleep-onset and/or sleep-maintenance insomnia cooccurring with hot flashes and depressive and/or	N=65 11 weeks	Primary: Changes in the Insomnia Severity Index (ISI) scale Secondary: Diary-based sleep parameters (wake time after sleep onset [WASO], sleep efficiency, sleep-onset	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 4 weeks of treatment in 87% of women on eszopiclone and in 34% of women on placebo. Sleep latency was reduced by 17.8 more minutes with eszopiclone than with placebo (P=0.04). Secondary: For both treatment periods together, WASO was reduced by 37.7 minutes more with eszopiclone than placebo (P=0.05), sleep efficiency improved by 14.6% more with eszopiclone than with placebo (P=0.01), and TST

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		latency, total sleep time (TST), and number of awakenings; number of hot flashes/night sweats, depressive symptoms, anxiety symptoms, menopause-related quality of life, and functional impairment	increased by 66.5 minutes more with eszopiclone than with placebo (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 with 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.[35] (2005) Eszopiclone 1 to 2 mg vs placebo	DB, MC, PC, RCT Community-dwelling elderly patients with primary insomnia	N=231 2 weeks	Primary: Patient-reported efficacy (sleep latency, TST) Secondary: Wake time after sleep onset (WASO), number of awakenings, number and length of naps, quality of	Primary: Patients treated with eszopiclone 1 mg and 2 mg had a significantly shorter sleep latency compared with 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 number of awakenings per night (P>0.1).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			sleep, depth of sleep, ratings of daytime alertness, sense of physical well-being, morning sleepiness, ability to function, quality of life (Quality of Life Enjoyment and Satisfaction Questionnaire [Q-LES-Q]), safety	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 with 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 placebo (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 5 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.[64] (2010) Eszopiclone 2 mg vs placebo	RCT, DB, PC Patients 65-85 years of age with primary insomnia	N=388 12 weeks	Primary: Change from baseline in patient-reported total sleep time (sTST) Secondary: Change from baseline in patient-reported sleep latency (sSL), wake time after sleep onset	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; P<0.0001). 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 minutes vs 19.92 minutes; respectively; P=0.0014). Patients receiving eszopiclone experienced a greater decrease in WASO compared to those receiving placebo (mean decreased of 36.4 minutes vs 14.8 minutes; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			(sWASO), insomnia severity index (ISI), daytime function, adverse events	The reported number of awakenings 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. There was a significantly greater decrease in naps per week over the first 3 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 6 (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 placebo for the social life and family life/home responsibilities items (both P≤0.03) at week 6, but not at week 12. There was no significant difference on the work/school item at either time point. The overall incidence of AEs was 59.3% for eszopiclone and 50.5% for placebo. The most common AEs reported in the eszopiclone group were headache (13.9% vs 12.4% for placebo), unpleasant taste (12.4% vs 1.5%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				for placebo), and nasopharyngitis (5.7% vs 6.2% for placebo).
Lettieri et al.[63] (2009) Eszopiclone 3 mg 30 minutes prior to polysomnography (premedication) vs placebo30 minutes prior to polysomnography (premedication)	RCT, DB, PC 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 4-6 weeks of therapy Secondary: CPAP titration quality as assessed by wake after sleep onset (WASO), total sleep time (TST), total arousal index, sleep latency, sleep efficiency, apnea-hypopnea index (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 hours vs 3.9 hours, respectively; P=0.03) and for more hours per night for all nights of the study period (4.0 hours 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 polysomnography compared to placebo as evidenced by shortened sleep latency (19.4 min vs 31.8 min, respectively; P=0.08), improved sleep efficiency (87.8% vs 80.1%, respectively; P=0.002), expanded TST (350.9 min vs 319.7 min, respectively; P=0.007), and decreased WASO (39.3 min vs 59.9 min, respectively; P=0.009). The residual AHI tended to be lower following eszopiclone premedication (6.4 events/hour vs 12.8 events/hour, respectively; P=0.08).
Lettieri et al.[57] (2009) Eszopiclone 3 mg for 2 weeks vs placebo for 2 weeks	RCT, DB, PC 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 open-label 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 versus 2.42 hours per night, respectively for all study nights (P=0.005) and for 4.05 versus 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
To promote adherence with CPAP, open-label use of sedative-hypnotic agents was allowed after the first 4 weeks of treatment.				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 weeks and 19.7 weeks, respectively (P=0.033). A total of 24.7% of patients requested open-label 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.[54] (2010) Eszopiclone 2 to 3 mg vs placebo	RCT, DB, PC, MC Patients 35 to 85 years of age with Parkinson's disease and sleep maintenance insomnia or sleep latency insomnia, as well as clinically significant daytime distress or impairment secondary to insomnia	N=30 6 weeks	Primary: Patient-reported total sleep time (TST) Secondary: Wake after sleep onset (WASO), number of awakenings and Sleep Impairment Index (SII), as well as others	Primary: There was no significant difference in TST among the treatment groups (66.5 minutes with eszopiclone vs 47 minutes with placebo; P=0.1099). Secondary: There were significant differences in number of awakenings (P=0.035), quality of sleep (P=0.018), and CGI – improvement in sleep (P=0.035) among the treatment groups. There was no significant difference in WASO (P=0.071). There were no differences in the UPDRS motor, ADL, therapeutic complications, mood or Schwab subscales. There were no significant differences in sleep latency, Fatigue Severity Scale, Sleep Impairment Index, 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.[58] (2011) Eszopiclone 3 mg for 3 weeks vs	RCT, DB, PC, XO Patients 18 to 64 years of age with posttraumatic stress disorder (PTSD) with associated	N=24 7 weeks	Primary: Changes in scores on the Short PTSD Rating Interview (SPRINT) and the Pittsburgh Sleep Quality Index	Primary: Eszopiclone was associated with significant improvement in PTSD symptomatology as measured by the SPRINT compared to placebo (P=0.032). Treatment with eszopiclone was associated with a significantly greater reduction in PSQI score compared to placebo (P=0.011).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo for 3 weeks Each treatment period was separated by a 1-week washout period.	sleep disturbance		(PSQI) Secondary: Clinician-Administered PTSD Scale (CAPS), sleep latency and total sleep time, adverse events	Secondary: In phase 1, the CAPS was also significantly reduced with eszopiclone compared to placebo (P=0.003). Sleep latency was significantly reduced with eszopiclone compared to placebo (P=0.044). There was no significant difference in total sleep time 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%).
Johnson et al.[39] (2006) Ramelteon 16 to 160 mg vs triazolam 0.25 to 0.75 mg vs placebo	DB, XO Adults with a history of sedative abuse	N=14 18 days	Primary: Subject-rated measures (drug liking, street value, pharmacological classification), observer-rated measures (sedation, impairment), motor and cognitive performance (balance task, DSST, word recall)	Primary: Compared with 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 with placebo, ramelteon had no effect at any dose on any observer-rated or motor and cognitive performance measure (all P>0.05). Triazolam showed dose-related effects on subject-rated, observer-rated, and motor and cognitive performance measures.
Roth et al.[41] (2006) Ramelteon 4 mg vs ramelteon 8 mg	DB, PC, RCT Patients 64 to 93 years of age with chronic primary insomnia	N=829 5 weeks	Primary: Sleep latency at week 1 Secondary: TST at weeks 1, 3 and 5; reductions in sleep latency at weeks 3 and 5;	Primary: Significant reductions in sleep latency at week 1 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 with placebo. Secondary: Patients continued to report reduced sleep latency at week 3 with ramelteon 8 mg (P=0.003) and at week 5 with ramelteon 4 and 8 mg (P=0.028 and P<0.001, respectively) compared to placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo			sleep diaries; rebound insomnia and withdrawal effects during the 7-day placebo run out	Patient-reported TST at weeks 1 and 3 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 5 weeks and for ramelteon 8 mg at weeks 1, 3 and 5 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., number of awakenings, ease of falling back asleep after an awakening and sleep quality) yielded no statistically significant differences among treatment groups at weeks 1, 3 and 5. 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 mg and 8 mg ramelteon groups, respectively.
Erman et al.[42] (2006) Ramelteon 4 to 32 mg vs placebo	DB, PC, RCT, XO Patients 18-64 years of age with chronic insomnia	N=107 2 nights	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 with 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 placebo. There were no differences between placebo and any ramelteon dose group on next-day performance and alertness. 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.[47] (2009)	RCT, DB, PC	N=451	Primary: Latency to	Primary: Greater reductions in LPS occurred with ramelteon compared to placebo

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ramelteon 8 mg vs placebo	Patients ≥18 years of age with chronic primary insomnia	6 months	persistent sleep (LPS) measured by polysomnography Secondary: Total sleep time measured by polysomnography, total time spent in each sleep stage, latency to rapid eye movement (REM), self-reported efficacy	(P<0.05 for each time point). A greater change from baseline occurred with ramelteon (54%-56%) compared to placebo (30%-47%). Secondary A greater increase in TST occurred with ramelteon (381.1 minutes) compared to placebo (365.7 minutes) at week 1 (P<0.001), but not at any other time points. There were no significant changes in percent of time spent in Stage 1 or REM sleep with ramelteon versus 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 sleep latency with ramelteon compared to placebo at week 1, as well as months 1 and 5 (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 total sleep time, subjective number of awakenings, and sleep quality. No significant differences in subjective wake time after sleep onset was observed between ramelteon (90.89 minutes) and placebo (79.54 minutes) at any time point except month 6 (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.[60] (2011) Ramelteon 8 mg	RCT, DB, PC, MC Japanese patients 20 to 85 years of age	N=1,605 2 weeks	Primary: Mean patient-reported sleep latency	Primary: The mean sleep latency was reduced in week 1 in both the ramelteon and placebo groups (-15.98 min and -11.73 min, respectively; P=0.0010).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	with primary insomnia		during week 1 of treatment Secondary: Mean sleep latency during week 2 of treatment, mean patient-reported total sleep time for week 1 and for week 2, patient's global impression of treatment, rebound insomnia, and safety	Secondary: The mean sleep latency decreased further in week 2 in both groups; however, the difference between the groups of -2.36 min in favor of ramelteon did not achieve statistical significance (P=0.1093). Ramelteon increased total sleep time significantly more than placebo at week 1 (difference in LS mean of +4.2 min; P=0.0484), but not at week 2 (+2.4 min; P=0.2378). The mean number of awakenings reported by patients in the ramelteon group was significantly less than that in the placebo group at week 2 (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 1 (difference in LS mean of -0.12; P=0.0174), but not week 2 (-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 with placebo at the end of week 1 (1.52 vs 1.59; P=0.0041) and week 2 (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 1 and 2 for time to fall asleep (week 1, 53.1% vs 44.3%, P=0.0100; week 2, 58.3% vs 52.5%, P=0.0434), total sleep time (week 1, 42.0% vs 34.0%, P=0.0121; week 2, 47.6% vs 38.8%, P=0.0031), sleep quality (week 1, 56.4% vs 48.2%, P=0.0115; week 2, 62.5% vs 56.1%, P=0.0463), and usefulness of treatment (week 1, 58.2% vs 47.6%, P=0.0008; week 2, 64.6% vs 56.8%, P=0.0123), but not for daytime distress (week 1, 33.4% vs 31.9%, P=0.9116; week 2, 42.7% vs 37.7%, P=0.0881). A total of 26.4% of patients in the ramelteon group and 20.5% in the placebo group reported at least one treatment-emergent adverse event. All events were mild or moderate in severity. The most common adverse

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				event leading to discontinuation was nasopharyngitis.
Uchiyama et al.[61] (2011) Ramelteon 4 to 16 mg	OL, SB, MC 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 Secondary: Subjective sleep latency and total sleep time	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 c-glutamyltransferase, laryngopharyngitis, and headache. Endocrine adverse events that were considered drug-related included metrorrhagia, dysmenorrhea, polymenorrhea, increased estradiol, increased cortisol, and decreased cortisol. The mean change in next-morning residual scores significantly improved from baseline with ramelteon (P<0.05). The mean change from baseline in sleep latency at week 24 and the placebo run-out period using the full analysis set with 8 mg were -30.4 and -28.6 min 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 sleep latency decreased significantly during the study. In the group that continuously received ramelteon 8 mg, it decreased from a baseline of 70.5 min to 54.4 min after 1 week (P<0.0001) and 33.8 min after 20 weeks (P<0.0001), then plateaued until the end of the study. The mean subjective total sleep time was 5.52 hours at baseline, increasing to 5.78 hours at week 1 (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.[56] (2010) Ramelteon 8 mg vs	RCT, DB, PC Patients ≥60 years of age with obstructive sleep apnea and complaints of	N=21 4 weeks	Primary: Objective change in sleep onset latency using polysomnography Secondary:	Primary: Using polysomnography, there was a 10.7 minute decrease in sleep onset latency in the ramelteon arm compared to a 17.8 minute increase in the placebo arm (difference of 28.5 minutes; P=0.008). For self-reported sleep onset latency, there was no significant difference among the 2 study arms (−1.3 min; P=0.9). Neither objective nor

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo	insomnia		Global perception of sleep quality (Pittsburgh Sleep Quality Index [PSQI]), insomnia severity (Insomnia Severity Index [ISI]), daytime functioning (Functional Out-comes of Sleepiness Scale [FOSQ]), quality of life (RAND Medical Outcomes Study Short Form [SF-36]), and APAP adherence	subjective sleep efficiency differed significantly between study arms. Secondary: There were no significant differences in the PSQI, ISI, FOSQ, or SF-36 among the treatment groups. APAP adherence did not differ significantly between the ramelteon and placebo groups (159.1 minutes vs 226.9 minutes; P=0.4). APAP adherence (≥4 hours of use for ≥4 nights per week) was 47.1% and was not affected by the treatment used. The adverse events reported with ramelteon were diarrhea, skin ulcer, sinusitis, and fracture after being hit by a bicyclist. For placebo, the 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.
Elie et al.[46] (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 sleep latency Secondary: Patient's assessment of sleep duration, sleep quality, number of awakenings, rebound insomnia, withdrawal effects, safety	Primary: Median sleep latency was significantly lower with zaleplon 10 mg and 20 mg than with placebo during all 4 weeks of treatment, and with zaleplon 5 mg and zolpidem 10 mg for the first 3 weeks. Secondary: Zaleplon 20 mg significantly (P<0.05) increased sleep duration compared with placebo in all but week 3 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 1 with zaleplon 10 mg and 20 mg, and for all weeks with zolpidem 10 mg. No significant differences were observed in number of awakenings 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				discontinuation of 4 weeks of treatment. Significant differences in sleep latency (P<0.05) and number of awakenings (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 number of awakenings with zaleplon 10 mg and 20 mg than with placebo, and on the third night there were significantly fewer patients (P<0.05) showing rebound for the number of awakenings with zaleplon 20 mg. There was no evidence of withdrawal symptoms after discontinuation of 4 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 2 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.
Dunbar et al.[45] (2004) Zaleplon 5 to 20 mg vs zolpidem 5 to 10 mg	MA Patients 16-85 years of age with insomnia	N=1,539 (6 trials) 2 nights to 4 weeks	Primary: Sleep onset latency, TST, quality of sleep, adverse events, rebound insomnia	Primary: Of the 2 studies that directly compared sleep onset latency, 1 study reported a significantly shorter sleep latency with zaleplon (P<0.001), whereas the other study reported results in favor of zolpidem (P=0.03). Of the 2 studies that directly compared TST, 1 study reported that sleep duration was significantly less in the zaleplon group (290.7 minutes vs 308.6 minutes for zolpidem, P=0.05) but another study found no difference (8 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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 2 trials noted that patients receiving zaleplon were less likely to experience rebound insomnia compared with those on zolpidem (sleep latency OR: 0.27; 95% CI: 0.17 to 0.44, sleep duration OR: 0.25; 95% CI 0.15 to 0.41, and number of awakenings OR: 0.34; 95% CI 0.18 to 0.61). In a crossover study, 62.3% of patients favored zolpidem compared with 37.7% of patients who favored zaleplon (P=0.08).
Zammit et al.[26] (2006) 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.	RCT, DB, PC, XO Patients 18-65 years of age with primary sleep-maintenance insomnia	N=37 2 nights	Primary: Latency to persistent sleep (LPS) and total sleep time (TST), daytime sleep latency	Primary: LPS after the administration of zaleplon 10 mg, zolpidem 10 mg, and 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 minutes 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 minutes and 30 minutes, respectively (overall P<0.001). Daytime sleep latency 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 4 (P<0.001), 5 (P<0.001), and 7 (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 sleep latency testing (SLT) performed at 4 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 4, 5, and 6 hours after treatment (overall P<0.05).
Huang et al.[53]	RCT, DB, AC	N=48	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2011) Zaleplon 10 mg vs zolpidem 10 mg	Patients 20 to 65 years of age with primary insomnia	2 weeks	Change in subjective sleep latency from baseline to week 2 Secondary: Sleep duration, number of awakenings, sleep quality and incidence of rebound insomnia	There was a significant reduction in subjective sleep latency 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 sleep latency (P=0.084). Secondary: There was no significant difference in sleep duration, number of awakenings, or sleep quality among the treatment groups. None of the patients experienced 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.
Scharf et al.[48] (1994) Zolpidem 10 to 15 mg vs placebo	DB, MC, PC, RCT Adults with chronic insomnia	N=75 5 weeks	Primary: LPS, sleep efficiency, sleep maintenance, sleep quality, effects on sleep stages, residual drug effects, safety	Primary: Zolpidem had a significant (P<0.05) effect on LPS and sleep efficiency from weeks 2 through 5 in the 10 mg group and at weeks 2 through 6 in the 15 mg group. Polysomnographic measures of sleep maintenance were not significantly different among the 3 treatment groups (P>0.05). Patients receiving zolpidem 15 mg reported significantly better quality of sleep than those receiving the 10 mg dose at week 2 and placebo at week 5. Stages 1, 2, and 3-4 sleep were not significantly affected by either the 10- or 15 mg doses of zolpidem compared with placebo. However, there were significant (P<0.05) decreases in REM sleep at weeks 3 and 4 with zolpidem 15 mg compared with 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 3-4 sleep (P<0.05 for both zolpidem doses compared to placebo).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There were no significant treatment differences between the 10 mg zolpidem group and placebo in LPS, sleep efficiency, wake time during sleep or sleep quality during the posttreatment period when zolpidem was discontinued. The 15 mg zolpidem group did not differ significantly from the placebo group on LPS or sleep efficiency on the first night posttreatment, but did result in a significantly greater wake time during sleep and poorer quality of sleep (P<0.05 compared to placebo) during the first night posttreatment. Comparison of the subsequent 2 nights posttreatment 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, 2 patients in the 15 mg zolpidem group withdrew from the study: 1 patient experienced drowsiness, dizziness, and nausea; and 1 patient experienced visual disturbance and over-sedation. The 15 mg zolpidem dosage provided no clinical advantage over the 10 mg zolpidem dosage.
Roehrs et al.[55] (2011) Zolpidem 10 mg vs placebo	RCT, DB, PC 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	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 3 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 1, 4, and 12. The total number of placebo capsules self-administered by the placebo group increased significantly during month 4

