Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Clinical Packet
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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
February 10, 2010

I. Overview

Alzheimer's disease is a progressive neurodegenerative disorder in older adults that affects cognition, behavior and activities of daily living.[1] 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.[1-3] Diagnostic features include memory impairment and one or more of the following: aphasia, apraxia, agnosia, and/or disturbance in executive functioning.[1]

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

There are 5 agents approved for the treatment of Alzheimer's disease, including cholinesterase inhibitors (donepezil, galantamine, rivastigmine and tacrine) and an NMDA receptor antagonist (memantine). Although none of these 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.[8-11] Memantine blocks NMDA receptors and inhibits their overstimulation by glutamate.[12]

The Alzheimer's agents that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Galantamine is the only agent that is available in a generic formulation. This class was last reviewed in November 2007.

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®	Aricept®, Aricept ODT®
Galantamine	extended-release capsule, solution, tablet	Razadyne®*, Razadyne ER®*	galantamine
Rivastigmine	capsule, solution, transdermal patch	