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				and month 12 compared to month 1 (P<0.02). Within the zolpidem group, the nightly number of placebo versus zolpidem capsules self-administered each month did not differ. On average, the zolpidem group self-administered a 9.1 mg dose nightly in month 1, a 9.4 mg dose in month 4, 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 4 to month 12. A significantly greater percent of patients receiving zolpidem compared to placebo decreased the dose they self-administered in month 4 and month 12 compared to month 1 (P<0.001). The self-administration rates did not differ when at the laboratory versus at home for patients receiving zolpidem. These rates also did not differ over the 3 assessments.
Hindmarch et al.[49] (2006) Zolpidem ER 6.25 mg vs zolpidem ER 12.5 mg vs flurazepam 30 mg vs placebo	DB, DD, RCT, XO Healthy volunteers ≥65 years of age	N=24 Single dose	Primary: Psychometric tests performed 8 hours after study medication (CFF, CRT, word recall, CTT, DSST), subjective evaluation of sleep (LSEQ), safety, pharmacokinetics (zolpidem ER only)	Primary: There were no significant differences in psychometric tests between either dose of zolpidem and placebo (P<0.05). Psychometric performance was significantly impaired (P<0.05) 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 ER and with flurazepam (all P<0.05). Neither zolpidem ER 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 ER, which is consistent with dose linearity.
Krystal et al.[44]	RCT, MC, DB, PC	N=1,025	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2008) Zolpidem ER 12.5 mg vs placebo Treatments were taken 3-7 nights per week.	Patients 18-64 years of age with chronic primary insomnia	26 weeks	Score on the Patient's Global Impression (PGI), Item 1, (aid to sleep) at week 12 of the treatment period in the intent-to-treat (ITT) population Secondary: Scores on CGI-I, PGI, Patient Morning Questionnaire (PMQ), total sleep time (TST), wake time after sleep onset (WASO), sleep onset latency (SOL), quality of sleep (QOS), and number of awakenings (NAW) in the ITT population	At week 12, PGI, Item 1 (aid to sleep) was scored as favorable (i.e., "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 1-4) was higher in the zolpidem extended-release group compared to placebo at each 4-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 extended-release group compared with the placebo group at all 4-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 extended-release group compared to the placebo group for the TST (P<0.0001), WASO (P<0.0001), SOL (P≤0.0014), QOS (P<0.0001), and NAW (month 1, P=0.0515; months 2 to 6, P<0.0001). Patients in the zolpidem extended-release group demonstrated improvements in their ability to concentrate in the morning at each month throughout the treatment period, as compared with those in the placebo group (months 1 to 5, P<0.0001; month 6, P=0.0014). Patients in the zolpidem extended-release 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.
Staner et al.[25] (2009) Zolpidem 5 mg	RCT, OL, XO Healthy volunteers in a post-nap	N=21 Single dose	Primary: Latency to persistent sleep (LPS), sleep onset	Primary: For zolpidem 10 mg SL tablets, LPS was significantly decreased by 6.11 min as compared to zolpidem 10 mg tablets (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
SL tablet vs zolpidem 10 mg SL tablet vs zolpidem 10 mg tablet	model of insomnia		latency (SOL), latency to stage 1 (LTS1), total sleep time, sleep efficiency, awakening after sleep onset, REM sleep latency (RSL), stage 4 duration (ST4)	Zolpidem 10 mg SL tablets decreased SOL by 5.81 min as compared to zolpidem 10 mg tablets (P<0.05). Zolpidem 10 mg SL tablets decreased LST1 by 6.17 min as compared to zolpidem 10 mg tablets (P<0.05). Similar differences were demonstrated for sleep initiation parameters between zolpidem 5 mg and 10 SL tablets (7.28 min difference for LPS, 6.69 min difference for SOL and 6.06 min difference for LTS1; all P<0.05). There were no significant differences in the three sleep initiation parameters between zolpidem 5 mg and 10 mg SL tablets. There were no significant differences between the three treatments for sleep maintenance parameters, including total sleep time, sleep efficiency or awakening after sleep onset. There were no differences in sleep maintenance between zolpidem 5 mg and 10 mg SL tablets. Significant treatment effects were evidenced for REM sleep latency (RSL) and stage 4 duration (ST4). Both RSL and ST4 were similar with zolpidem 5 mg and 10 SL tablets. Both parameters were significantly shorter in patients receiving zolpidem 5 mg SL tablets compared to zolpidem 10 mg tablets (RSL: -19.22 min, P<0.01; ST4: -11.89 min, P<0.01). There were no differences in sleep architecture between zolpidem 5 mg 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, 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.
Staner et al.[62] (2010) Zolpidem 10 mg	RCT, DB, MC, XO Patients 18 to 65 years of age with	N=70 Single dose	Primary: Latency to persistent sleep (LPS), sleep onset	Primary: Sublingual zolpidem shortened the LPS by about 34% or 10.3 minutes (P=0.001), SOL with about 8.6 min (P<0.01) and ST1L with about 7.4 min (P<0.01) compared to oral zolpidem.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
SL tablet vs zolpidem 10 mg tablet	primary insomnia		latency (SOL), time spent in sleep stage 1 (ST1L) Secondary: Total sleep time (TST), wake after sleep onset (WASO), sleep efficiency index (SEI), total time spent awake (TTA), time spent in stage 2 (ST2), time spent in slow wave sleep (SWS); time spent in REM sleep (REM); REM sleep latency (RSL), Leeds Sleep Evaluation Questionnaire (LSEQ), Digit Symbol Substitution Test (DSST), Critical Flicker Fusion Test (CFFT), MCRT	Secondary: There were no significant differences on in TST and WASO among the treatment groups. The TST was 432 minutes for sublingual zolpidem and 425 minutes for oral zolpidem. WASO was 31 minutes and 30 minutes for sublingual zolpidem and oral zolpidem, respectively. There was a significant difference in SEI (P<0.05) and TTA (P<0.05), favoring sublingual zolpidem. No differences were found between the treatments for the sleep architecture parameters ST1, SWS, REM and RSL. The difference found for ST2 reached statistical significance (P<0.05), favoring sublingual zolpidem. 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 VAS. There were no significant differences in MCRT and DSST between the two treatments. CFFT results indicated that, during the descending runs, patients had a lower flicker fusion threshold after sublingual zolpidem than after oral 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 sublingual zolpidem were somnolence and dysgeusia. Nausea, dysgeusia, somnolence and dizziness were the most common adverse events with oral zolpidem.

*Not available in the United States
Drug regimen abbreviations: AM=morning, BID=twice daily, ER=extended-release, HS=bedtime, MAOI=monoamine oxidase inhibitor, PM=evening, QD=once daily, QID=four times daily, SL=sublingual, SSRI=selective serotonin-reuptake inhibitor, TID=three times daily, XR=extended-release
Study abbreviations: CI=confidence interval, DB=double-blind, DD=double dummy, HR=hazard ratio, MA=meta-analysis, MC=multicenter, NNT=numbers needed to treat, NS=not significant, OL=open-label, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial, XO=crossover, WMD=weighted mean difference
Miscellaneous abbreviations: CFF=Critical Flicker Fusion, CGI=Clinical Global Impression, CGI-S=Clinical Global Impressions-Severity, CRT=Choice Reaction Time, CTT=Continuous Tracking Test, DSST=Digit-Symbol Substitution Test, FARD=Ferreri Anxiety Rating Diagram, GAD=generalized anxiety disorder, HAD=Hospital Anxiety and Depression, HAM-A=Hamilton Rating Scale for Anxiety, HAM-D=Hamilton Rating Scale for Depression, LARS=Leeds Analogue Rating Scales, LSEQ=Leeds Sleep Evaluation Questionnaire, LPS=latency to persistent sleep, LSAS=Liebowitz Social Anxiety Scale, MADRS=Montgomery-Asberg Depression Rating Scale, PSG=polysomnography, Q-LES-Q=Quality of Life Enjoyment and Satisfaction Questionnaire, TST=total sleep time, WASO=wake time 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 11. 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	$-$$$
Chloral hydrate	capsule, syrup	N/A	N/A	$-$$$
Dexmedetomidine	injection	Precedex®	$$$-$$$$	N/A
Droperidol	injection	N/A	N/A	$
Eszopiclone	tablet	Lunesta®	$$$$-$$$$$	N/A
Hydroxyzine	capsule, injection, syrup, tablet	Vistaril®*	$$$-$$$$	$
Meprobamate	tablet	N/A	N/A	$$$
Ramelteon	tablet	Rozerem®	$$$$	N/A
Zaleplon	capsule	Sonata®*	$$$	$
Zolpidem	extended-release tablet, oral spray, sublingual tablet, tablet	Ambien®*, Ambien CR®*, Edluar®, ZolpiMist®	$-$$$$	$-$$$$

*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, as well as treatment of pruritus. All of the products are available in a generic formulation, with the exception of dexmedetomidine, eszopiclone and ramelteon.

The agents that are approved for the treatment of anxiety disorders include buspirone, hydroxyzine and meprobamate.[1-3] 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.[22] Buspirone and sedating antihistamines are not effective as monotherapy for the treatment of panic disorder.[15,22] 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.[15] Sedating antihistamines are one of several options for the short-term, immediate treatment of generalized anxiety disorder.[15] Buspirone is not recommended for the initial treatment of obsessive-compulsive disorder or posttraumatic stress disorder.[23-24] The available guidelines do not provide any recommendations regarding the use of meprobamate for the treatment of anxiety disorders.[15,22-24]

Chloral hydrate, eszopiclone, ramelteon, zaleplon and zolpidem are approved for the treatment of insomnia.[1-3,5,7-12] 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.[17] They do not give preference to one agent over another. Chloral hydrate is not recommended for the treatment of insomnia.[17] 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.[17] 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.[17-18] Hypnotic treatments should be combined with behavioral and cognitive therapies.[17] 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.[17] Results from clinical trials demonstrate that these agents are effective for the treatment of insomnia.[17-18,26,34-38,40-48,53,55-57-64] Relatively few studies were found in the medical literature directly comparing the efficacy and safety of these agents.

There is insufficient evidence to support that one brand miscellaneous anxiolytic/sedative/hypnotic agent is more efficacious than another within its given indication. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and OTC 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.

XII. References

1. Drug Facts and Comparisons. Drug Facts and Comparisons 4.0 [online]. 2012. Available from Wolters Kluwer Health, Inc. Accessed May 2012.
2. Lexi-Comp Online, Lexi-Drugs Online, Hudson, Ohio: Lexi-Comp, Inc.; 2012; May 2012.
3. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed May 2012.
4. Precedex® [package insert]. Lake Forest, IL: Hospira; September 2010.
5. Lunesta® [package insert]. Marlborough, MA: Sunovion Pharmaceuticals, Inc.; November 2010.
6. Vistaril® [package insert]. New York, NY: Pfizer Labs; April 2004.
7. Rozerem® [package insert]. Deerfield, IL: Takeda Pharmaceuticals America, Inc.; November 2010.
8. Sonata® [package insert]. Bristol, TN: King Pharmaceuticals; August 2011.
9. Ambien® [package insert]. Bridgewater, NJ: Sanofi-Aventis US. August 2010.
10. Ambien CR® [package insert]. Bridgewater, NJ: Sanofi-Aventis US; October 2010.
11. Edluar® [package insert]. Somerset, NJ: Meda Pharmaceuticals, Inc.; October 2010.
12. ZolpiMist® [package insert]. Richmond, VA: ECR Pharmaceuticals; Septebmer 2010.
13. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th ed., text revision (DSM-IV-TR). Washington, DC: American Psychiatric Association; 2000:356.
14. Morin AK, Jarvis CI, Lynch AM. Therapeutic options for sleep-maintenance and sleep-onset insomnia. Pharmacotherapy. 2007;27(1):89-110.
15. National Institute for Clinical Excellence. Generalized anxiety disorder and panic disorder (with or without agoraphobia) in adults. National Institute for Clinical Excellence (NICE); January 2011. Available at: http://www.nice.org.uk/nicemedia/live/13314/52599/52599.pdf. Accessed May 2012.
16. Connolly S, Bernstein G, AACAP Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with anxiety disorders. American Academy of Child and Adolescent Psychiatry (AACAP). J Am Acad Child Adolesc Psychiatry 2007;46(2):267-283.
17. Schutte-Rodin S, Broch L, Buysse D, et al. Clinical guideline for the evaluation and management of chronic insomnia in adults. American Academy of Sleep Medicine (AASM). J Clin Sleep Med 2008;4:487-504.
18. NIH state-of-the-science conference statement on manifestations and management of chronic insomnia in adults. [internet] NIH Consens Sci Statements. 2005 [cited 2007 Jul 16]. Jun 13-15; 22(2) 1-30.
19. Lichtenstein DR, Jagannath S, Baron TH, et al. Sedation and anesthesia in GI endoscopy. American Society for Gastrointestinal Endoscopy Gastrointest Endosc 2008;68:815-26.
20. Gan T, Meyer T, Apfel C, et al. Consensus guidelines for managing postoperative nausea and vomiting. Anesth Analg. 2003;97:62-71.
21. American Gastroenterological Association medical position statement: nausea and vomiting. Gastroenterology 2001;120:263-286.
22. Stein M, Goin M, Pollack M, et al. Practice guideline for the treatment of patients with panic disorder, second edition. American Psychiatric Association; 2009. Available at: http://psychiatryonline.org/data/Books/prac/PanicDisorder_2e_PracticeGuideline.pdf. Accessed May 2012.
23. Koran L, Hanna G, Hollander E, Nestadt G, Simpson H; American Psychiatric Association. Practice guideline for the treatment of patients with obsessive-compulsive disorder. Arlington (VA): American Psychiatric Association; July 2007. Available at: http://psychiatryonline.org/data/Books/prac/OCDPracticeGuidelineFinal05-04-07.pdf. Accessed May 2012.
24. Ursano RJ, Bell C, Eth S, et al. Practice guideline for the treatment of patients with acute stress disorder and posttraumatic stress disorder. American Psychiatric Association; November 2004. Available at: http://psychiatryonline.org/data/Books/prac/ASD_PTSD_Inactivated_04-16-09.pdf. Accessed May 2012.
25. Staner L, Eriksson M, Cornette F, et al. Sublingual zolpidem is more effective than oral zolpidem in initiating early onset of sleep in the post-nap model of transient insomnia: a polysomnographic study. Sleep Med 2009;10:616-20.
26. Zammit G, Corser B, Doghramji K, et al. Sleep and residual sedation after administration of zaleplon, zolpidem, and placebo during experimental middle-of-the-night awakening. J Clin Sleep Med 2006;2:417-23.
27. Gammans RE, Stringfellow JC, Hvizdos AJ, Seidehamel RJ, Cohn JB, Wilcox CS, et al. Use of buspirone in patients with generalized anxiety disorder and coexisting depressive symptoms. A meta-analysis of eight randomized, controlled studies. Neuropsychobiology. 1992;25(4):193-201.
28. Chessick CA, Allen MH, Thase M, Batista Miralha da Cunha AB, Kapczinski FF, de Lima MS, et al. Azapirones for generalized anxiety disorder. Cochrane Database Syst Rev. 2006 Jul 19;3:CD006115.

29. Mitte K, Noack P, Steil R, Hautzinger M. A meta-analytic review of the efficacy of drug treatment in generalized anxiety disorder. J Clin Psychopharmacol. 2005 Apr;25(2):141-50.
30. Blanco C, Schneier F, Schmidt A, Blanco-Jerez C, Marshall R, Sanchez-Lacay A et al. Pharmacological treatment of social anxiety disorder: a meta-analysis. Depress Anxiety. 2003;18(1):29-40.
31. Lader M, Scotto JC. A multicentre double-blind comparison of hydroxyzine, buspirone and placebo in patients with generalized anxiety disorder. Psychopharmacology. 1998 Oct;139(4):402-6.
32. Llorca PM, Spadone C, Sol O, Danniau A, Bougerol T, Corruble E, et al. Efficacy and safety of hydroxyzine in the treatment of generalized anxiety disorder: a 3-month double-blind study. J Clin Psychiatry. 2002 Nov;63(11):1020-7.
33. Piccione P, Zorick F, Lutz T, Grissom T, Kramer M, Roth T. The efficacy of triazolam and chloral hydrate in geriatric insomniacs. J Int Med Res. 1980;8(5):361-7.
34. Zammit G, McNabb L, Caron J, Amato D, Roth T. Efficacy and safety of eszopiclone across 6 weeks of treatment for primary insomnia. Curr Med Res Opin. 2004 Dec;20(12):1979-91.
35. Scharf M, Erman M, Rosengerg R, Seiden D, McCall WV, Amato D, Wessel TC. A 2-week efficacy and safety study of eszopiclone in elderly patients with primary insomnia. Sleep. 2005;28(6):720-7.
36. Krystal AD, Walsh JK, Laska E, Caron J, Amato DA, Wessel TC, Roth T. Sustained efficacy of eszopiclone over 6 months of nightly treatment: results of a randomized, double-blind, placebo-controlled study in adults with chronic insomnia. Sleep. 2003 Nov 1;26(7):793-9.
37. Walsh JK, Krystal AD, Amato DA, Rubens R, Caron J, Wessel TC, Schaefer K, Roach J, Wallenstein F, Roth T. Nightly treatment of primary insomnia with eszopiclone for six months: effect on sleep, quality of life, and work limitations. Sleep. 2007:30(8):959-68.
38. Buscemi N, Vandermeer B, Friesen C, Bialy L, Tubman M, Ospina M, Klassen TP, Witmans M. The efficacy and safety of drug treatments for chronic insomnia in adults: a meta-analysis of RCTs. J Gen Intern Med. 2007 Sep;22(9):1335-50.
39. Johnson MW, Suess PE, Griffiths RR. Ramelteon: a novel hypnotic lacking abuse liability and sedative adverse effects. Arch Gen Psych. 2006 Oct;63:1149-57.
40. Erman MK, Zammit G, Rubens R, et al. A polysomnographic placebo-controlled evaluation of the efficacy and safety of eszopiclone relative to placebo and zolpidem in the treatment of primary insomnia. J Clin Sleep Med 2008;4:229-34.
41. Roth T, Seiden D, Sainati S, Wang-Weigand S, Zhang J, Zee P. Effects of ramelteon on patient-reported sleep latency in older adults with chronic insomnia. Sleep Med. 2006 Jun;7(4):312-8.
42. Erman M, Seiden D, Zammit G, Sainati S, Zhang J. An efficacy, safety, and dose response study of ramelteon in patients with chronic primary insomnia. Sleep Med. 2006;7:17-24.
43. Nowell PD, Mazumdar S, Buysse DJ, Dew MA, Reynolds CF, Kupfer DJ. Benzodiazepines and zolpidem for chronic insomnia. A meta-analysis of treatment efficacy. JAMA. 1997 Dec 24/31;278(24):2170-7.
44. Krystal AD, Erman M, Zammit GK, et al. Long-term efficacy and safety of zolpidem extended-release 12.5 mg, administered 3 to 7 nights per week for 24 weeks, in patients with chronic primary insomnia: a 6-month, randomized, double-blind, placebo-controlled, parallel-group, multicenter study. Sleep 2008;31:79-90.
45. Dundar Y, Dodd S, Strobl J, Boland A, Dickson R, Walley T. Comparative efficacy of newer hypnotic drugs for the short-term management of insomnia: a systematic review and meta-analysis. Hum Psychopharmacol Clin Exp. 2004:19:305-22.
46. Elie R, Ruther E, Farr I, Emilien G, Salinas E. Sleep latency is shortened during 4 weeks of treatment with zaleplon, a novel nonbenzodiazepine hypnotic. Zaleplon Clinical Study Group. J Clin Psychiatry. 1999 Aug;60(8):536-44.
47. Mayer G, Wang-Weigand S, Roth-Schechter B, et al. Efficacy and safety of 6-month nightly ramelteon administration in adults with chronic primary insomnia. Sleep 2009;32:351-60.
48. Scharf M, Roth T, Vogel G, Walsh J. A multicenter, placebo-controlled study evaluating zolpidem in the treatment of chronic insomnia. J Clin Psychiatry. 1994 May;55(5):192-9.
49. Hindmarch I, Legangneux E, Stanley N, Emegbo S, Dawson J. A double-blind, placebo-controlled investigation of the residual psychomotor and cognitive effects of zolpidem-MR in healthy elderly volunteers. Br J Clin Pharmacol. 2006;62(5):538-45.
50. Smith M, Perlis M, Park A, Smith M, Pennington J, Giles D, et al. Comparative meta-analysis of pharmacotherapy and behavior therapy for persistent insomnia. Am J Psychiatry. 2002 Jan;159(1):5-11.
51. National Institute for Health and Clinical Excellence (NICE). Alcohol-use disorders. Diagnosis, assessment and management of harmful drinking and alcohol dependence. London (UK): National Institute for Health and Clinical Excellence (NICE); 2011 Feb. 54 p. (Clinical guideline; no. 115). Available at: http://www.nice.org.uk/nicemedia/live/12995/48991/48991.pdf. Accessed May 2012.

52. Kleber HD, Weiss RD, Anton RF Jr, Treatment of patients with substance use disorders, second edition. American Psychiatric Association. Am J Psychiatry 2007;164(4 Suppl):5-123.
53. Huang YS, Hsu SC, Liu SI, et al. A double-blind, randomized, comparative study to evaluate the efficacy and safety of zaleplon versus zolpidem in shortening sleep latency in primary insomnia. Chang Gung Med J 2011;34:50-6.
54. Menza M, Dobkin RD, Marin H, et al. Treatment of insomnia in Parkinson's disease: a controlled trial of eszopiclone and placebo. Mov Disord 2010;25:1708-14.
55. Roehrs TA, Randall S, Harris E, et al. Twelve months of nightly zolpidem does not lead to dose escalation: a prospective placebo-controlled study. Sleep 2011;34:207-12.
56. Gooneratne NS, Gehrman P, Gurubhagavatula I, et al. Effectiveness of ramelteon for insomnia symptoms in older adults with obstructive sleep apnea: a randomized placebo-controlled pilot study. J Clin Sleep Med 2010;6:572-80.
57. Lettieri CJ, Shah AA, Holley AB, et al. Effects of a short course of eszopiclone on continuous positive airway pressure adherence: a randomized trial. Ann Intern Med 2009;151:696-702.
58. Pollack MH, Hoge EA, Worthington JJ, et al. Eszopiclone for the treatment of posttraumatic stress disorder and associated insomnia: a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry 2011;72:892-7.
59. Joffe H, Petrillo L, Viguera A, et al. Eszopiclone improves insomnia and depressive and anxious symptoms in perimenopausal and postmenopausal women with hot flashes: a randomized, double-blinded, placebo-controlled crossover trial. Am J Obstet Gynecol 2010;202:171.e1-171.e11.
60. Uchiyama M, Hamamura M, Kuwano T, et al. Evaluation of subjective efficacy and safety of ramelteon in Japanese subjects with chronic insomnia. Sleep Med 2011;12:119-26.
61. Uchiyama M, Hamamura M, Kuwano T, et al. Long-term safety and efficacy of ramelteon in Japanese patients with chronic insomnia. Sleep Med 2011;12:127-33.
62. Staner C, Joly F, Jacquot N, et al. Sublingual zolpidem in early onset of sleep compared to oral zolpidem: polysomnographic study in patients with primary insomnia. Curr Med Res Opin 2010;26:1423-31.
63. Lettieri CJ, Collen JF, Eliasson AH, et al. Sedative use during continuous positive airway pressure titration improves subsequent compliance: a randomized, double-blind, placebo-controlled trial. Chest 2009;136:1263-8.
64. Ancoli-Israel S, Krystal AD, McCall WV, et al. A 12-week, randomized, double-blind, placebo-controlled study evaluating the effect of eszopiclone 2 mg on sleep/wake function in older adults with primary and comorbid insomnia. Sleep 2010;33:225-34.

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I. Overview

Urinary incontinence (UI) is the involuntary leakage of urine, which may be classified as urge, stress, overflow or mixed incontinence.[15] Urge 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. Overactive bladder (OAB) is a functional disorder characterized by urinary urgency, daytime frequency (>8 voids during the daytime), nocturia (>1 void at night), with or without incontinence.[17,82] UI and OAB may be due to lower urinary tract dysfunction or secondary to non-genitourinary disorders. The most common cause of OAB 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.[15,17] UI and OAB cause both physical and psychological morbidity, as well as adversely impact quality of life.[15] Initial treatment options include lifestyle modifications (weight loss and dietary changes), behavioral therapy (bladder training, physical therapy and toileting assistance) and pharmacologic therapy.[16-17] Neurogenic lower urinary tract disorder (NLUTD) is caused by a lesion at any level of the nervous system.[18-19] The lesion interferes with the normal nerve pathways associated with urination. Early diagnosis and treatment of NLUTD is essential for both congenital and acquired disorders as irreversible changes may occur.[19]

Normal voiding is dependent on acetylcholine-induced stimulation of muscarinic receptors on bladder smooth muscle. There are 5 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.[1-13,16] 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.[16]

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, and trospium are available in a generic formulation. This class was last reviewed in August 2010.

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
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®	none
Trospium	extended-release capsule, tablet	Sanctura®*, Sanctura XR®	trospium

*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 genitourinary smooth muscle relaxants are summarized in Table 2.

Table 2. Treatment Guidelines Using the Genitourinary Smooth Muscle Relaxants

Clinical Guideline	Recommendation(s)
European Association of Urology (EAU): **Guidelines on Urinary Incontinence[83] (2012)**	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 (PFMT), bladder training, electrical or magnetic stimulation, and posterior tibial nerve stimulation. • PFMT 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 PFMT 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 3 months, should be offered as a first-line therapy to women with stress or mixed urinary incontinence. In patients with mixed incontinence, PFMT 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 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 superior 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. • It is recommended to offer immediate-release (IR) or extended-release (ER) formulations of antimuscarinic drugs as initial drug therapy 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. • 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 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 IR 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

Clinical Guideline	Recommendation(s)

	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, 80 mg daily, can modestly improve symptoms of stress incontinences and urgency incontinence in women and men. But, it causes significant gastrointestinal and CNS side effects leading to a high rate of treatment discontinuation. Due to these adverse effects, duloxetine should be initiated using dose titration.
	Intravaginal Estrogen
	• Women using systemic estrogen should be counseled that they have an increased risk for developing urinary incontinence or worsening their existing incontinence.
	• Post-menopausal women with urinary incontinence should be offered local estrogen therapy, despite the ideal duration and best delivery method being unknown.
	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 4 hours of taking oral desmopressin, but not after 4 hours. Desmopressin should be offered to patients requiring occasional short-term relief from 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.
	Incontinence in Men
	• For men with stress, urgency or mixed urgency/stress incontinence, initial treatment should include:
	  o Lifestyle and behavioral interventions
	  o Pelvic floor muscle training ± biofeedback
	  o Scheduled voiding (bladder training)
	  o Antimuscarinics (mixed or urgency incontinence)
	Incontinence in Women

Clinical Guideline	Recommendation(s)
	• For women with stress, urgency or mixed urgency/stress incontinence, initial treatment should include: o Lifestyle and behavioral interventions o Supervised, intensive pelvic floor muscle training ± biofeedback ± bladder training (stress or mixed incontinence) o Bladder training (mixed or urgency incontinence) o Antimuscarinics (mixed or urgency incontinence)
International Scientific Committee (ISC): **Evaluation and Treatment of Urinary Incontinence, Pelvic Organ Prolapse, and Fecal Incontinence**[81] **(2010)**	<u>Initial Management of Urinary Incontinence in Men</u> • 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 SUI o Scheduled voiding regimes for OAB o Antimuscarinic drugs for OAB 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 <u>Initial Management of Urinary Incontinence in Women</u> • 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 OAB o If estrogen deficiency and/or UTI is found, the patient should be treated at initial assessment and then reassessed after a suitable interval o Antimuscarinics for OAB 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 UI (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 UI. • Conservative and behavioral therapy for UI 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

Clinical Guideline	Recommendation(s)
	considered. Antimuscarinics may be added to conservative therapy of urgency UI. • 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 (NBS): **Clinical Guidelines for Overactive Bladder[17] (2009)**	Behavioral Therapy • 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 OAB. • The efficacy of combined behavioral therapy and drug therapy over monotherapy has yet to be determined, but it is the recommended treatment approach. Drug Therapy • Drug therapy forms the basis of treatment for overactive bladder (OAB). • The drugs for which efficacy and safety have been investigated are the antimuscarinic agents. These are most commonly used for the treatment of OAB. • When using antimuscarinic drugs, it is necessary to consider adverse reactions due to blockade of the systemic muscarine receptors. Antimuscarinic Drugs • 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 with the salivary glands, is highly selective for the bladder. It has been extensively evaluated and there is substantial evidence for efficacy and safety in OAB patients, including the elderly and patients with severe OAB. • 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 OAB. • 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.

Clinical Guideline	Recommendation(s)

	Antidepressants
	• 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 OAB is yet to be adequately evaluated.
	Botulinum Toxin
	• 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 OAB, but its usefulness is yet to be adequately explored.
	Efficacy of Drug Therapy for OAB Symptoms in BPH Patients
	• α_1-blockers are first-line drug therapy for OAB symptoms in BPH 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 OAB symptoms associated with BPH have yet to be performed.
	• Despite the fact that antimuscarinic drugs may be effective in some BPH patients with OAB 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 BPH patients with OAB symptoms.
	Practical Guidelines for Drug Therapy for Overactive Bladder: Rules for Treatment with Anticholinergic Drugs, Classified by Sex and Age
	• OAB in Women:
	  o Antimuscarinic drugs can be administered immediately.
	  o If voiding symptoms, as well as OAB symptoms, are present, antimuscarinic drugs should be administered with caution.
	  o Since OAB 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).
	• OAB in men under 50 years of age:
	  o For OAB 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.
	• OAB in men aged 50 years or older:
	  o Because there is a high probability of OAB 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 OAB 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.

National Institute for Health and	Behavioral Therapy

Clinical Guideline	Recommendation(s)
Clinical Excellence (NICE): **Urinary Incontinence: The Management of Urinary Incontinence in Women[20] (2006)**	• Bladder training should be offered as first-line treatment to women with urge or mixed urinary incontinence (UI). • 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 UI who also have cognitive impairment, prompted and timed voiding toileting programs are recommended as strategies for reducing leakage episodes. <u>Pharmacologic Therapy</u> • Immediate-release oxybutynin should be offered to women with OAB or mixed UI as first-line drug treatment if bladder training has been ineffective. • If immediate-release oxybutynin is not well tolerated, darifenacin, solifenacin, tolterodine, trospium, or an extended-release or transdermal formulation of oxybutynin should be considered as alternatives. • Propiverine should be considered as an option to treat frequency of urination in women with OAB, but is not recommended for the treatment of UI. • Flavoxate, propantheline and imipramine should not be used for the treatment of UI or OAB in women. • The use of desmopressin may be considered to reduce nocturia in women with UI or OAB who find it a troublesome symptom. • Duloxetine is not recommended as a first-line treatment for women with predominant stress UI. Duloxetine should not routinely be used as a second-line treatment for women with stress UI, 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 UI. • Intravaginal estrogens are recommended for the treatment of OAB symptoms in postmenopausal women with vaginal atrophy. <u>Complementary Therapy</u> • Complementary therapies are not recommended for the treatment of UI or OAB.
American College of Obstetricians and Gynecologists (ACOG): **Urinary Incontinence in Women[21] (2005)**	• Behavioral therapy (e.g., bladder training and prompted voiding) improves symptoms of urge and mixed incontinence and can be recommended as a noninvasive treatment in many women. • Pelvic floor training appears to be an effective treatment for adult women with stress and mixed incontinence and can be recommended as a noninvasive treatment for many women. • Pharmacologic agents may have a small beneficial effect on improving symptoms of detrusor overactivity in women. • The antimuscarinic drugs, oxybutynin and tolterodine, have been shown to have a small beneficial effect as therapy for urge incontinence. However, for many of the outcomes studied, the observed differences between treatment with antimuscarinic medications and placebo may be of questionable clinical significance. No significant difference among these agents was reported. • The most typical side effect of antimuscarinic therapy is dry mouth. Other side effects most frequently reported include blurred vision, constipation, nausea, dizziness, and headache. • Alternative drugs, new drugs, and new formulations of existing drugs are all available, but limited data exist on which to base recommendations.

Clinical Guideline	Recommendation(s)
	• Oral estrogen regimens cannot be recommended as treatment or prevention for any type of urinary incontinence.
Scottish Intercollegiate Guidelines Network (SIGN): **Management of Urinary Incontinence in Primary Care: A National Clinical Guideline[22] (2004)**	Behavioral Therapy • Pelvic floor muscle exercises should be the first choice of treatment offered to patients suffering from stress or mixed incontinence. • Pelvic floor muscle exercises should be considered as part of a treatment plan for patients with urge urinary incontinence. • Pelvic floor muscle exercise treatment should be considered for patients following radical prostate surgery. • Bladder retraining should be offered to patients with urge urinary incontinence. Pharmacologic Therapy of Stress Incontinence • Published studies have reported conflicting evidence for the efficacy of estrogens in treating stress incontinence. • Imipramine has been used clinically to treat stress incontinence, but there are no studies available to support its use. • Duloxetine should be used only as part of an overall management strategy in addition to pelvic floor muscle exercises. A 4-week trial of is recommended for female patients with moderate-to-severe stress incontinence. Patients should be reviewed again after 12 weeks of therapy to assess progress and determine whether it is appropriate to continue treatment. Pharmacologic Therapy of Detrusor Overactivity and Urge Incontinence • Oxybutynin, tolterodine, trospium and propiverine are effective in reducing detrusor overactivity (urgency and urge incontinence). Comparative studies of the effectiveness of detrusor selective antimuscarinics have shown all the drugs to be equally effective. • The most common side effects of antimuscarinic drugs are dry mouth, blurred vision, abdominal discomfort, drowsiness, nausea and dizziness. • Oxybutynin immediate-release preparation has the highest incidence of side effects. • Several studies have shown sustained-release antimuscarinic preparations are associated with a lower incidence and severity of side effects than immediate-release preparations. • A trial of oxybutynin, propiverine, tolterodine, or trospium should be given to patients with significant urgency with or without urge incontinence. • Antimuscarinic therapy should be tried for a period of 6 weeks to enable an assessment of the benefits and side effects. Treatment should be reviewed after 6 months to assess continued need. • Studies of the efficacy of flavoxate have shown mixed results; few adverse events were reported. • There is inadequate evidence to support the use of imipramine for the treatment of detrusor overactivity. • There is no evidence to date for combining therapy in a patient with mixed urge and stress incontinence.
European Association of Urology (EAU)/European Society for Paediatric Urology (ESPU): **Guidelines on Pediatric Urology: Management of Neurogenic Bladder in Children[18] (2012)**	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.

Clinical Guideline	Recommendation(s)
	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 ER formulation has been found to be as effective as the IR 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 tool 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 (EAU): **Guidelines on Neurogenic Lower Urinary Tract Dysfunction (NLUTD)[19] (2012)**	Treatment Goals
	• The primary goals for the treatment of NLUTD 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) the normal lower urinary tract function.
	• Other considerations include the patient's disability, cost-effectiveness, technical complexity, and possible complications.
	Assisted Bladder Emptying
	• 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 NLUTD 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 (PFMT), and biofeedback
	Lower Urinary Tract Rehabilitation
	• Bladder rehabilitation aims to re-establish bladder function in patients with NLUTD. While improving voluntary control of lower urinary tract dysfunction has been described in non-neurogenic patients,

Clinical Guideline	Recommendation(s)
	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 prolonged effects in patients with neurogenic bladder due to multiple sclerosis (MS). In MS patients, a combined approach of PFMT + neuromuscular electrostimulation + biofeedback was superior to electrostimulation alone in achieving a substantial reduction in lower urinary tract dysfunction. • Biofeedback can be used for supporting the voiding pattern modification. • 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 Drug Treatment • An optimal medical treatment for NLUTD 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. • Detrusor over activity can be treated with antimuscarinic agents and they are the first-line choice for treating NLUTD. Antimuscarinic therapy is both safe and effective for the management of neurogenic detrusor over activity. Treatment is generally life-long; however, increased drug tolerance and adverse events are problematic in patients with NLUTD. These patients need a higher dose then other patients with overactive detrusor, which may lead to discontinuation of the therapy because of adverse events. Alternative ways of administration of antimuscarinic agents, such as transdermally and intravesically, should be considered with the goal of reducing adverse effects • Oxybutynin, tolterodine tartrate, trospium chloride, and propiverine are established, effective, well-tolerated, and safe treatment choices. These agents have different tolerability profiles and an alternative antimuscarinic agent may be prescribed if the patient experiences adverse effects with one. • Darifenacin was recently evaluated in neurogenic overactive bladder secondary to MS and had results similar to other antimuscarinic drugs. • Outcomes for neurogenic detrusor over activity can be maximized by considering a combination of antimuscarinic agents • In pilot studies, phosphodiesterase inhibitors have shown promising effects on detrusor over activity • Additional treatment with desmopressin might improve the efficacy of therapy. • 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. These agents may be a preventive measure in spinal cord injury to prevent autonomic dysreflexia • Several drugs have been shown to be effective for the treatment of mild stress incontinence, but there are few studies in patients with NLUTD. External Appliances

Clinical Guideline	Recommendation(s)
	• 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. Minimal Invasive Treatment • Intermittent catheterization is the standard treatment of NLUTD 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 9 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[1-13]

Indication	Darifenacin	Fesoterodine	Flavoxate	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 6 years and older with symptoms of detrusor overactivity associated with a neurological condition (e.g., spina bifida)				✔ §			

†Transdermal formulations.
‡Immediate-release oral formulation.
§Extended-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[1-13]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Darifenacin	15-19	98	Liver; Intestinal wall	Renal (60) Feces (40)	13-19
Fesoterodine	52	50	Liver	Renal (70) Feces (7)	4-7
Flavoxate	Not reported	Not reported	Not reported	Renal (57)	Not reported
Oxybutynin	IR: 6 ER: 156-187	>99	Liver; Intestinal wall	Renal (<0.1)	Gel: 64 ER: 13.2 IR: 2-3 Patch: 6-7
Solifenacin	90	98	Liver	Renal (69) Feces (22.5)	45-68
Tolterodine	IR: 77	96	Liver	Renal (77) Feces (17)	IR: 2.2 ER: 6.9
Trospium	IR: 9.6	IR: 50-85 ER:48-78	Liver	Renal (5.8) Feces (85.2)	IR: 18.3 ER: 36

ER=extended-release formulation, IR=immediate-release formulation

V. Drug Interactions

Significant drug interactions with the genitourinary smooth muscle relaxants are listed in Table 5.

Table 5. Significant Drug Interactions with the Genitourinary Smooth Muscle Relaxants[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Genitourinary smooth muscle relaxants (darifenacin, fesoterodine, solifenacin, tolterodine)	2	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 (darifenacin, fesoterodine, solifenacin, tolterodine)	2	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 (darifenacin, fesoterodine, solifenacin, tolterodine)	2	Nefazodone	Inhibition of cytochrome P450 3A4 by nefazodone may decrease the metabolic elimination of genitourinary smooth muscle relaxants. Plasma concentrations and pharmacologic effects of

Generic Name(s)	Significance Level	Interaction	Mechanism
			genitourinary smooth muscle relaxants may be increased.
Genitourinary smooth muscle relaxants (oxybutynin, trospium)	2	Phenothiazines	The antipsychotic effectiveness of phenothiazines may be decreased by genitourinary smooth muscle relaxants, which may cause additive antimuscarinic toxicity. This may be due to additive central and peripheral antimuscarinic effects, as well as decreased phenothiazine bioavailability.
Genitourinary smooth muscle relaxants (darifenacin, fesoterodine, flavoxate, oxybutynin, solifenacin, tolterodine, trospium)	2	Potassium preparations	Antimuscarinic agents may slow gastrointestinal motility and cause delay in tablet passage through the gastrointestinal tract.
Genitourinary smooth muscle relaxants (darifenacin, fesoterodine, solifenacin, tolterodine)	2	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 increased.

Significance Level 1 = major severity
Significance Level 2 = moderate severity

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[1-13]

Adverse Events	Darifenacin	Fesoterodine	Flavoxate	Oxybutynin (Oral)	Oxybutynin (Transdermal)	Solifenacin	Tolterodine	Trospium
Cardiovascular								
Arrhythmia	-	-	-	1-5		-	-	<1
Chest pain	-	✔	-	1-5	✔ §	-	2	✔
Hypertension	≥1	-	-	1-5	-	≤1	-	✔
Hypotension	-	-	-	1-5	-	-	-	-
Myocarditis	-	-	-	-	✔ §	-	-	-
Palpitations	✔	✔	✔	1-5	-	-	✔	✔
Peripheral edema	≥1	1	-	1-5	-	-	✔	-
QT_c prolongation	-	✔	-	1-5	-	✔	-	-
Supraventricular tachycardia	-	-	-	-	-	-	-	✔
Syncope	-	-	-	-	-	-	-	✔
T-wave inversion	-	-	-	-	-	-	-	✔
Tachycardia	-	✔	✔	1-5	✔ §	-	✔	1-2
Torsade de pointes	-	-	-	-	-	✔	-	-
Central Nervous System								
Agitation	-	-	-	1-5	-	-	-	-
Anxiety	-	-	-	-	-	-	1†	-
Confusion	✔	-	✔	-	-	✔	✔	-
Delirium	-	-	-	-	-	-	-	✔
Depression	-	-	-	1-5	-	≤1	-	-
Disorientation	-	-	-	-	-	-	✔	-
Dizziness	1-2	-	-	4-17	2-3‡	≤1	2†, 5γ	-
Drowsiness	-	-	✔	-	-	-	-	-
Fatigue	-	-	✔	1-5	2‡	1-2	2†, 4γ	2
Hallucinations	✔	-	-	1-5	✔ §	✔	✔	✔
Headache	7	-	✔	6-10	2‡	3-6	7†, 6γ	4-7
Heat prostration	-	✔	-	-	-	-	-	-
Hyperpyrexia	-	-	✔	-	-	-	-	-
Insomnia	-	1	-	1-6	-	-	-	-
Memory impairment	-	-	-	1-5	-	-	✔	-
Nervousness	-	-	✔	1-7	-	-	-	-

Adverse Events	Darifenacin	Fesoterodine	Flavoxate	Oxybutynin (Oral)	Oxybutynin (Transdermal)	Solifenacin	Tolterodine	Trospium
Psychotic disorder	-	-	-	1-5	-	-	-	-
Seizure	-	-	-	1-5	-	-	-	-
Somnolence	-	-	✔	2-14	-	-	3	✔
Vertigo	-	-	✔	-	-	-	5γ	-
Dermatological								
Application site reaction	-	-	-	-	5‡, 17§	-	-	-
Dermatitis	-	-	-	-	5‡	-	-	-
Dry skin	≥1	-	-	1-5	-	-	1γ	✔
Erythema	-	-	-	-	5‡, 6-8§	✔	-	-
Flushing	-	-	-	1-5	-	-	-	-
Irritation	-	-	-	-	5‡	-	-	-
Papules	-	-	-	-	5‡	-	-	-
Pruritus	≥1	-	-	1-5	1-5‡, 14§	✔	-	-
Rash	≥1	≤1	✔	1-5	3§	✔	-	✔
Stevens-Johnson syndrome	-	-	-	-	-	-	✔	✔
Sweating decreased	-	-	-	1-5	✔ §	-	-	-
Urticaria	-	-	✔	-	-	✔	-	-
Vesicles	-	-	-	-	3§	-	-	-
Gastrointestinal								
Abdominal pain	2-4	1	-	1-5	-	1-2	4†, 5γ	1-3
Aptyalism	-	-	-	1-5	-	-	-	-
Constipation	15-21	4-6	✔	7-15	1‡, 3§	5-13	6†, 7γ	9-10
Diarrhea	1-2	-	-	1-9	3§	-	✔	-
Diverticulitis	-	<1	-	-	-	-	-	-
Dysgeusia	-	-	-	1-5	-	-	-	-
Dyspepsia	3-8	2	-	5-7	-	1-4	3†, 4γ	1-2
Dysphagia	-	-	-	1-5	-	-	-	-
Eructation	-	-	-	1-5	-	-	-	-
Fecal impaction	-	-	-	-	-	✔	-	-
Feces hard	-	-	-	-	-	-	-	✔
Flatulence	-	-	-	1-5	-	-	-	1-2
Gastritis	-	-	-	-	-	-	-	✔
Gastroenteritis	-	<1	-	-	2‡	-	-	-
Gastrointestinal obstruction	-	-	-	-	-	✔	-	-
GERD	-	-	-	1-5	-	-	-	-
GI motility decreased	-	-	-	1-5	-	-	-	-

Adverse Events	Darifenacin	Fesoterodine	Flavoxate	Oxybutynin (Oral)	Oxybutynin (Transdermal)	Solifenacin	Tolterodine	Trospium
Hoarseness	-	-	-	1-5	-	-	-	-
Irritable bowel syndrome	-	<1	-	-	-	-	-	-
Loose stools	-	-	-	1-5	-	-	-	-
Nausea	2-4	1-2	✔	2-12	-	2-3	-	≤1
Taste abnormality	-	-	-	1-5	-	-	-	✔
Thirst	-	-	-	1-5	-	-	-	-
Tongue coated	-	-	-	1-5	-	-	-	-
Vomiting	≥1	-	✔	1-5	-	≤1	-	✔
Weight gain	≥1	-	-	-	-	-	1	-
Xerostomia	19-35	19-35	✔	29-71	7-8‡, 4-10§	11-28	23†, 35γ	10-22
Genitourinary								
Cystitis	-	-	-	1-5	-	-	-	-
Dysuria	-	1-2	✔	1-5	2§	-	1†, 2γ	-
Impotence	-	-	-	1-5	✔ §	-	-	-
Pollakiuria	-	-	-	1-5	-	-	-	-
Urinary retention	✔	1-2	-	6	-	≤1	-	≤1
Urinary tract infection	4-5	2-4	-	5-7	7‡	3-5	-	1-7
Vaginitis	≥1	-	-	-	-	-	-	-
Hepatic								
ALT increased	-	≤1	-	-	-	-	-	-
GGT increased	-	≤1	-	-	-	-	-	-
Musculoskeletal								
Arthralgia	≥1	-	-	1-5	-	-	2	-
Back pain	≥1	1-2	-	1-5	-	-	-	✔
Rhabdomyolysis	-	-	-	-	-	-	-	✔
Weakness	<3	-	-	3-7	-	-	-	-
Respiratory								
Asthma	-	-	-	1-5	-	-	-	-
Bronchitis	≥1	-	-	1-5	-	-	-	-
Cough	-	1-2	-	1-5	-	≤1	-	-
Dry throat	-	1-2	✔	1-5	-	-	-	-
Nasal congestion	-	-	-	1-5	-	-	-	-
Nasal dryness	-	-	-	1-5	-	-	-	1
Nasopharyngitis	-	-	-	1-5	3‡	-	-	3
Pharyngitis	≥1	-	-	-	-	-	-	-
Rhinitis	≥1	-	-	2-6	-	-	-	-

Adverse Events	Darifenacin	Fesoterodine	Flavoxate	Oxybutynin (Oral)	Oxybutynin (Transdermal)	Solifenacin	Tolterodine	Trospium
Sinus congestion	-	-	-	1-5	-	-	-	-
Sinus headache	-	-	-	1-5	-	-	-	-
Sinusitis	≥1	-	-	1-5	-	-	2†	-
Upper respiratory tract infection	-	2-3	-	1-5	-	-	-	-
Special Senses								
Abnormal vision	≥1	-	-	-	-	-	1†, 2γ	-
Blurred vision	-	✔	✔	1-10	-	4-5	-	1
Cycloplegia	-	-	-	1-5	✔ §	-	-	-
Dry eyes	1.5-2	1-4	-	3-6	-	≤2	3	1-2
Eye irritation	-	-	-	1-5	-	-	-	-
Intraocular pressure increased	-	-	✔	-	-	-	-	-
Keratoconjunctivitis sicca	-	-	-	1-5	-	-	-	-
Mydriasis	-	-	-	1-5	-	-	-	-
Vision changes	-	-	✔	-	3§	-	-	-
Other								
Anaphylactoid reactions	-	-	-	-	-	-	✔	-
Anaphylaxis	-	-	-	-	-	✔	-	✔
Angioedema	✔	-	-	✔	-	-	✔	-
Angioneurotic edema	-	-	-	-	-	✔	-	✔
Edema	-	-	-	1-5	-	≤1	-	-
Extremity pain	-	-	-	1-5	-	-	-	-
Flank pain	-	-	-	1-5	-	-	-	-
Flu-like syndrome	1-3	-	-	-	-	-	3	-
Fungal infection	-	-	-	1-5	-	-	-	-
Hyperglycemia	-	-	-	1-5	-	-	-	-
Hypersensitivity	✔	-	-	-	-	✔	✔	-
Infection	-	-	-	-	-	-	1	-
Influenza	-	-	-	-	-	≤2	-	2
Lactation suppression	-	-	-	1-5	✔ §	-	-	-
Leukopenia	-	-	✔	-	-	-	-	-
Pain	≥1	-	-	1-7	-	-	-	-
Pharyngolaryngeal pain	-	-	-	1-5	-	-	-	-

✔ Percent not specified
- Event not reported
‡Transdermal gel formulation.
§Transdermal patch formulation.
†Extended-release 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[1-13]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Darifenacin	Overactive Bladder: 7.5 to 15 mg once daily	Safety and efficacy in children have not been established.	Tablet (ER): 7.5 mg 15 mg
Fesoterodine	Overactive Bladder: 4 to 8 mg once daily	Safety and efficacy in children have not been established.	Tablet (ER): 4 mg 8 mg
Flavoxate	Urinary Tract Symptoms: 100 to 200 mg 3 or 4 times/day	Urinary Tract Symptoms: ≥12 years of age: 100 to 200 mg 3 or 4 times/day	Tablet: 100 mg
Oxybutynin	Bladder Instability: Tablet/syrup (IR): 5 mg 2 to 3 times/day; maximum, 5 mg 4 times/day Overactive Bladder: Tablet (ER): 5 to 10 mg once daily; maximum, 30 mg/day Transdermal gel: the contents of one sachet should be applied once daily Transdermal patch: one 3.9 mg/day system applied twice weekly (every 3 to 4 days)	Bladder Instability: ≥5 years of age: Tablet/syrup (IR): 5 mg twice daily; maximum, 5 mg 3 times daily Detrusor Overactivity Associated with a Neurological Condition: ≥6 years of age: 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: 10% Transdermal patch: 3.9 mg/24 hours
Solifenacin	Overactive Bladder: 5 to 10 mg once daily	Safety and efficacy in children have not been established.	Tablet: 5 mg 10 mg
Tolterodine	Overactive Bladder: 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	Overactive Bladder: 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
Chapple et al.[23] (2005) Darifenacin ER 7.5 to 15 mg once daily vs placebo	RCT, DB, PG, MC (Pooled analysis) Men and women aged ≥18 years with symptoms of OAB for ≥6 months, 5–50 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=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 urgency, number of nocturnal awakenings caused by OAB, responder rates, proportion of patients experiencing three or more dry days/week, or at least 7 consecutive dry days, in the last 2 weeks of study treatment, adverse events	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 P=0.06 for darifenacin 7.5 mg 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 with 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 with 17% of patients in the placebo group (P<0.005). The odds ratios for improvement compared with placebo were consistent for both doses across all responder rates analyzed (odds ratio 1.8–1.9 for 7.5 mg and 1.8–2.2 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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 7 days, compared with 16% in the corresponding placebo group (P=0.011). More patients (55% and 61%) had ≥3 dry days/week in the darifenacin 7.5 mg and 15 mg groups, respectively, than in those taking placebo (43% and 48%, respectively, both P<0.001). The overall incidence of adverse events (AEs) 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 AEs were dry mouth and constipation, most of which were mild to moderate. The incidence of nervous system AEs reported by patients taking 7.5 mg or 15 mg of darifenacin was comparable to placebo. The most common nervous system AEs were CNS-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 AEs with darifenacin 7.5 mg (6.2%) or 15 mg (3.6%) was also comparable with that of placebo (2.3%).
Foote et al.[24] (2005) Darifenacin ER 7.5 to 15 mg once daily vs placebo	RCT, DB, MC (Pooled analysis) Men and women aged ≥65 years with symptoms of OAB for ≥6 months, 5–50 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				not increase with increasing dose of darifenacin.
Haab et al.[25] (2006) Darifenacin ER 7.5 to 15 mg once daily	OL, MC, ES Men and women aged ≥65 years who had completed one of two RCTs (feeder studies) who had previously had symptoms of OAB for ≥6 months, 5–50 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	Primary: All-causality adverse events (AEs) were reported by 80% of patients at some time during the 2-year extension and resulted in discontinuation in 8.9% of patients. The most commonly reported AEs 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 extension-study end in the overall group. There were few treatment-related cardiovascular and nervous system AEs; 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. 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 2 years.
Hill et al.[26] (2007) Darifenacin ER 7.5 to 15 mg once daily	OL, MC, ES Men and women aged ≥18 years who had completed one of two RCTs (feeder studies) who had previously had symptoms of OAB	N=214 2 years	Primary: Safety, tolerability and efficacy	Primary: Dry mouth and constipation were the most common treatment-related (adverse events) AEs 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/CNS AEs were infrequently reported (1.4% and 3.3%, respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	for ≥6 months, 5–50 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)			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 3 months of darifenacin treatment and this effect was maintained in approximately the same number of patients at the end of the 2-year study (33.8%).
Zinner et al.[78] (2005) Darifenacin ER 15 to 30 mg once daily vs oxybutynin IR 5 mg three times daily vs placebo	RCT, DB, PC, XO Patients 18 to 85 years of age with urge incontinence with ≥4 significant incontinent episodes/week (defined as leakage that would normally require a change of clothing or absorbent pad) and urinary frequency ≥8 voids/24 hours	N=76 2 weeks	Primary: Incontinence episodes/week, urgency episodes/day, severity of urgency episodes, and micturitions/day	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. 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 2.0 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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.
Chapple et al.[32] (2005) Cohort 1 Darifenacin IR 2.5 mg three times daily (t.i.d.) for 7 days vs oxybutynin 2.5 mg three times daily (t.i.d.) 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	RCT, DB, XO Patients aged 18–75 years with detrusor overactivity within the previous 6 months (either idiopathic or neurogenic with ≥2 associated symptoms (average of ≥7 micturitions per day, ≥7 episodes of urgency/week, ≥1 urge incontinence episode/week necessitating change of clothing or pads)	N=65 7 days	Primary: Urodynamic parameters, salivary flow, tolerability and safety	Primary: All urodynamic pressure parameters significantly decreased from baseline after 7 days' therapy with each treatment. No significant differences between treatments were observed for any dose of darifenacin versus 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 mg and 30 mg) than with oxybutynin (5 mg t.i.d.). Salivary flow was comparable for darifenacin IR (2.5 mg t.i.d.) and oxybutynin (2.5 mg t.i.d.). The mean maximum decrease in salivary flow from baseline to day 7 was significantly greater with oxybutynin 5 mg t.i.d. than with darifenacin ER 15 mg (P<0.01). There were no differences in mean heart rate for darifenacin and oxybutynin on day 7. 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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs oxybutynin 5 mg three times daily for 7 days				
Wyndaele et al.[31] (2009) Fesoterodine ER 4 to 8 mg once daily	OL, MC Men and women aged ≥18 years 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 treated with tolterodine or tolterodine ER for OAB within 2 years who reported being 'somewhat dissatisfied' or 'very dissatisfied' with tolterodine treatment on the Treatment Satisfaction Question (TSQ)	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 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	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 (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 HRQL (26-point improvement) and all four HRQL 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 with baseline (P<0.0001). The improvements for all scales and domains were above the minimally important difference of 10 points, indicating that these changes

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			scores at week 12	were clinically meaningful. Dry mouth (23%) and constipation (5%) were the most frequently reported adverse events (AEs).
Nitti et al.[27] (2007) Fesoterodine ER 4 to 8 mg once daily vs placebo	RCT, DB, PC, MC 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 urgency urinary incontinence (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, urgency episodes/24 hours and continent days/week	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). Secondary: Fesoterodine 4 mg showed significant improvements in the mean change from baseline compared with 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 (AEs) occurred in 55%, 61% and 69% of patients receiving placebo, and 4 and 8 mg fesoterodine, respectively. Dry mouth was the most commonly reported AE. 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.[28] (2007)	RCT, DB, PC, AC Men and women	N=1,135 12 weeks	Primary: Micturitions/24 hours and	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Fesoterodine ER 4 to 8 mg once daily vs tolterodine ER 4 mg once daily vs placebo	≥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 urgency urinary incontinence (UUI)/24 hours, and self-reported perception of moderate problems using a Likert scale		treatment response Secondary: Mean volume voided/micturition, daytime micturitions/24 hours, nocturnal micturitions/24 hours, urgency episodes/24 hours, continent days/week, adverse events	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 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 with placebo

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				in number of continent days/week were observed in patients receiving fesoterodine 4 mg or 8 mg. The most frequent adverse event (AE) was dry mouth, which was mild to moderate in most patients; however, 3% of patients receiving fesoterodine 8 mg reported severe dry mouth.
Chapple et al.[29] (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)	RCT, DB, PC, AC (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 urgency urinary incontinence (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 mg 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				groups vs placebo), compared with 25% on placebo. Adverse events reported in ≥2% of patients in the active-treatment groups and occurring more frequently than placebo included dry mouth, 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%.
Van Kerrebroeck et al.[87] (2010) Fesoterodine ER 4 to 8 mg once daily	OL, ES 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 urgency urinary incontinence (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 TEAE, of which 219 cases were related to fesoterodine. The most common TEAE were dry mouth (34%), constipation (7%), and urinary tract infection (15%). Overall, ≥88% of patients rated treatment tolerance with fesoterodine "good" or "excellent" at months 4, 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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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 4, 12, and 24 (P<0.0001 for all). In the overall population, patient-reported treatment satisfaction was 97% at month 24.
Scarpero et al.[88] (2011) Fesoterodine ER 4 to 8 mg once daily	OL, ES (Pooled analysis) 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 urgency urinary incontinence (UUI)	N=890 (2 trials) 24 to 36 months	Primary: Safety and tolerability Secondary: Bladder diary entries (number of UUI episodes, micturitions, and urgency episodes	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 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 TEAE. A total of 351 women (50%) and 86 men (47%) experienced ≥1 TEAE that were determined to be related to fesoterodine. The most commonly reported TEAEs in men were dry mouth (24%) and constipation (6%), compared with dry mouth (32%) and urinary tract infection (18%) in women. The majority of men and women (≥92% and ≥91%, respectively) reported "good" or "excellent" treatment tolerance at months 4, 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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 1, 4, 8, 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.[30] (2008) Fesoterodine ER 4 to 8 mg once daily vs tolterodine ER 4 mg once daily vs placebo	RCT, DB, PC, MC (Pooled analysis) Men and women aged ≥18 years with OAB syndrome for ≥6 months	N=1,971 (2 trials) 12 weeks	Primary: Treatment-related effects on HRQoL using the KHQ (disease-specific questionnaire to 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	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 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 1–3 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 2 weeks and 12 weeks.
Herschorn et al.[84] (2010) Fesoterodine ER	DB, PC, MC, RCT Men and women ≥18 years of age	N=1,697 12 weeks	Primary: Changes from baseline to week 12 in UUI episodes	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
4 to 8 mg once daily vs tolterodine ER 4 mg once daily vs placebo	with symptoms of OAB for ≥3 months		Secondary: Total and nocturnal voids, urgency episodes, severe urgency episodes, frequency-urgency sum per 24 hours, and MVV per void, UPS, OAB-q, and PPBC	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 (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 not significant. Improvements in the OAB-q scores were significantly greater in the fesoterodine than the placebo group on the Symptom Brother scale, total HRQL scale, and all four HRQL 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 HRQL (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,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				and 42 (6%) receiving fesoterodine discontinued treatment due to treatment-emergent adverse effects (TEAEs). The most frequent TEAEs 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 AE during treatment, 2 of which were considered related to fesoterodine. One patient with benign prostatic hyperplasia developed urinary retention requiring catheterization.
Kaplan et al.[94] (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, 3-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 4. 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 3-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 TEAEs in all groups were dry mouth, constipation, and headache.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Anderson et al.[33] (1999) Oxybutynin ER 5 to 30 mg daily vs oxybutynin IR 5 mg 1-4 times/day	RCT, MC, DB, AC 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 extended-release group and from 23.4 to 3.1 in the immediate-release group (P=0.6). The percentage reduction in weekly urge incontinence episodes was 84% in the extended-release group and 88% in the immediate-release group (P=0.71). Secondary: Of the participants, 52% in the extended-release group and 51% in the immediate-release 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 in the extended-release group and from 26.3 to 3.8 in the immediate-release group from baseline to the end of the study (P=0.6). The percentage reduction in any incontinence episodes was 82% in the extended-release group and 88% in the immediate-release group (P=0.5). The proportions of patients who were totally continent was 41% in the extended-release group and 40% in the immediate-release group (P=0.9). Normal void frequency increased 54% in the extended-release group and 17% in the immediate-release group (P<0.001). At least one anticholinergic event occurred in 87% of patients in the extended-release group and 94% of patients in the immediate-release group. The most common anticholinergic event in both groups was dry mouth (68% of the extended-release group and 87% of the immediate-release group; P=0.04). Fewer participants reported moderate or severe dry mouth with extended-release oxybutynin (25% versus 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.[34] (2004)	RCT, DB, PG, MC Men and women	N=123 9 weeks	Primary: Void frequency, UI episodes,	Primary: The mean number of incontinence episodes/week decreased from 24.3 to 10.4 in the extended-release group (P<0.001 vs baseline) and from 23.0 to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Oxybutynin ER 15 mg daily vs oxybutynin IR 5 mg three times daily	>18 years of age with urge urinary incontinence (UI) who demonstrated >7 UI episodes/week and >8 voids/day		treatment-related changes in quality of life (QoL) as assessed by the Incontinence Impact Questionnaire (IIQ) and Urogenital Distress Inventory (UDI), and adverse events	6.1 in the immediate-release 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 extended-release group (P<0.001 vs baseline) and from 11.0 to 8.6 in the immediate-release 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 extended-release group (2.3. to 1.7; P<0.001); however, there was no change from baseline in the immediate-release 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 with the IR group (P=0.020). More patients discontinued treatment in the IR oxybutynin group than in the ER oxybutynin group (P=0.047), primarily due to adverse events.
Birns et al.[35] (2000) Oxybutynin ER 10 mg once daily vs	RCT, DB, PC, MC Patients aged 18-76 years with detrusor instability or detrusor hyperreflexia whose	N=130 6 weeks	Primary: Proportion of patients with daytime continence at completion of the study	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
oxybutynin IR 5 mg twice daily	symptoms were stabilized on conventional oral oxybutynin tablets (5 mg twice daily) for 2 weeks		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	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 not significant (P=NS).
Versi et al.[36] (2000) Oxybutynin ER 5 to 20 mg/day vs oxybutynin IR 5 to 20 mg/day	RCT, DB, MC, PG Patients with 7 to 45 urge incontinence episodes/week and ≥4 days of incontinence/week who had previously responded to treatment with antimuscarinic drugs	N=226 Not specified	Primary: Number of incontinence episodes and total incontinence episodes	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 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.
Nilsson et al.[37] (1997)	XO	N=17	Primary: Frequency of	Primary: The frequency of voids/24 hr was reduced by 23% with oxybutynin ER

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Oxybutynin ER 10 mg daily for 60 days vs oxybutynin IR 5 mg twice daily for 60 days	Female patients 37 to 65 years of age with symptoms of urge incontinence and detrusor instability	120 days	voluntary voiding, the maximal volume of urine/single void, and the total volume of voluntarily voided urine/24 hr	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).
Appell et al.[39] (2001) Oxybutynin ER 10 mg daily vs tolterodine IR 2 mg twice daily	RCT, DB, PG, MC Participants with OAB who had between 7 and 50 episodes of urge incontinence/week and 10 or more voids/24 hours	N=378 12 weeks	Primary: Number of urge incontinence episodes/week, number of total incontinence episodes/week and micturition frequency episodes/week	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). 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 overactive bladder significantly from baseline to the end of the study as assessed by the 3 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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).
Sand et al.[40] (2004) Oxybutynin ER 10 mg once daily vs tolterodine IR 2 mg twice daily	RCT, DB 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	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). There was no significant difference in dry mouth, central nervous system events or other adverse events among the treatment groups.
Diokno et al.[41] (2003) Oxybutynin ER 10 mg daily vs tolterodine ER 4 mg daily	RCT, DB, MC, AC Women ≥18 years of age with OAB who documented 21-60 urge urinary incontinence (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	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 with tolterodine participants (P=0.003). The proportion of participants who reported total dryness (no incontinence episodes) in their last 7-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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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.
Reinberg et al.[42] (2003) Oxybutynin ER 5 mg/day vs tolterodine ER 2 mg/day vs tolterodine IR 2 mg/day	OL Pediatric patients with a history of non-neurogenic diurnal urinary incontinence and symptoms of overactive bladder	N=132 Not specified	Primary: Urinary frequency, incontinence and safety	Primary: 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.
Nelken et al.[91] (2011) Oxybutynin IR 5 mg twice daily vs estradiol vaginal ring 7.5 mcg/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 quality of life scores, as assessed by the Urogenital	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Distress Inventory (UDI-6) and the Incontinence Impact Questionnaire (IIQ-7)	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 group reported vaginal discharge.
Davila et al.[38] (2001) Oxybutynin transdermal 2-4 patches applied twice weekly vs oxybutynin IR 5-7.5 mg orally two or three times daily	RCT, DB, MC, PC 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 visual analog scale for efficacy, dry mouth on an anticholinergic symptoms questionnaire, cystometric comparisons	Primary: The average daily incontinence episodes were reduced by approximately 5 episodes in both groups (P<0.0001), with no significant difference between transdermal and oral therapy. The change in the mean visual analog scale score for each group was 5.8 versus 6.0 cm for the transdermal and oral groups, respectively (P<0.0001). The difference in mean visual analog scale 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 with 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 ml 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 ml and 16 ml in the oral and transdermal groups, respectively (P=NS). The most frequent treatment related adverse events were dry mouth,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				constipation, somnolence, dizziness, blurred vision and impaired urination, which occurred more frequently in the oral group.
Dmochowski et al.[43] (2003) Oxybutynin transdermal delivery system (OXY-TDS) 3.9 mg/day applied twice weekly vs tolterodine ER (TOL-LA) 4 mg daily vs placebo	RCT, DB Patients ≥18 years of age who were receiving pharmacologic treatment for OAB and who had a beneficial response to the pre-study treatment	N=361 12 weeks	Primary: Change from baseline in the number of incontinence episodes/day, average daily urinary frequency, average urinary volume/void, and changes in the quality of life instruments	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 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				symptoms of the Urogenital Distress Inventory 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 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%). 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.
Metello et al.[44] (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 urgency severity scale (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% had a mild reduction, and 59% had a great reduction.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Chancellor et al.[45] (2008) Solifenacin 5 to 10 mg once daily	OL, MC Patients ≥18 years of age with symptoms of OAB 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)	N=441 12 weeks	Primary: Change in urgency episodes compared with pre-washout (when patients were receiving tolterodine ER 4 mg) Secondary: Change in micturitions, incontinence episodes, nocturia episodes, and nocturnal voids compared with pre-washout and post-washout. Patient-reported outcomes (PRO) using the Patient Perception of Bladder Condition (PPBC) and the Overactive Bladder Questionnaire (OAB-q) was also assessed.	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%. 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%), 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 with 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 HRQL. The most common adverse events were dry mouth (17.5%), constipation (11.6%), and blurred vision (2.3%).
Zinner et al.[46] (2008) Solifenacin 5 to 10 mg once daily	OL, MC Patients ≥18 years of age with OAB symptoms for ≥3	N=441 12 weeks	Primary: Work Productivity and Activity Impairment Questionnaire –	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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	months who were previously treated with tolterodine ER 4 mg/day for ≥4 weeks, and who wished to switch to solifenacin due to lack of sufficient improvement in urgency episodes while receiving tolterodine (≥3 urgency episodes/24 hours)		Specific Health Problem (WPAI-SHP), Health Utilities Index (HUI), and a resource utilization questionnaire administered at pre-washout and week 12	There were no significant differences in the numbers of skin rashes or falls reported at end of the study compared with pre-washout. Patients reported using fluid management as a behavioral management strategy on fewer days with solifenacin compared to when they were 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.
Wong et al.[47] (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)	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-questionnaire (OAB-q) showed a value of 60.8% at baseline and 32.0% at 12 weeks with solifenacin (P=0.001). The health-related quality-of-life (HRQL) domain of the OAB-q showed a value of 45.5% at baseline and 73.3% at 12 weeks with solifenacin (P=0.0006).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Garely et al.[48] (2006) Solifenacin 5 to 10 mg once daily	OL, MC Patients ≥18 years of age with OAB (urgency, urge urinary incontinence, frequency, and/or nocturia for ≥3 months)	N=2,225 12 weeks	Primary: Patient Perception of Bladder Condition (PPBC) scale, overactive bladder questionnaire (OAB-q), and a visual analog scale (VAS) for the degree of bother caused by individual OAB symptoms	Primary: The mean PPBC scale score decreased significantly to 2.9 (mean change, -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 AEs that resulted in discontinuation were dry mouth (1.9%) and constipation (1.9%).
Haab et al.[49] (2005) Solifenacin 5 to 10 mg once daily	OL, ES 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 symptomatic urgency at end point.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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.[90] (2010) Solifenacin 0.15 to 0.25 mg/kg once daily	PRO, OL 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	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 50-89% decrease in 6 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).
Chapple et al.[50] (2006) Solifenacin 5 to 10 mg once daily vs placebo	RCT, DB, MC, PC (Pooled analysis) Patients ≥18 years of age with OAB (≥8 micturitions/24 hours, and either a mean of ≥1 incontinence episode/24 hours or a mean of ≥1	N=2,848 (4 trials) 12 weeks	Primary: Urgency episodes (mean absolute values and median percentage values), incontinence episodes, micturition frequency, nocturia episodes/24 hours, and volume	Primary: Treatment with solifenacin 5 mg 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 mg and 10 mg resulted in a -1.5 (-100%) and -1.8 (-100%) reduction in incontinence episodes, respectively compared to 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;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	urgency episode/24 hours)		voided/micturition	-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 mg 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 are follows: 4.4%, 2.8%, and 6.8% with placebo, solifenacin 5 mg and solifenacin 10 mg.
Abrams et al.[51] (2005) Solifenacin 5 to 10 mg once daily vs placebo	RCT, DB, MC, PC (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	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 ml) were significantly greater with solifenacin 5 mg 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). 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				comparable with or less than that of the placebo group (6.2%).
Millard et al.[52] (2006) Solifenacin 5 to 10 mg once daily vs placebo	RCT, DB, MC, PC (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	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. The incidence of adverse events was comparable among the treatment groups. Dry mouth, constipation, urinary tract infection, 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.
Wagg et al.[53] (2006)	RCT, DB, MC, PC (Pooled analysis)	N=1,554 (5 trials)	Primary: Urgency episodes	Primary: In the 12-weeks studies, elderly patients had significantly greater

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Solifenacin 5 to 10 mg once daily vs placebo	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)	12 to 40 weeks	(mean absolute values and median percentage values), incontinence episodes, micturition frequency, nocturia episodes/24 hours, and volume voided/micturition	decreases in the mean number of incontinence episodes/24 hours with solifenacin 5 mg 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 mg 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 mg 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 mg 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 mg 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 mg 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 mg 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 mg 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. In 12-week studies, elderly patients had a significantly greater increase in the mean volume voided/micturition with solifenacin 5 mg 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%) f with solifenacin 5 mg 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 with baseline. A

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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 urinary tract infection. 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 urinary tract infection. A total of 9.2% of patients discontinued therapy due to any type of adverse event.
Kelleher et al.[54] (2005) Solifenacin 5 to 10 mg once daily vs placebo	RCT, DB, MC, PC (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) for >3 months	N=3,237 (3 trials) 12 to 40 weeks	Primary: QoL data using the King's Health Questionnaire (KHQ)	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 extension study, there was a significant improvement in all QoL domains with solifenacin (17% for the general health perception and 35-48% for all the other domains).
Herschorn et al.[95] (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: 3-day diary changes in urgency, frequency, incontinence,	Primary: Significantly fewer patients on solifenacin reported dry mouth after direct questioning compared to oxybutynin IR (35% vs 83%, 95% CI 33-62, 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 volume voided per micturition from baseline to end of treatment. PPBC and OAB-q scores also significantly improved with both groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			nocturia, voided volume, PPBC, and the OAB-q	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.[96] (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	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 3.91-20.17). 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.
Hsiao et al.[85] (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	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 4, 8 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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Changes in the heart rate differed significantly between these two groups at visit 2 (solifenacin vs tolterodine ER, -4.3 [95% CI, -7.2 to -1.3] vs 3.8 [95% CI, 0.3-7.3], P=0.02) and visit 3 (-3.2 [95% CI, -7.4-1] 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).
Ho et al.[92] (2010) Solifenacin 5 mg once daily vs tolterodine ER 4 mg once daily	PRO, OL, RCT Male or female patients ≥18 years of age with OAB symptoms (urinary frequency, urgency, or urge incontinence) ≥3 months, who experienced frequency (defined as ≥8 micturitions per 24 hours)	N=75 12 weeks	Primary: Change from baseline to endpoint for the mean number of 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	Primary: Compared to baseline, both treatment groups showed significant improvements in reducing mean micturition numbers per 24 hours from week 4. At week 12, the mean changes were not significantly different between solifenacin and tolterodine (-2.56 vs -2.44, P=0.58). Secondary: 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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The most common adverse events for solifenacin and tolterodine were dry mouth (18% vs 8.3%, P=0.31) and constipation (12.8% vs 2.8%, P=0.2).
Chapple et al.[57] (2005) Solifenacin 5 to 10 mg once daily vs tolterodine ER 4 mg once daily	RCT, DB, MC 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 6-point categorical scale to assess perception of bladder condition (PBC)	Primary: The mean number of micturitions was reduced with solifenacin (-2.45) compared to treatment with tolterodine (-2.24; P=0.004 for noninferiority). 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 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 with tolterodine (31 ml; P=0.010). Solifenacin decreased the number of incontinence pads used compared to tolterodine (P=0.0023). Patient-reported PBC was significantly improved with solifenacin compared to tolterodine (P=0.006).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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.[55] (2004) Solifenacin 2.5 to 20 mg once daily vs tolterodine IR 2 mg twice daily vs placebo	RCT, DB, PC Patients 18 to 80 years of age with OAB and urodynamic evidence of detrusor overactivity (>8 voids/24 hours and >3 episodes of incontinence or urgency)	N=225 6 weeks	Primary: Number of voids/24 hours Secondary: Volume voided/ void; incontinence episodes/24 hours; urgency episodes/24 hours; and total sum score of Contilife items 1-27, sum scores of the five Contilife domains (i.e., daily activities, effort, self-image, emotional consequences, and sexuality), and overall Contilife QoL score	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: The mean volume voided/void was significantly greater for solifenacin 5 mg, 10 mg 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 with 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 with 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 mg and 20 mg, P<0.05), emotional consequences (5 mg, 10 mg and 20 mg, P<0.05) and sexuality (10 mg and 20 mg, P<0.05) compared to placebo. Tolterodine resulted in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				significant improvements in the daily life activities domain only compared to placebo (P<0.05). Solifenacin 10 mg 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 mg and 10 mg (14% each). Constipation was reported in 19% of patients taking solifenacin 20 mg.
Chapple et al.[56] (2004) Solifenacin 5 to 10 mg once daily vs tolterodine IR 2 mg twice daily vs placebo	RCT, DB, MC Patients ≥18 years with symptoms of OAB (including urgency, urge incontinence, or frequency) for ≥3 months (≥8 voids/24 hours, ≥3 episodes of urgency and/or ≥3 episodes of incontinence)	N=1,081 12 weeks	Primary: Urgency episodes, all incontinence episodes, urge incontinence episodes, voids/24 hours and voided volume/void	Primary: There was a significant decrease in the mean number of urgency episodes/24 hours with solifenacin 5 mg 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 mg and 10 mg with tolterodine resulted in estimated differences 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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 mg 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%). Constipation was reported in 7.2% and 7.8% of patients treated with solifenacin 5 mg 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.
Yamaguchi et al.[93] (2011) Solifenacin 2.5 mg plus tamsulosin 0.2 mg once daily (TAM+SOL 2.5) vs solifenacin 5 mg plus tamsulosin 0.2	MC, DB, 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	N=638 12 weeks	Primary: Mean change in urgency episodes per 24 hours Secondary: Mean changes in micturitions, nocturia episodes, urgency incontinence episodes, IPSS,	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 with 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg once daily (TAM+SOL 5) vs tamsulosin 0.2 mg once daily plus placebo (TAM+PBO)	≥5 mL/s, and PVR volume <50 ml		IPSS-QOL, and OABSS	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 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 4 patients in TAM+SOL 5 had urinary retention requiring temporary cauterization.
Kreder et al.[73] (2002) Tolterodine ER 4 mg once daily	OL, ES 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%). 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%), urinary tract infection (0.7%), dyspepsia (0.6%), constipation (0.6%), xerophthalmia (0.5%), and micturition disorders (0.5%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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.[74] (2005) Tolterodine ER 4 mg once daily	OL, ES Japanese patients ≥20 years of age with OAB symptoms including urinary urgency, urinary frequency (≥8 micturitions/24 hours) and urge incontinence (≥5 episodes/week) for ≥6 months	N=188 12 months	Primary: Safety and tolerability Secondary: Efficacy	Primary: The most common adverse event was dry mouth (33.5%). The incidence decreased during the course of the open-label extension (24.5% during the first 3 months vs 4.3% during the 6–12-month periods). Approximately 23% of patients withdrew prematurely due to adverse events (10%), lack of efficacy (8%), 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.[70] (2008) Tolterodine ER 4 mg once daily	OL Patients ≥18 years of age with OAB who had urinary frequency (≥8 micturitions/24	N=60 12 weeks	Primary: Rate of patient-reported goal achievement (PGA) by a visual analogue scale	Primary: The median rate of patient-reported goal achievement (PGA) was: frequency (60%; 95% CI, 46.9–63.6), urgency (60%; 95% CI, 46.2–64.9), urge incontinence (80%; 95% CI, 34.2–80.0), nocturia (50%; 95% CI, 39.4–57.6) and tenesmus (30%; 95% CI, 25.4–52.2). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	hours) and urgency (≥2 episodes/24 hours) with or without urgency incontinence		Secondary: Changes in symptom severity, voiding diary and patient perception of bladder condition (PPBC), global impression of improvement (GII), and willingness to continue treatment	The median percentage reduction in symptom severity was as follows: frequency (45%; 95% CI, 36.2–54.4), urgency (55%; 95% CI, 40.1– 60.4), urgency incontinence (71%; 95% CI, 39.2– 76.8), nocturia (52%; 95% CI, 40.2–59.7) and tenesmus (26%; 95% CI, 16.9–50.4). Patients reported that the most troublesome symptoms were daytime frequency (50%), 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. After 12 weeks of treatment, 53.6% of patients experienced much improvement, 39.3% experienced little improvement, and 7.1% experienced no improvement on the GII questionnaire. A total of 73.2% of patients wished to continue treatment after receiving 3 months of treatment. The most common adverse events were dry mouth (21.7%), constipation or indigestion (10%), headache (5%), urinary tract infection (3.3%) and peripheral edema (1.7%).
Van Kerrebroeck et al.[68] (2001) Tolterodine ER 4 mg once daily vs tolterodine IR	RCT, DB, MC, PC Patients ≥18 years of age with urinary frequency (≥8 micturitions/24 hours) and urge incontinence (≥5 incontinence episodes/week) for	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	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
2 mg twice daily vs placebo	≥6 months			(-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%).
Swift et al.[69] (2003) Tolterodine ER 4 mg once daily vs tolterodine IR 2 mg twice daily vs placebo	RCT, DB, PC, MC (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	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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 urinary tract infection 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%).
Homma et al.[66] (2003) Tolterodine ER 4 mg once daily vs oxybutynin IR 3 mg three times daily vs placebo	RCT, DB, PC, AC Patients ≥20 years of age with OAB and symptoms of urinary urgency, urinary frequency (≥8 micturitions/24 hours) and urge incontinence (≥5 episodes/week) for ≥6 months	N=608 12 weeks	Primary: Incontinence episodes/week 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 King's Health Questionnaire (KHQ)	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 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 not significant (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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(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 with 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 not significant for any of these domains. 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.[67] (2002) Trial 1 Tolterodine ER 2 to 4 mg once daily Trial 2	RCT, OL 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:	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Oxybutynin ER 5 to 10 mg once daily			Physician assessment of treatment benefit	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). 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 with oxybutynin 10 mg (P=0.03).
Chung et al.[86] (2010) Tolterodine ER 4 mg once daily and dutasteride 0.5 mg once daily	OL Men ≥45 years on dutasteride 0.5 mg for at least 6 months who failed alpha-blocker therapy, prostate >30 grams, an IPSS ≥12, IPSS quality-of-life 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"	N=51 12 weeks	Primary: Change in frequency, nocturnal OAB micturition, IPSS, Qmax, change in PVR, adverse events, and episodes of urinary retention requiring a catheter	Primary: 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 3 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, 1 patient (2%) had constipation, and sexual function decreased in 2 patients (3.9%).
Chung et al.[97] (2011)	OS, PRO, RCT	N=153	Primary: Improvement in	Primary: The mean IPSS-voiding (8.5 to 2.88 with tolterodine [P<0.001], 9.83 to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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	Male patients ≥70 years of age with an IPSS score >8 and a storage subscore of >5, quality of life index score >3, total prostate volume >20 ml, Qmax <15 ml/sec, and with urodynamic confirmed BPH/BOO	12 months	IPSS subscores (voiding and storage) at 12 months Secondary: Change in PVR volume, and QoL-I	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 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.[72] (2001) Tolterodine IR 2 mg twice daily	OL, ES 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	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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.
Appell et al.[71] (2001) Tolterodine IR 2 mg twice daily	OL, ES 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 open-label trial, 30% did not complete 9 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 9 months of therapy.
Kilic et al.[98] (2006)	PRO, RCT	N=60	Primary: Urodynamic	Primary: The tolterodine group had a significant increase in the bladder capacity

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Tolterodine IR 1 mg twice daily vs oxybutynin IR 0.4 mg/kg three times daily	Children with detrusor instability (most with symptoms of nocturnal enuresis associated with daytime incontinence, frequency, urgency, and/or small bladder volume)	≥6 months	investigations before and after treatment, episodes of UUI, and adverse events	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 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 6 months (100% to 30% for tolterodine and 100% to 23.3% for oxybutynin). Clinical response was also similar between tolterodine and oxybutynin (73.3% for tolterodine and 80% 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.
Appell et al.[60] (1997) Tolterodine IR 1 to 2 mg twice daily vs oxybutynin IR 5 mg three times daily vs	RCT, DB, MC, PC (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	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 mg 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 mg and 2 mg) and oxybutynin compared to placebo (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				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. 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).
Lee et al.[58] (2002) Tolterodine IR 2 mg twice daily vs oxybutynin IR 5 mg twice daily	RCT, DB, MC, PG 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	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				significantly higher with oxybutynin than tolterodine (P=0.001). There was a higher frequency of moderate-to-severe dry mouth with oxybutynin (28%) than tolterodine (9%).
Malone-Lee et al.[59] (2001) Tolterodine IR 2 mg twice daily vs oxybutynin IR 5 mg twice daily	RCT, DB, MC 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	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%).
Abrams et al.[61] (1998) Tolterodine IR 2 mg twice daily vs oxybutynin IR	RCT, DB, MC, PC Patients ≥18 years of age with OAB, increased urinary frequency (≥8 micturitions/24 hours), and symptoms of	N=293 12 weeks	Primary: Number of micturition/24 hours, incontinence episodes/24 hours and volume voided/micturition	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 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

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) for ≥6 months			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.
Drutz et al.[62] (1999) Tolterodine IR 2 mg twice daily vs oxybutynin IR 5 mg three times daily vs placebo	RCT, DB, MC, PC Patients ≥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=277 12 weeks	Primary: Number of micturition/24 hours, incontinence episodes/24 hours and volume voided/micturition	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) 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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.
Leung et al.[63] (2002) Tolterodine IR 2 mg twice daily vs oxybutynin IR 5 mg three times daily	RCT, DB, MC 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.
Giannitsas et al.[64] (2004) Tolterodine IR 2 mg twice daily for 6 weeks vs oxybutynin IR	RCT, OL, XO Patients ≥18 years of age with OAB who were categorized according to the characteristics of the first overactive detrusor contraction	N=128 12 weeks	Primary: Volume voided/micturition, number of micturition/24 hours, incontinence episodes/24 hours, and other urodynamic parameters in the	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
5 mg three times daily for 6 weeks	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)		total population and individual severity 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 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 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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. High volume–High pressure Overactivity (Group II) 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. High volume–Low pressure Overactivity (Group I) The small number of patients in this group did not allow for statistical analyses to be performed.
Harvey et al.[65] (2001) Tolterodine IR 1 to 2 mg twice daily vs oxybutynin IR 2.5 to 5 mg three times daily	MA Patients ≥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)	4 trials 12 weeks	Primary: Incontinent episodes/24 hours, quantity of pad used/24-hour period, micturitions/24 hours, and voided volume/micturition Secondary: Adverse events	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). 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 with 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				from studies due to dry mouth with tolterodine compared to oxybutynin (RR, 0.63; 95% CI, 0.46 to 0.88).
Staskin et al.[75] (2004) Trospium 20 mg twice daily vs placebo	RCT, DB, PC, MC Patients with OAB	N=658 12 weeks	Primary: CNS adverse effects and daytime sleepiness using the Stanford Sleepiness Scale (SSS)	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 CNS 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.
Halaska et al.[76] (2003) Trospium (TCl) 20 mg twice daily vs oxybutynin IR (OXY) 5 mg twice daily	RCT, DB, MC, AC Patients ≥18 years of age with urge syndrome, urge incontinence, urge incontinence as one component of mixed incontinence, or urge incontinence due to a neurological condition (detrusor hyperreflexia)	N=358 52 weeks	Primary: Safety and efficacy	Primary: Blood chemistry, nitrogenous metabolites, uric acid, sodium and potassium, GPT and LDH were not adversely affected by either treatment. 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 with 6 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. Urinary tract infection 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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 (Relative risk of 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 ml 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 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 2 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 2 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 2weeks, 3.2 at 6 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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Madersbacher et al.[77] (1995) Trospium (TCl) 20 mg twice daily vs oxybutynin IR (Oxy) 5 mg three times daily	RCT, DB, MC 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 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.[89] (2011) Trospium ER 60 mg once daily	OL, ES Patients ≥18 years of age with symptoms of OAB	N=944 48 weeks	Primary: Changes in the mean number of toilet voids per day and UUI episodes	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	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		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	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. Overall, 552 patients (58.5%) experienced ≥1 TEAE, 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.[14] (2009) Combination antimuscarinic therapy (oxybutynin 10-30 mg, tolterodine ER 4 mg, and/or solifenacin 5-10 mg)	PRO, OL 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 2 patients (6%) rated 100% improvement (complete dryness), a >90% decrease in incontinence episodes and a 50-89% decrease, respectively. MVV in 3-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). 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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Chapple et al.[79] (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 LUTS Secondary: Tolerability, safety, and health-related quality of life (HRQL)	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. 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 13–40 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				condition was significantly higher for fesoterodine 4 mg/day 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 mg/day 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 7.5–10 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). 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 7.5–10 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 TDS 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 TDS 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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 7.5–10 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 (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 HRQL were reported for darifenacin, fesoterodine, oxybutynin TDS, solifenacin, tolterodine ER and IR, and trospium compared to placebo.
Hay-Smith et al.[80] (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	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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 (4 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>Extended (ER) versus immediate release (IR) oxybutynin (4 trials)</u> There was no significant difference in patient's perception of improvement (1 trial). There was no significant difference between the groups in the number of 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 versus IR tolterodine (1 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 versus IR tolterodine (1 trial)</u>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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 versus IR oxybutynin (1 trial)</u> The risk of dry mouth was less for those taking ER tolterodine compared to oxybutynin IR. <u>Tolterodine ER versus oxybutynin ER (2 trials)</u> There was no significant difference in change in leakage episodes or micturitions/24 hours (1 trial). 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.

Drug regimen abbreviations: BID=twice daily, ER=extended-release, IR=immediate-release, QD=once daily, QID=four times daily, SR=sustained-release, TID=three times daily
Study abbreviations: AC=active control, CI=confidence interval, DD=double-dummy, DB=double-blind, MC=multicenter, NS=not significant, OL=open-label, PC=placebo-controlled, PG=parallel-group, 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, IPSS=international prostate symptoms score, IPS-QOL=international prostate symptoms score quality of life, ITT=intent-to-treat, 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, PP=per protocol, PPBC=Patient Perception of Bladder Condition Questionnaire, PRO=patient reported outcome, PVD=postvoid residual, Qmax=maximum flow rate, QoL-I=Quality of Life Index, SSS=Stanford Sleepiness Scale, TSQ=Treatment Satisfaction Questionnaire, UPS=Urgency Perception Scale, USS=Urinary Sensation Scale, UUI=urgency urinary incontinence, 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/Rx
$$	$31-$50/Rx
$$$	$51-$100/Rx
$$$$	$101-$200/Rx
$$$$$	Over $200/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®	$$$$	N/A
Fesoterodine	extended-release tablet	Toviaz®	$$$$	N/A
Flavoxate	tablet	N/A	N/A	$$$
Oxybutynin	extended-release tablet, syrup, tablet, transdermal gel, transdermal patch	Ditropan XL®*, Gelnique®, Oxytrol®	$$-$$$$	$-$$
Solifenacin	tablet	Vesicare®	$$$$	N/A
Tolterodine	extended-release capsule, tablet	Detrol®, Detrol LA®	$$$$	N/A
Trospium	extended-release capsule, tablet	Sanctura®*, Sanctura XR®	$$$$	$$$$

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

X. Conclusions

Urinary incontinence (UI) and overactive bladder (OAB) cause both physical and psychological morbidity, as well as adversely impact quality of life.[15] Initial treatment options include lifestyle modifications (weight loss and dietary changes), behavioral therapy (bladder training, physical therapy and toileting assistance) and

pharmacologic therapy.[16-17] Antimuscarinic drugs with antimuscarinic effects increase bladder capacity, decrease urgency and are useful for the treatment of urge incontinence.[16] Flavoxate, oxybutynin 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 UI and OAB. Antimuscarinic agents are the primary treatment for patients with OAB symptoms (with or without urge incontinence), in addition to lifestyle modifications and behavioral therapy.[17,20-22,81,83] In general, the guidelines do not give preference to one particular agent over another.

In clinical trials, the genitourinary smooth muscle relaxants have been shown to modestly improve urinary symptoms, including frequency, urgency, nocturia and incontinence episodes.[23-80] The majority of the studies were 6 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 very 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 (IR) and extended-release (ER) formulations of the same drug found no differences in efficacy.[33-38,69] Studies directly comparing IR formulations of different drugs, as well as studies directly comparing ER formulations of different drugs, also demonstrated similar efficacy.[29,32,41-43,58-64,76-77,85,92,95,98] Very few studies have demonstrated greater efficacy with one genitourinary smooth muscle relaxant over another.[39-40,57,67,84,94] The use of the genitourinary smooth muscle relaxants for the treatment of UI and OAB has also been associated with an improvement in quality of life.[29-30,34,48,54-55,57,66]

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.[16] The incidence of adverse events varies among the agents and depends upon the formulation used (ER, IR or transdermal). Adverse events tend to be higher with the IR formulations compared to ER 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 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 generics and OTC 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

1. Drug Facts and Comparisons. Drug Facts and Comparisons 4.0 [online]. 2012. Available from Wolters Kluwer Health, Inc. Accessed April 2012.
2. Lexi-Comp Online, Lexi-Drugs Online, Hudson, Ohio: Lexi-Comp, Inc.; 2012; April 2012.
3. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed April 2012.
4. Enablex® [package insert]. Rockaway, NJ: Warner Chilcot, U.S., LLC; March 2012.
5. Toviaz® [package insert]. New York, NY: Pfizer, Inc.; December 2011.
6. Ditropan XL® [package insert]. Raritan, NJ: Ortho-McNeil-Janssen Pharmaceuticals, Inc.; March 2012.
7. Gelnique® [package insert]. Corona, CA: Watson Pharmaceuticals, Inc.; March 2012.
8. Oxytrol® [package insert]. Corona, CA: Watson Pharmaceuticals, Inc.; April 2011.
9. Vesicare® [package insert]. Deerfield, Illinois: Astellas Pharma US, Inc.; January 2012.
10. Detrol® [package insert]. New York, NY: Pfizer, Inc.; September 2011.
11. Detrol LA® [package insert]. New York, NY: Pfizer, Inc.; February 2012.
12. Sanctura® [package insert]. Irvine, CA: Allergan, Inc.; September 2011.
13. Sanctura XR® [package insert]. Irvine, CA: Allergan, Inc.; September 2011.
14. Bolduc S, Moore K, Lebel S, et al. Double anticholinergic therapy for refractory overactive bladder. J Urol 2009;182(4 suppl):2033-8.
15. DuBeau C. Clinical presentation and diagnosis of urinary incontinence. In: UpToDate, Sokol, H (Ed), UpToDate, Waltham, MA, 2012.
16. DuBeau C. Treatment of urinary incontinence. In: UpToDate, Sokol, H (Ed), UpToDate, Waltham, MA, 2012.
17. Yamaguchi O, Nishizawa O, Takeda M, et al. Clinical guidelines for overactive bladder. Neurogenic Bladder Society. Int J Urol 2009;16:126-142.
18. Tekgül S, Riedmiller H, Dogan HS, et al. European Association of Urology/European Society for Paediatric Urology 2012 guidelines on paediatric urology: management of neurogenic bladder in children. Available at: http://www.uroweb.org/gls/pdf/21_Paediatric_Urology_LR%20[correctie%20Hoebeke].pdf. Accessed May 2012.
19. Pannek J, Stöhrer M, Blok B, et al. European Association of Urology 2011 guidelines on neurogenic lower urinary tract dysfunction. Available at: http://www.uroweb.org/gls/pdf/19_Neurogenic_LR%20II.pdf. Accessed May 2012.
20. National Institute for Health and Clinical Excellence (NICE). Urinary incontinence: the management of urinary incontinence in women. London (UK): National Institute for Health and Clinical Excellence (NICE); 2006 Oct. 36 p. Available at: http://www.nice.org.uk/nicemedia/live/10996/30282/30282.pdf. Accessed May 2012.
21. American College of Obstetricians and Gynecologists (ACOG). Urinary incontinence in women. Washington (DC): American College of Obstetricians and Gynecologists (ACOG); 2005 Jun. 13 p. (ACOG practice bulletin; no. 63).
22. Scottish Intercollegiate Guidelines Network (SIGN). Management of urinary incontinence in primary care: a national clinical guideline. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network (SIGN); 2004 Dec. 46 p. (SIGN publication; no. 79). Available at: http://www.sign.ac.uk/pdf/sign79.pdf. Accessed May 2012.
23. Chapple C, Steers W, Norton P,et al. A pooled analysis of three phase III studies to investigate the efficacy, tolerability and safety of darifenacin, a muscarinic M3 selective receptor antagonist, in the treatment of overactive bladder. BJU Int 2005;95:993-1001.
24. Foote J, Glavind K, Kralidis G, et al. Treatment of overactive bladder in the older patient: pooled analysis of three phase III studies of darifenacin, an M3 selective receptor antagonist. Eur Urol 2005;48:471-7.
25. Haab F, Corcos J, Siami P, et al. Long-term treatment with darifenacin for overactive bladder: results of a 2-year, open-label extension study. Br J Urol Int 2006;98:1025-32.
26. Hill S, Elhilali M, Millard RJ, et al. Long-term darifenacin treatment for overactive bladder in patients aged 65 years and older: analysis of results from a 2-year, open-label extension study. Curr Med Res Opin 2007;23:2697-704.
27. Nitti V, Dmochowski R, Sand P et al. Efficacy, safety, and tolerability of fesoterodine in patients with overactive bladder. J Urol 2007;178:2488–94.
28. Chapple C, Van Kerrebroeck P, Tubaro A et al. Clinical efficacy, safety, and tolerability of once-daily fesoterodine in patients with overactive bladder. Eur Urol 2007; 52: 1204–12.

29. Chapple CR, Van Kerrebroeck PE, Jünemann KP, et al. Comparison of fesoterodine and tolterodine in patients with overactive bladder. BJU Int 2008;102:1128-32.
30. Kelleher CJ, Tubaro A, Wang JT, K et al. Impact of fesoterodine on quality of life: pooled data from two randomized trials. BJU Int 2008;102:56-61.
31. Wyndaele JJ, Goldfischer ER, Morrow JD, et al. Effects of flexible-dose fesoterodine on overactive bladder symptoms and treatment satisfaction: an open-label study. Int J Clin Pract 2009;63:560-7.
32. Chapple CR, Abrams P. Comparison of darifenacin and oxybutynin in patients with overactive bladder: assessment of ambulatory urodynamics and impact on salivary flow. Eur Urol 2005;48:102-9.
33. Anderson RU, Mobley D, Blank B, et al. Once daily controlled versus immediate release oxybutynin chloride for urge urinary incontinence. J Urol 1999;161:1809-12.
34. Barkin J, Corcos J, Radomski S, et al. A randomized, double-blind, parallel-group comparison of controlled- and immediate-release oxybutynin chloride in urge urinary incontinence. Clin Ther 2004;26:1026-36.
35. Birns J, Lukkari E, Malone-Lee JG, et al. A randomized controlled trial comparing the efficacy of controlled-release oxybutynin tablets (10 mg once daily) with conventional oxybutynin tablets (5 mg twice daily) in patients whose symptoms were stabilized on 5 mg twice daily of oxybutynin. BJU Int 2000;85:793-8.
36. Versi E, Appell R, Mobley D, et al. Dry mouth with conventional and controlled-release oxybutynin in urinary incontinence. The Ditropan XL Study Group. Obstet Gynecol 2000;95:718-21.
37. Nilsson CG, Lukkari E, Haarala M, et al. Comparison of a 10 mg controlled release oxybutynin tablet with a 5 mg oxybutynin tablet in urge incontinent patients. Neurourol Urodyn 1997;16:533-42.
38. Davila GW, Daugherty CA, Sanders SW, et al. A short-term, multicenter, randomized double-blind dose titration study of the efficacy and side effects of transdermal compared to immediate release oral oxybutynin treatment of patients with urge urinary incontinence. J Urol 2001;166:140-5.
39. Appell RA, Sand P, Dmochowski R, et al. Prospective randomized controlled trial of extended-release oxybutynin chloride and tolterodine tartrate in the treatment of overactive bladder: results of the OBJECT Study. Mayo Clin Proc 2001;76:358-63.
40. Sand PK, Miklos J, Ritter H, et al. A comparison of extended-release oxybutynin and tolterodine for treatment of overactive bladder in women. Int Urogynecol J Pelvic Floor Dysfunct 2004;15:243-8.
41. Diokno AC, Appell RA, Sand PK, et al. Prospective, randomized, double-blind study of the efficacy and tolerability of the extended-release formulations of oxybutynin and tolterodine for overactive bladder: results of the OPERA trial. Mayo Clin Proc 2003;78:687-95.
42. Reinberg Y, Crocker J, Wolpert J, et al. Therapeutic efficacy of extended release oxybutynin chloride, and immediate release and long acting tolterodine tartrate in children with diurnal urinary incontinence. J Urol 2003;169:317-9.
43. Dmochowski RR, Sand PK, Zinner NR, et al. Comparative efficacy and safety of transdermal oxybutynin and oral tolterodine versus placebo in previously treated patients with urge and mixed urinary incontinence. Urology 2003;62:237-42.
44. Metello J, Nogueira B, Torgal M, et al. Comparison of the efficacy and tolerability of solifenacin succinate with or without previous use of trospium chloride. Int Urogynecol J Pelvic Floor Dysfunct 2007;18:1021-5.
45. Chancellor MB, Zinner N, Whitmore K, et al. Efficacy of solifenacin in patients previously treated with tolterodine extended release 4 mg: results of a 12-week, multicenter, open-label, flexible-dose study. Clin Ther 2008;30:1766-81.
46. Zinner N, Noe L, Rasouliyan L, et al. Impact of solifenacin on resource utilization, work productivity and health utility in overactive bladder patients switching from tolterodine ER. Curr Med Res Opin 2008;24:1583-91.
47. Wong C, Duggan P. Solifenacin for overactive bladder in women unsuccessfully treated with immediate release oxybutynin: a pilot study. J Obstet Gynaecol 2009;29:31-4.
48. Garely AD, Kaufman JM, Sand PK, et al. Symptom bother and health-related quality of life outcomes following solifenacin treatment for overactive bladder: the VESIcare Open-Label Trial (VOLT). Clin Ther 2006;28:1935-46.
49. Haab F, Cardozo L, Chapple C, et al. Long-term open-label solifenacin treatment associated with persistence with therapy in patients with overactive bladder syndrome. Eur Urol 2005;47:376-84.
50. Chapple CR, Cardozo L, Steers WD, et al. Solifenacin significantly improves all symptoms of overactive bladder syndrome. Int J Clin Pract 2006;60:959-66.
51. Abrams P, Swift S. Solifenacin is effective for the treatment of OAB dry patients: a pooled analysis. Eur Urol 2005;48:483-7.
52. Millard RJ, Halaska M. Efficacy of solifenacin in patients with severe symptoms of overactive bladder: a pooled analysis. Curr Med Res Opin 2006;22:41-8.

53. Wagg A, Wyndaele JJ, Sieber P, et al. Efficacy and tolerability of solifenacin in elderly patients with overactive bladder syndrome: a pooled analysis. Am J Geriatr Pharmacother 2006;4:14-24.
54. Kelleher CJ, Cardozo L, Chapple CR, et al. Improved quality of life in patients with overactive bladder symptoms treated with solifenacin. BJU Int 2005;95:81-5.
55. Chapple CR, Rechberger T, Al-Shukri S, et al. Randomized, double-blind placebo- and tolterodine-controlled trial of the once-daily antimuscarinic agent solifenacin in patients with symptomatic overactive bladder. BJU Int 2004;93:303-10.
56. Chapple CR, Araño P, Bosch JL, et al. Solifenacin appears effective and well tolerated in patients with symptomatic idiopathic detrusor overactivity in a placebo- and tolterodine-controlled phase 2 dose-finding study. BJU Int 2004;93:71-7.
57. Chapple C, Martinez-Garcia R, Selvaggi L, et al. A comparison of the efficacy and tolerability of solifenacin succinate and extended release tolterodine at treating overactive bladder syndrome: results of the STAR trial. Eur Urol 2005;48:464–70.
58. Lee JG, Hong JY, Choo MS, et al. Tolterodine: as effective but better tolerated than oxybutynin in Asian patients with symptoms of overactive bladder. Int J Urol 2002;9:247-52.
59. Malone-Lee J, Shaffu B, Anand C, et al. Tolterodine: superior tolerability than and comparable efficacy to oxybutynin in individuals 50 years old or older with overactive bladder: a randomized controlled trial. J Urol 2001;165:1452-6.
60. Appell RA. Clinical efficacy and safety of tolterodine in the treatment of overactive bladder: a pooled analysis. Urology 1997;50 (6A Suppl):90-6.
61. Abrams P, Freeman R, Anderström C, et al. Tolterodine, a new antimuscarinic agent: as effective but better tolerated than oxybutynin in patients with an overactive bladder. Br J Urol 1998;81:801-10.
62. Drutz HP, Appell RA, Gleason D, et al. Clinical efficacy and safety of tolterodine compared to oxybutynin and placebo in patients with overactive bladder. Int Urogynecol J Pelvic Floor Dysfunct 1999;10:283-9.
63. Leung HY, Yip SK, Cheon C, et al. A randomized controlled trial of tolterodine and oxybutynin on tolerability and clinical efficacy for treating Chinese women with an overactive bladder. BJU Int 2002;90:375-80.
64. Giannitsas K, Perimenis P, Athanasopoulos A, et al. Comparison of the efficacy of tolterodine and oxybutynin in different urodynamic severity grades of idiopathic detrusor overactivity. Eur Urol 2004;46:776-82.
65. Harvey MA, Baker K, Wells GA. Tolterodine versus oxybutynin in the treatment of urge urinary incontinence: a meta-analysis. Am J Obstet Gynecol 2001;185:56-61.
66. Homma Y, Paick JS, Lee JG, et al. Clinical efficacy and tolerability of extended-release tolterodine and immediate-release oxybutynin in Japanese and Korean patients with an overactive bladder: a randomized, placebo-controlled trial. BJU Int 2003;92:741-7.
67. Sussman D, Garely A. Treatment of overactive bladder with once-daily extended-release tolterodine or oxybutynin: the antimuscarinic clinical effectiveness trial (ACET). Curr Med Res Opin 2002;18:177-84.
68. Van Kerrebroeck P, Kreder K, Jonas U, et al. Tolterodine once-daily: superior efficacy and tolerability in the treatment of the overactive bladder. Urology 2001;57:414-21.
69. Swift S, Garely A, Dimpfl T, et al. A new once-daily formulation of tolterodine provides superior efficacy and is well tolerated in women with overactive bladder. Int Urogynecol J Pelvic Floor Dysfunct 2003;14:50-4.
70. Choo MS, Doo CK, Lee KS, et al. Satisfaction with tolterodine: assessing symptom-specific patient-reported goal achievement in the treatment of overactive bladder in female patients (STARGATE study). Int J Clin Pract 2008;62:191-6.
71. Appell RA, Abrams P, Drutz HP, et al. Treatment of overactive bladder: long-term tolerability and efficacy of tolterodine. World J Urol 2001;19:141-7.
72. Abrams P, Malone-Lee J, Jacquetin B, et al. Twelve-month treatment of overactive bladder: efficacy and tolerability of tolterodine. Drugs Aging 2001;18:551-60.
73. Kreder K, Mayne C, Jonas U, et al. Long-term safety, tolerability and efficacy of extended-release tolterodine in the treatment of overactive bladder. Eur Urol 2002;41:588-95.
74. Takei M, Homma Y. Long-term safety, tolerability and efficacy of extended-release tolterodine in the treatment of overactive bladder in Japanese patients. Int J Urol 2005;12:456-64.
75. Staskin DR, Harnett MD. Effect of trospium chloride on somnolence and sleepiness in patients with overactive bladder. Curr Urol Rep 2004;5:423-6.

76. Halaska M, Ralph G, Wiedemann A, et al. Controlled, double-blind, multicentre clinical trial to investigate long-term tolerability and efficacy of trospium chloride in patients with detrusor instability. World J Urol 2003;20:392-9.
77. Madersbacher H, Stöhrer M, Richter R, et al. Trospium chloride versus oxybutynin: a randomized, double-blind, multicentre trial in the treatment of detrusor hyper-reflexia. Br J Urol 1995;75:452-6.
78. Zinner N, Tuttle J, Marks L. Efficacy and tolerability of darifenacin, a muscarinic M3 selective receptor antagonist (M3 SRA), compared with oxybutynin in the treatment of patients with overactive bladder. World J Urol 2005;23:248-52.
79. Chapple CR, Khullar V, Gabriel Z, et al. The effects of antimuscarinic treatments in overactive bladder: an update of a systematic review and meta-analysis. Eur Urol 2008;54:543-62.
80. Hay-Smith J, Herbison P, Ellis G, et al. Which anticholinergic drug for overactive bladder symptoms in adults. Cochrane Database Syst Rev 2009; (3); Cochrane AN: CD005429.
81. Abrams P, Andersson KE, Birder L, et al. Fourth International Consultation on Incontinence Recommendations of the International Scientific Committee: Evaluation and treatment of urinary incontinence, pelvic organ prolapse, and fecal incontinence. Neurourol Urodyn 2010;29:213-40.
82. Abrams P, Cardozo L, Fall M, et al. The standardisation of terminology in lower urinary tract function: report from the standardisation sub-committee of the International Continence Society. Urology 2003;61:37-49.
83. Lucas MG, Bosch JLHR, Cruz FR, et al. European Association of Urology (EAU) 2012 guidelines on urinary incontinence. Available at http://www.uroweb.org/gls/pdf/18_Urinary_Incontinence_LR%20May%203rd.pdf. Accessed May 2012.
84. Herschorn S, Swift S, Guan Z, et al. Comparison of fesoterodine and tolterodine extended release for the treatment of overactive bladder: a head-to-head placebo-controlled trial. BJU Int 2010;105:58-66.
85. Hsiao SM, Chang TC, Wu WY, et al. Comparisons of urodynamic effects, therapeutic efficacy and safety of solifenacin versus tolterodine for female overactive bladder syndrome. J Obstet Gynaecol Res 2011;37:1084-91.
86. Chung DE, Te AE, Staskin DR, et al. Efficacy and safety of tolterodine extended release and dutasteride in male overactive bladder patients with prostates >30 grams. Urology 2010;75:1144-8.
87. Van Kerrebroeck PE, Heesakkers J, Berriman S, et al. Long-term safety, tolerability and efficacy of fesoterodine treatment in subjects with overactive bladder symptoms. Int J Clin Pract 2010;64:584-93.
88. Scarpero H, Sand PK, Kelleher CJ, et al. Long-term safety, tolerability, and efficacy of fesoterodine treatment in men and women with overactive bladder symptoms. Curr Med Res Opin 2011;27:921-30.
89. Zinner NR, Dmochowski RR, Staskin DR, et al. Once-daily trospium chloride 60 mg extended-release provides effective, long-term relief of overactive bladder syndrome symptoms. Neurourol Urodyn 2011;30:1214-9.
90. Bolduc S, Moore K, Nadeau G, et al. Prospective open label study of solifenacin for overactive bladder in children. J Urol 2010;184 (4 Suppl):1668-73.
91. Nelken RS, Ozel BZ, Leegant AR, et al. Randomized trial of estradiol vaginal ring versus oral oxybutynin for the treatment of overactive bladder. Menopause 2011;18:962-6.
92. Ho CH, Chang TC, Lin HH, et al. Solifenacin and tolterodine are equally effective in the treatment of overactive bladder symptoms. J Formos Med Assoc 2010;109:702-8.
93. Yamaguchi O, Kakizaki H, Homma Y, et al. Solifenacin as add-on therapy for overactive bladder symptoms in men treated for lower urinary tract symptoms--ASSIST, randomized controlled study. Urology 2011;78:126-33.
94. Kaplan SA, Schneider T, Foote JE, et al. Superior efficacy of fesoterodine over tolterodine extended release with rapid onset: a prospective, head-to-head, placebo-controlled trial. BJU Int 2011;107:1432-40.
95. Herschorn S, Stothers L, Carlson K, et al. Tolerability of 5 mg solifenacin once daily versus 5 mg oxybutynin immediate release 3 times daily: results of the VECTOR trial. J Urol 2010;183:1892-8.
96. Herschorn S, Pommerville P, Stothers L, et al. Tolerability of solifenacin and oxybutynin immediate release in older (>65 years) and younger (≤ 65 years) patients with overactive bladder: sub-analysis from a Canadian, randomized, double-blind study. Curr Med Res Opin 2011;27:375-82.
97. Chung SD, Chang HC, Chiu B, et al. The efficacy of additive tolterodine extended release for 1-year in older men with storage symptoms and clinical benign prostatic hyperplasia. Neurourol Urodyn 2011;30:568-71.
98. Kilic N, Akgoz S, Sen N, et al. Comparison of the effectiveness and side-effects of tolterodine and oxybutynin in children with detrusor instability. Int J Urol 2006;13:105-08.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
New Drug Pharmacotherapy Review – Tradjenta® (linagliptin)
Dipeptidyl Peptidase-4 (DPP-4) Inhibitors, AHFS Class 682005
August 8, 2012

I. Overview

Diabetes mellitus is a chronic condition which results in hyperglycemia. It is differentiated into 4 main classes: 1) type 1 diabetes; 2) type 2 diabetes; 3) gestational diabetes; and 4) other types (drug- or chemical-induced, genetic defects in β-cell function or insulin action, and diseases of the exocrine pancreas). Type 2 diabetes is the most prevalent form of the disease in the United States, which can be associated with physical inactivity and other lifestyle characteristics. A diagnosis of type 2 diabetes is not dependent on plasma insulin levels, which may be decreased, increased, or normal. Glucose-stimulated secretion of endogenous insulin is frequently reduced, and decreased peripheral sensitivity to insulin is almost always associated with glucose intolerance. Obesity is often a confounder as it contributes to insulin resistance. Inadequate glycemic control may lead to both acute and long-term complications, including microvascular and macrovascular events. There are a variety of oral and injectable antidiabetic agents currently available to treat this devastating disease.

Linagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor, which was approved by the FDA in May 2011. It is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.[1] Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are human incretin hormones that are released from the small intestine in response to food intake.[1-4] These hormones have multiple effects on the stomach, liver, pancreas and brain to control glucose concentrations; however, they are inactivated by the DPP-4 enzyme within minutes. Endogenous GLP-1 levels have been shown to be reduced in patients with type 2 diabetes. The DPP-4 inhibitors slow the inactivation of the incretin hormones and increase their concentration in the bloodstream. This effect enhances glucose-dependent insulin secretion by pancreatic beta cells and suppresses glucagon secretion from pancreatic alpha cells.[1-4]

The linagliptin products that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Linagliptin is not currently available in a generic formulation. The DPP-4 inhibitors were last reviewed in May 2010.

Table 1. Linagliptin Products Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Linagliptin	tablet	Tradjenta®	none

PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the DPP-4 inhibitors are summarized in Table 2.

Table 2. Treatment Guidelines Using the DPP-4 Inhibitors

Clinical Guideline	Recommendation(s)
American Diabetes Association (ADA): **Standards of Medical Care in Diabetes[6] (2012)**	Therapy Type 2 Diabetes • At the time of type 2 diabetes diagnosis, initiate metformin therapy along with lifestyle interventions, unless metformin is contraindicated. • In newly diagnosed type 2 diabetic patients with markedly symptomatic and/or elevated blood glucose levels or A1C, consider insulin therapy, with or without additional agents, from the outset. • If noninsulin monotherapy at maximal tolerated dose does not achieve or maintain the A1C target over 3–6 months, add a second oral agent, a GLP-1 receptor agonist, or insulin. • Refer to the ADA/EASD consensus statement on the management of

Clinical Guideline	Recommendation(s)
	individuals with type 2 diabetes for specific treatment recommendations.[7]
American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD): **Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach**[7] **(2012)**	Initial Drug Therapy • In most patients, begin with lifestyle changes. Metformin monotherapy is added at, or soon after, diagnosis, especially in patients in whom lifestyle intervention alone has not achieved, or is unlikely to achieve, HbA1c goals. • Patients with a high baseline HbA1c (e.g., ≥9.0%) have a low probability of achieving a near-normal target with monotherapy. It may be justified to start directly with a combination of two noninsulin agents or with insulin itself. • If a patient presents with significant hyperglycemic symptoms and/or has dramatically elevated plasma glucose concentrations (e.g., 300–350 mg/dl) or HbA1c (e.g., ≥10.0–12.0%), insulin therapy should be strongly considered from the outset. • If metformin cannot be used, another oral agent could be chosen, such as a sulfonylurea/glinide, pioglitazone, or a DPP-4 inhibitor. In occasional cases where weight loss is seen as an essential aspect of therapy, initial treatment with a GLP-1 receptor agonist might be useful. • Less commonly used drugs (AGIs, colesevelam, bromocriptine) might also be considered in selected patients, but their modest glycemic effects and side-effect profiles make them less attractive candidates. • Specific patient preferences, characteristics, susceptibilities to side effects, potential for weight gain and hypoglycemia should play a major role in drug selection. Dual Combination Therapy • If monotherapy alone does not achieve/maintain an HbA1c target over 3 months, the next step would be to add a second oral agent, a GLP-1 receptor agonist, or basal insulin. • The choice is based on patient and drug characteristics. The goal is to improve glycemic control while minimizing side effects. Shared decision making with the patient may help in the selection of therapeutic options. • Uniform recommendations on the best agent to be combined with metformin cannot be made due to a lack of data. Advantages and disadvantages of specific drugs for each patient should be considered. Triple Combination Therapy • Some studies have shown advantages of adding a third noninsulin agent to a two-drug combination that is not achieving the glycemic target. However, the most robust response will usually be with insulin. • In using triple combinations, agents with complementary mechanisms of action should be used.
Institute for Clinical Systems Improvement (ICSI): **Diagnosis and Management of Type 2 Diabetes Mellitus in Adults**[11] **(2012)**	• Metformin is recommended as first-line therapy for the treatment of type 2 diabetes due to the low risk of hypoglycemia, side effects, and lack of weight gain. • Sulfonylureas and thiazolidinediones are acceptable secondary choices if metformin is contraindicated. • Combination therapy may be required to achieve goals. • If treatment goals are not met on oral agents, or if oral agents are contraindicated, then it is necessary to begin insulin either alone or as an adjunct to oral therapy.
American Association of Clinical Endocrinologists (AACE): **Medical Guidelines**	Antihyperglycemic Pharmacotherapy • The choice of therapeutic agents should be based on their differing metabolic actions and adverse effect profiles as described in the 2009

Clinical Guideline	Recommendation(s)
for Clinical Practice for Developing a Diabetes Mellitus Comprehensive Care Plan[9] (2011)	AACE/ACE Diabetes Algorithm for Glycemic Control.[8] • Insulin should be considered for patients with type 2 diabetes mellitus (T2DM) when noninsulin antihyperglycemic therapy fails to achieve target glycemic control or when a patient, whether drug naïve or not, has symptomatic hyperglycemia. • Antihyperglycemic agents may be broadly categorized by whether they predominantly target fasting plasma glucose (FPG) or postprandial plasma glucose (PPG) levels. These effects are not exclusive; drugs acting on FPG passively reduce PPG, and drugs acting on PPG passively reduce FPG, but these broad categories can aid in therapeutic decision-making. • TZDs and sulfonylureas are examples of oral agents primarily affecting FPG. Metformin and incretin enhancers (DPP-4 inhibitors) also favorably affect FPG. • When insulin therapy is indicated in patients with T2DM to target FPG, therapy with long-acting basal insulin should be the initial choice in most cases; insulin analogues glargine and detemir are preferred over intermediate-acting NPH because they are associated with less hypoglycemia. • The initial choice of an agent targeting FPG or PPG involves comprehensive patient assessment with emphasis given to the glycemic profile obtained by self-monitoring of blood glucose (SMBG). • When postprandial hyperglycemia is present, glinides and/or α-glucosidase inhibitors, short- or rapid-acting insulin, and metformin should be considered. Incretin-based therapy (DPP-4 inhibitors and GLP-1 receptor agonists) also target postprandial hyperglycemia in a glucose-dependent fashion, which reduces the risks of hypoglycemia. • When control of postprandial hyperglycemia is needed and insulin is indicated, rapid-acting insulin analogues are preferred over regular human insulin because they have a more rapid onset and offset of action and are associated with less hypoglycemia. • Pramlintide can be used as an adjunct to prandial insulin therapy to reduce postprandial hyperglycemia, A1C, and weight. • Premixed insulin analogue therapy may be considered for patients in whom adherence to a drug regimen is an issue; however, these preparations lack component dosage flexibility and may increase the risk for hypoglycemia compared with basal insulin or basal-bolus insulin. Basal-bolus insulin therapy is flexible and is recommended for intensive insulin therapy. • Intensification of pharmacotherapy requires glucose monitoring and medication adjustment at appropriate intervals when treatment goals are not achieved or maintained. • Most patients with an initial A1C level >7.5% will require combination therapy using agents with complementary mechanisms of action.

American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE): **An Algorithm for Glycemic Control[8] (2009)**	<u>Management of Patients With A1C Levels of 6.5% to 7.5%</u>
	• Monotherapy:
	  o Metformin, TZDs, DPP-4 inhibitors, and α-glucosidase inhibitors (AGIs) are all appropriate for use as monotherapy. These agents have a minimal risk of hypoglycemia.
	  o Metformin is the cornerstone of monotherapy because of its safety and efficacy.
	• Dual therapy:
	  o Metformin is the cornerstone of dual therapy because of its safety and efficacy.
	  o The second component of the dual therapy regimen includes

Clinical Guideline	Recommendation(s)
	the agents in the following order: incretin mimetic, DPP-4 inhibitor, or an insulin secretagogue (glinide and sulfonylurea). o The combination of a TZD with metformin is recommended with a higher priority than a glinide or sulfonylurea because of a lower risk of hypoglycemia and greater flexibility in timing of administration. o Additional dual therapy regimens include (1) metformin combined with colesevelam, and (2) metformin combined with an AGI. • Triple therapy: o The following combinations are considered for triple therapy in the following order: 1. Metformin + GLP-1 agonist + TZD 2. Metformin + GLP-1 agonist + glinide 3. Metformin + GLP-1 agonist + sulfonylurea 4. Metformin + DPP-4 inhibitor + TZD 5. Metformin + DPP-4 inhibitor + glinide 6. Metformin + DPP-4 inhibitor + sulfonylurea o Metformin is the cornerstone of triple therapy because of its safety and efficacy. o Exenatide is the second preferred component because of the low risk of hypoglycemia, potential for inducing weight loss, as well as the ability to increase satiety and delay gastric emptying. • Insulin therapy: o Metformin is the most commonly used and safest medication to combine with insulin. o Exenatide has not been approved by the FDA for concomitant use with insulin. <u>Management of Patients With A1C Levels of 7.6% to 9.0%</u> • Dual therapy should be started initially if the patient has an A1C of 7.6% to 9.0% because no single agent is likely to achieve the A1C goal. • Dual therapy: o The following combinations are recommended for dual therapy in the following order: 1. Metformin + GLP-1 agonist 2. Metformin + DPP-4 inhibitor 3. Metformin + TZD 4. Metformin + sulfonylurea 5. Metformin + glinide o Metformin is the cornerstone of dual therapy because of its safety, mechanism of action, and insulin sensitization. o A GLP-1 agonist or a DPP-4 inhibitor is the preferred second component due to the safety and efficacy of these agents in combination with metformin. A GLP-1 agonist is given a higher priority than a DPP-4 inhibitor due to the greater effect on reducing postprandial glucose and potential for weight loss. • Triple therapy: o The following combinations are recommended for triple therapy in the following order: 1. Metformin + GLP-1 agonist + TZD 2. Metformin + DPP-4 inhibitor + TZD 3. Metformin + GLP-1 agonist + sulfonylurea

Clinical Guideline	Recommendation(s)
	4. Metformin + DPP-4 inhibitor + sulfonylurea 5. Metformin + TZD + sulfonylurea o Metformin is the cornerstone of triple therapy because of its safety and efficacy. o A GLP-1 agonist or a DPP-4 inhibitor is the preferred second component due to the lower risk of hypoglycemia with these agents. A GLP-1 agonist is given a higher priority than a DPP-4 inhibitor due to its greater effect on reducing postprandial glucose and potential for weight loss. • Insulin therapy: o Insulin therapy for patients with an A1C of 7.6% to 9.0% follows the same principles as outlined previously for patients with an A1C level of 6.5% to 7.5%. <u>Management of Patients With A1C Levels of >9.0%</u> • If the A1C is >9.0%, then the probability of reaching an A1C ≤6.5% is low. If the patient is asymptomatic, initiating a triple therapy regimen may be appropriate. If the patient is symptomatic, or therapy with medications has failed, it is appropriate to initiate insulin therapy, either with or without additional oral agents. Metformin is the most commonly used and safest medication to combine with insulin. • Combination therapy: o The following 8 combinations are considered: 1. Metformin + GLP-1 agonist 2. Metformin + GLP-1 agonist + sulfonylurea 3. Metformin + DPP-4 inhibitor 4. Metformin + DPP-4 inhibitor + sulfonylurea 5. Metformin + TZD 6. Metformin + TZD + sulfonylurea 7. Metformin + GLP-1 + TZD 8. Metformin + DPP-4 inhibitor + TZD o Metformin is the cornerstone of combination therapy because of its safety and efficacy. o A GLP-1 agonist or DPP-4 inhibitor may be added to metformin. It may be preferable to use a GLP-1 agonist due to its greater effect on reducing postprandial glucose and potential for weight loss. <u>Insulin Therapy</u> • Insulin therapy for patients with A1C levels exceeding 9.0% follows the same principles as outlined previously for patients with A1C values of ≤9.0%.
National Institute for Health and Clinical Excellence (NICE): **Type 2 Diabetes: Newer Agents[10]** **(2011)**	• Consider adding a DPP-4 inhibitor to metformin (as second-line therapy) instead of a sulfonylurea when blood glucose control is inadequate (A1C ≥6.5%) if the person is at risk of hypoglycemia, does not tolerate a sulfonylurea, or a sulfonylurea is contraindicated. • Consider adding a DPP-4 inhibitor to sulfonylurea (as second-line therapy) when control of blood glucose is inadequate (A1C ≥6.5%) if the person does not tolerate metformin or if metformin is contraindicated. • Consider adding a DPP-4 inhibitor as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose remains or becomes inadequate (A1C ≥7.5%) and insulin is unacceptable or inappropriate. • Only continue DPP-4 inhibitor therapy if the person has had a beneficial metabolic response (>0.5% reduction in A1C in 6 months). • A DPP-4 inhibitor may be preferable to a thiazolidinedione if:

Clinical Guideline	Recommendation(s)
	o Further weight gain would cause or exacerbate significant problems associated with a high body weight OR o A thiazolidinedione is contraindicated OR o The person has previously had a poor response to, or did not tolerate, a thiazolidinedione • There may be some individuals for whom either a DPP-4 inhibitor or a TZD may be suitable. The choice of treatment should be based on patient preference.
National Institute for Health and Clinical Excellence (NICE): **Type 2 Diabetes: National Clinical Guideline for Management in Primary and Secondary Care (Update)[12] (2008)**	• Metformin is recommended as first-line therapy for the treatment of type 2 diabetes. • Refer to the updated NICE recommendations for specific treatment recommendations using the DPP-4 inhibitors.[10]
International Diabetes Federation (IDF): **Global Guideline for Type 2 Diabetes[5] (2005)**	• Metformin is recommended as first-line therapy for the treatment of type 2 diabetes. • This guideline does not discuss the role of the DPP-4 inhibitors in the treatment of type 2 diabetes mellitus. • The DPP-4 inhibitors were approved by the FDA following the release of this guideline.

III. Indications

The Food and Drug Administration (FDA)-approved indications for linagliptin 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 Linagliptin[1-4]

Indication	Linagliptin†
Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	✔

†Linagliptin has not been studied in combination with insulin.

IV. Pharmacokinetics

The pharmacokinetic parameters of linagliptin are listed in Table 4.

Table 4. Pharmacokinetic Parameters of Linagliptin[1-4]

Generic Name	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Elimination (%)	Half-Life (hours)
Linagliptin	30	70-99	Limited	Renal (5-7) Bile (80)	>100

V. Drug Interactions

There are no significant drug interactions reported with linagliptin.[2] Use of alternative treatments is strongly recommended when linagliptin is to be administered with a P-glycoprotein or CYP3A4 inducer.

VI. Adverse Drug Events

The most common adverse drug events reported with linagliptin are listed in Table 5.

Table 5. Adverse Drug Events (%) Reported with the Linagliptin[1-4]

Adverse Events	Linagliptin
Central Nervous System	
Headache	6
Endocrine and Metabolic	
Hyperuricemia	3
Hypoglycemia	<1-15
Lipids increased	3
Triglycerides increased	2
Weight gain	2
Musculoskeletal	
Arthralgia	6
Back pain	6
Respiratory	
Cough	2
Nasopharyngitis	6
Other	
Angioedema	<1
Hypersensitivity	<1
Pancreatitis	<1

VII. Dosing and Administration

The usual dosing regimens for linagliptin are listed in Table 6.

Table 6. Usual Dosing Regimens for Linagliptin[1-4]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Linagliptin	Type 2 Diabetes Mellitus: 5 mg once daily	Safety and efficacy in children have not been established.	Tablet: 5 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of linagliptin are summarized in Table 7.

Table 7. Comparative Clinical Trials with Linagliptin

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Del Prato et al.[16] (2011) Linagliptin 5 mg QD vs placebo	RCT, DB, PC, MC Patients 18-80 years of age with type 2 diabetes who were treatment-naïve or who had received one oral antidiabetic drug	N=503 24 weeks	Primary: Change in A1C at week 24 Secondary: Percentage of patients achieving A1C <7% and A1C lowered by ≥0.5%, change from baseline in fasting plasma glucose (FPG), change in 2-hour postprandial glucose (2hPPG) from baseline	Primary: After 24 weeks, the adjusted mean change in A1C was -0.44% with linagliptin and 0.25% with placebo. The adjusted mean difference in the change in A1C was −0.69% (P<0.0001). The difference between linagliptin and placebo increased over time (−0.46% at 6 weeks to −0.69% at 24 weeks, all P<0.0001). Secondary: The percentage of patients who achieved A1C <7.0% after 24 weeks' treatment with linagliptin was 25.2% compared with 11.6% in the placebo group (P=0.0006). A total of 47.1% and 19.0% of patients receiving linagliptin and placebo, respectively, achieved an A1C reduction ≥0.5% at 24 weeks (P<0.0001). Treatment with linagliptin resulted in a greater reduction in FPG (−1.3 mmol/l; P<0.0001) and 2hPPG (−3.2 mmol/l; P<0.0001) compared to placebo. Hyperglycemia was the most frequently reported adverse event (22.8% with placebo and 8.6% with linagliptin). The most frequently reported adverse events that were more common with linagliptin than placebo were headache (2.7 vs 1.2%, respectively), hypertension (3.6 vs 1.2%, respectively) and back pain (2.7 vs 1.8%, respectively). A total of 5.1 and 3.6% of the linagliptin and placebo groups, respectively, experienced drug-related adverse events.
Forst et al.[15] (2010) <u>RCT</u> Linagliptin 1 to 10 mg QD added to	RCT, DB, MC, PC Patients 21 to 75 years of age with type 2 diabetes for ≥3 months who had	N=333 12 weeks	Primary: Change from baseline in A1C at week 12 Secondary:	Primary: After 12 weeks, the adjusted mean change in A1C was 0.24% with placebo, -0.14% with linagliptin 1 mg, -0.50% with linagliptin 5 mg, and -0.42% with linagliptin 10 mg. The mean placebo-corrected reductions in A1C at week 12 were -0.40% for linagliptin 1 mg (P=0.006), -0.73% for linagliptin 5 mg (P<0.001) and -0.67% for linagliptin 10 mg (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
existing metformin therapy vs placebo added to existing metformin therapy OL Glimepiride 1 to 3 mg QD added to existing metformin therapy	inadequate glycemic control with metformin alone (A1C 7.5-10%) or metformin and one other oral antidiabetic agent (A1C 7-9%)		Change from baseline in FPG, percentage of patients achieving A1C ≤7%, percentage of patients achieving A1C lowering ≥0.5%	After 12 weeks, the adjusted mean change in A1C was -0.68% with glimepiride and the mean placebo-corrected reduction in A1C was -0.90% (P<0.0001). Secondary: After 12 weeks, the adjusted mean change in FPG was 0.70 mmol/l with placebo, -0.36 mmol/l with linagliptin 1 mg, -1.22 mmol/l for linagliptin 5 mg, and -0.90 mmol/l with linagliptin 10 mg. The mean placebo-corrected FPG reductions were -1.1 mmol/l for linagliptin 1 mg (P=0.0020), -1.9 mmol/l for linagliptin 5 mg (P<0.0001), and -1.6 mmol/l for linagliptin 10 mg (P<0.0001). One patient (1.4%) in the placebo group achieved an A1C ≤7.0%. Ten patients (~15%) who received linagliptin 1 mg, 9 patients (~15%) who received linagliptin 5 mg and 14 patients (~21%) who received linagliptin 10 mg achieved an A1C ≤7%. Approximately 3% of the patients in the linagliptin 1- and 5-mg groups and 8% of the patients receiving linagliptin 10 mg achieved an A1C level ≤6.5%. A greater proportion of patients who received linagliptin (43.8% to 53.2%) showed reductions in A1C from baseline of ≥0.5% compared with placebo (12.9%). A1C declined by ≥1% in 27.4% and 22.7% of the patients treated with linagliptin 5 mg and 10 mg, respectively. In the placebo and linagliptin 1-mg groups, 7.1% and 14.1% of patients, respectively, showed A1C reductions of ≥1%. The proportion of patients reporting adverse events was similar across the linagliptin groups combined (44.2%), glimepiride (44.6%), and placebo (46.5%) groups. The most frequently reported adverse events were nasopharyngitis, diarrhea and nausea, which were similarly distributed across all treatments. There were no hypoglycemic events for linagliptin or placebo, whereas three patients (5%) receiving glimepiride experienced hypoglycemia.
Taskinen et al.[13] (2011)	RCT, DB, MC, PC Patients 18 to 80	N=701 24 weeks	Primary: Change from baseline in A1C at	Primary: After 24 weeks, the adjusted mean change in A1C was -0.49% with linagliptin compared to 0.15% with placebo (treatment difference,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Linagliptin 5 mg QD added to existing metformin therapy vs placebo added to existing metformin therapy	years of age with type 2 diabetes who were being treated with metformin ≥1,500 mg alone (A1C 7-10%) or metformin and one other oral antidiabetic agent (A1C 6.5-9%)		week 24 Secondary: Change from baseline in FPG and 2hPPG, change from baseline in A1C and FPG over time, percentage of patients achieving A1C ≤7% and 6.5%, percentage of patients achieving A1C lowering ≥0.5%	−0.64%; P<0.0001). The significant difference between treatments in mean A1C change increased over time from 6 weeks (−0.43%) to 18 weeks (−0.65%) and then remained stable until the end of the 24 weeks (−0.64%). Secondary: Treatment with linagliptin led to a significant reduction in adjusted mean FPG compared to placebo (−0.6 vs 0.6 mmol/l, respectively; P<0.0001). Treatment with linagliptin led to a significant reduction in the adjusted 2hPPG compared to placebo (-2.7 mmol/l vs +1.0 mmol/l, respectively; P<0.0001). The adjusted mean change in FPG decreased over time with linagliptin compared to an increase with placebo. The difference between treatments in adjusted mean change from baseline in FPG increased over time (−0.9 mmol/l to −1.2 mmol/l; all P<0.0001). A total of 26% of patients receiving linagliptin and 9% of patients receiving placebo group achieved an A1C level <7.0% at 24 weeks (P=0.0001). A total of 10% of patients receiving linagliptin and 2% of patients receiving placebo achieved an A1C level <6.5% P=0.0016). A total of 50% of patients receiving linagliptin and 22% of patients receiving placebo achieved a reduction in A1C ≥0.5% (P<0.0001). Linagliptin was well tolerated and there was no difference in adverse events among the treatment groups.
Haak et al.[18] (2012) Linagliptin 5 mg QD vs metformin 500 mg	RCT, DB, MC, PC Patients 18-80 years of age with type 2 diabetes who were treatment-naïve (A1C 7.5-11%) or who had received one other oral	N=791 24 weeks	Primary: Change from baseline in A1C at week 24 Secondary: Change from baseline in FPG, change from	Primary: After 24 weeks, the mean change in A1C was 0.1% with placebo, -0.5% with linagliptin 5 mg QD, -0.6% with metformin 500 mg BID, -1.1% with metformin 1,000 mg BID, -1.2% with linagliptin + metformin 500 mg, and -1.6% with linagliptin + metformin 1,000 mg. The adjusted placebo-corrected mean changes in A1C were −1.7% (95% CI, −2.0 to −1.4) for linagliptin + metformin 1,000 mg; −1.3% (95% CI. −1.6 to −1.1) for linagliptin + metformin 500 mg; −1.2% (95% CI, −1.5 to −0.9) for metformin 1,000 mg; −0.8% (95% CI, −1.0 to −0.5) for metformin 500 mg

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
BID vs metformin 1,000 mg BID vs linagliptin 2.5 mg BID and metformin 500 mg BID vs linagliptin 2.5 mg BID and metformin 1,000 mg BID vs placebo	antidiabetic drug (A1C 7-10.5%)		baseline in A1C and FPG over time, proportion of patients requiring rescue therapy after failing to achieve pre-specified glycemic targets or discontinuing because of lack of efficacy	and −0.6% (95% CI, −0.9 to −0.3) for linagliptin monotherapy (all, P<0.0001). The mean treatment differences for linagliptin + metformin 1,000 mg versus metformin and linagliptin monotherapy were−0.5% (95% CI, −0.7 to −0.3) and −1.1% (95% CI, −1.4 to −0.9), respectively. For linagliptin + metformin 500 mg, the respective mean differences were −0.6% (95% CI, −0.8 to −0.4) and−0.8% (95% CI, −1.0 to −0.6; all, P<0.0001). Secondary: The adjusted placebo-corrected mean changes in FPG from baseline were −3.3 mmol/l (95% CI, −4.0 to −2.6) and−2.4 mmol/l (95% CI, −3.1 to −1.7) in the linagliptin+ metformin 1,000 mg and linagliptin + metformin 500 mg groups, respectively. This is compared to −2.3 mmol/l (95% CI, −3.0 to −1.7), −1.4 mmol/l (95% CI, −2.1 to −0.8) and −1.0 mmol/l (95% CI, −1.7 to −0.3) in the metformin 1,000 mg, metformin 500 mg and linagliptin monotherapy groups, respectively (all, P<0.0001). The proportion of patients requiring rescue therapy for inadequate glycemic control at week 24 was lower in the combination therapy groups (linagliptin + metformin 1,000 mg, 4.3%; linagliptin + metformin 500 mg, 7.3%) than with either monotherapy alone (metformin 1,000 mg, 8.0%; metformin 500 mg, 13.5%; linagliptin, 11.1%). The proportion of patients reporting adverse events were comparable across the active treatment groups.
Gomis et al.[14] (2011) Linagliptin 5 mg QD and pioglitazone 30 mg QD vs placebo and pioglitazone 30 mg	RCT, DB, MC, PC Patients 18 to 80 years of age with type 2 diabetes who were drug-naïve or previously treated with oral antidiabetic agents who had insufficient glycemic control (A1C 7.5-11%)	N=389 24 weeks	Primary: Change from baseline in A1C at week 24 Secondary: Percentage of patients achieving A1C ≤7%, percentage of patients achieving A1C lowering	Primary: After 24 weeks, the adjusted mean change in A1C was -1.06% with linagliptin and pioglitazone compared to -0.56% for placebo plus pioglitazone (P<0.0001). Secondary: After 24 weeks, 42.9% of patients in the linagliptin and pioglitazone group achieved A1C <7.0% compared to 30.5% of patients in the placebo plus pioglitazone group (P=0.0051). A total of 75.0% of patients in the linagliptin and pioglitazone group and 50.8% of patients in the placebo and pioglitazone group achieved an A1C

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
QD			≥0.5%, change in FPG, change in A1C over time	reduction of ≥0.5% (P<0.0001). After 24 weeks, the adjusted mean change in FPG in the linagliptin and pioglitazone group was -1.8 mmol/l compared to -1.0 mmol/l for placebo plus pioglitazone (P<0.0001). Linagliptin plus pioglitazone produced a larger reduction in non-adjusted A1C over time than placebo plus pioglitazone (P<0.0001 at each visit). The proportion of patients that experienced at least one adverse event was similar in both groups (52.5% and 53.1% in the linagliptin plus pioglitazone and placebo plus pioglitazone groups, respectively).
Owens et al.[17] (2011) Linagliptin 5 mg QD added to existing metformin and sulfonylurea therapy vs placebo added to existing metformin and sulfonylurea therapy	RCT, DB, MC, PG Patients 18 to 80 years of age with type 2 diabetes and an A1C of 7-10% despite receiving metformin ≥1,500 mg and the maximum tolerated dose of a sulfonylurea	N=1,058 24 weeks	Primary: Change from baseline in A1C at week 24 Secondary: Percentage of patients achieving A1C <6.5% or <7.0%, percentage of patients achieving A1C lowering ≥0.5%, and change in FPG	Primary: After 24 weeks, the adjusted mean change in A1C was greater with linagliptin (-0.72%) than with placebo (-0.10%; P<0.0001). Secondary: Among patients with an A1C ≥7% at baseline, 29.2% of those receiving linagliptin and 8.1% of those receiving placebo achieved an A1C level <7.0% (P<0.0001). Of those with an initial A1C level of 7.0% to <8.0%, 46.3% on linagliptin and 14.4% on placebo achieved an A1C level of <7%. This was also achieved by a greater proportion of patients on linagliptin vs placebo with a baseline A1C level of 8.0% to <9.0%, 22.2% vs 4.2%, respectively, and those with baseline A1C >9.0%, 5.9% vs 2.1%, respectively. The proportion of patients achieving a reduction in A1C of ≥0.5% was 58.2% with linagliptin and 30.2% with placebo. The proportion of patients achieving a reduction in A1C of ≥1% was 32.5% with linagliptin and 11.5% with placebo. The adjusted mean change in FPG was greater with linagliptin than placebo (placebo-corrected adjusted mean change from baseline at week 24: -0.7 mmol/l; P<0.0001). Overall, 66.3% of the linagliptin group and 59.7% of the placebo group experienced adverse events. A total of 17.9% of patients receiving

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				linagliptin experienced a drug-related adverse event compared to 11.4% of patients receiving placebo.
Monami et al.[19] (2011) Linagliptin, alogliptin, sitagliptin, saxagliptin, vildagliptin vs placebo or active comparator (oral hypoglycemic agents and/or insulin)	MA Patients with type 2 diabetes who were receiving a DPP-4 inhibitor	N=33,881 (53 trials) ≥24 weeks	Primary: Incidence of cancer Secondary: Incidence of pancreatitis, all-cause and cardiovascular mortality, and incidence of major cardiovascular events (MACE)	Primary: There were 176 cases of cancer (107 and 69 in patients treated with DPP-4 inhibitors and comparators, respectively); 12.5% were gastrointestinal, 5.7% were pancreatic, 6.2% were pulmonary, 14.7% were mammary gland/female genital tract, 11.3% were male urogenital tract, 3.4% were thyroid and 26.1% were of another origin. There was no difference in the proportion of cases between patients treated with a DPP-4 inhibitor or a comparator (P=0.90). Secondary: The risk of pancreatitis with DPP-4 inhibitors was 0.786 (P=0.55). The number of reported deaths was 28 and 31 with DPP-4 inhibitors and comparators, respectively. Cardiovascular deaths occurred in 10 patients receiving DPP-4 inhibitors and 20 patients receiving comparators. The risk for all-cause death and cardiovascular death in patients treated with a DPP-4 inhibitor was 0.668 (P=0.149 and P=0.054, respectively). There were 137 and 120 MACE events reported with DPP-4 inhibitors and comparators, respectively. DPP-4 inhibitors were associated with a significantly lower risk of MACE (MH-OR 0.689; P=0.006).

Drug regimen abbreviations: BID=twice daily, QD=once daily
Study abbreviations: DB=double-blind, MA=meta-analysis, MC=multicenter, OL=open-label, PC=placebo-controlled, RCT=randomized controlled trial
Miscellaneous abbreviations: A1C=glycosylated hemoglobin A1c, FPG=fasting plasma glucose, PPG=postprandial glucose

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 8. Relative Cost of Linagliptin

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Linagliptin	tablet	Tradjenta®	$$$$$	N/A

N/A=Not available

X. Conclusions

Linagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor, which was approved by the FDA in May 2011. It is approved as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.[1] Linagliptin is not currently available in a generic formulation.

There are several guidelines that provide recommendations regarding the treatment of type 2 diabetes. According to the ADA/EASD treatment algorithm, metformin is recommended as first-line therapy.[7] If monotherapy does not achieve A1C goals, a second agent should be combined with metformin. The choice of therapy should be based on patient preference, drug characteristics and adverse events. According to the AACE/ACE algorithm, metformin, thiazolidinediones, DPP-4 inhibitors and alpha-glucosidase inhibitors are all appropriate for use as monotherapy in patients with an A1C between 6.5% and 7.5% due to their minimal risk of hypoglycemia.[8] However, the guidelines state that metformin is the cornerstone of therapy in this A1C range due to its safety and efficacy. An incretin mimetic or a DPP-4 inhibitor is the preferred second agent to use in combination with metformin (regardless of the A1C range); however, the incretin mimetics are given a higher priority than DPP-4

inhibitors due to their greater effect on reducing postprandial glucose and potential for weight loss. Other guidelines do not address the use of the DPP-4 inhibitors or recommend them as a second- or third-line treatment option.[10-12] The available guidelines do not give preference to one particular DPP-4 inhibitor over another.

Linagliptin has been evaluated in several clinical trials as monotherapy, as well as in combination with metformin, sulfonylureas, and pioglitazone; however, it has not been studied in combination with insulin.[1,13-18] Monotherapy with linagliptin decreased the mean A1C by 0.4% to 0.5%.[16,18] When linagliptin was added on to metformin, the mean reduction in A1C ranged from 0.4% to 0.5%.[13,15] The mean decrease in A1C was 0.72% when linagliptin was added as a third agent to existing metformin and sulfonylurea therapy.[17] Initial combination therapy with linagliptin and metformin lowered the A1C 1.2% to 1.6%.[18] When used as initial therapy in combination with pioglitazone, the mean decrease in A1C was 1.06%.[14] There were no studies found in the medical literature that directly compared linagliptin to other DPP-4 inhibitors. There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with linagliptin or any other antidiabetic drug.[1]

Hypoglycemia was reported more frequently in patients receiving the combination of linagliptin and a sulfonylurea compared with those receiving the combination of placebo and sulfonylurea.[1] Hypersensitivity reactions have been reported with linagliptin and other DPP-4 inhibitors. Pancreatitis was reported more often in patients treated with linagliptin.

At this time, there is insufficient evidence to conclude that linagliptin offers a significant clinical advantage over other alternatives in general use. It should be available as adjunctive therapy through the medical justification portion of the prior authorization process.

XI. Recommendations

No brand linagliptin 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

1. Tradjenta® [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; May 2012.
2. Drug Facts and Comparisons. Drug Facts and Comparisons 4.0 [online]. 2012. Available from Wolters Kluwer Health, Inc. Accessed May 2012.
3. Lexi-Comp Online, Lexi-Drugs Online, Hudson, Ohio: Lexi-Comp, Inc.; 2012; May 2012.
4. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed May 2012.
5. IDF Clinical Guidelines Task Force. Global guideline for type 2 diabetes. Brussels: International Diabetes Federation, 2005. Available at: http://www.idf.org/webdata/docs/IDF%20GGT2D.pdf. Accessed May 2012.
6. American Diabetes Association. Position Statement: Standards of Medical Care in Diabetes—2012. Diabetes Care 2012;35:S11-S63.
7. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach: Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2012; Apr 19. [Epub ahead of print]
8. Rodbard, H, Jellinger, P, Davidson, J, et al. American Association of Clinical Endocrinologists/American College of Endocrinology consensus panel on type 2 diabetes mellitus: an algorithm for glycemic control. Endocrine Pract 2009;15:540-559.
9. Handelsman Y, Mechanick JI, Blonde L, et al.; AACE Task Force for Developing a Diabetes Comprehensive Care Plan. American Association of Clinical Endocrinologists Medical Guidelines for clinical practice for developing a diabetes mellitus comprehensive care plan: executive summary. Endocr Pract 2011;17:287-302.
10. National Institute for Health and Clinical Excellence Type 2 diabetes: newer agents for blood glucose control in type 2 diabetes. August 2011. Available at: www.nice.org.uk/CG87ShortGuideline. Accessed May 2012.
11. Institute for Clinical Systems Improvement (ICSI). Diagnosis and management of type 2 diabetes mellitus in adults. April 2012. Available at: http://www.icsi.org/diabetes_mellitus__type_2/management_of_type_2_diabetes_mellitus__9.html. Accessed May 2012.
12. National Collaborating Centre for Chronic Conditions. Type 2 diabetes: national clinical guideline for management in primary and secondary care (update). London: Royal College of Physicians, 2008. Available at: http://www.nice.org.uk/nicemedia/pdf/CG66FullGuideline0509.pdf. Accessed May 2012.
13. Taskinen MR, Rosenstock J, Tamminen I, et al. Safety and efficacy of linagliptin as add-on therapy to metformin in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled study. Diabetes Obes Metab 2011;13:65-74.
14. Gomis R, Espadero RM, Jones R, et al. Efficacy and safety of initial combination therapy with linagliptin and pioglitazone in patients with inadequately controlled type 2 diabetes: a randomized, double-blind, placebo-controlled study. Diabetes Obes Metab 2011;13:653-61.
15. Forst T, Uhlig-Laske B, Ring A, et al. Linagliptin (B1 1356), a potent and selective DPP-4 inhibitor, is safe and efficacious in combination with metformin in patients with inadequately controlled Type 2 diabetes. Diabet Med 2010;27:1409-19.
16. Del Prato S, Barnett AH, Huisman H, et al. Effect of linagliptin monotherapy on glycemic control and markers of β-cell function in patients with inadequately controlled type 2 diabetes: a randomized controlled trial. Diabetes Obes Metab 2011;13:258-67.
17. Owens DR, Swallow R, Dugi KA, et al. Efficacy and safety of linagliptin in persons with type 2 diabetes inadequately controlled by a combination of metformin and sulfonylurea: a 24-week randomized study. Diabet Med 2011;28:1352-61.
18. Haak T, Meinicke T, Jones R, et al. Initial combination of linagliptin and metformin improves glycaemic control in type 2 diabetes: a randomized, double-blind, placebo-controlled study. Diabetes Obes Metab 2012;14:565-74.
19. Monami M, Dicembrini I, Martelli D, et al. Safety of dipeptidyl peptidase-4 inhibitors: a meta-analysis of randomized clinical trials. Curr Med Res Opin 2011;27 Suppl 3:57-64.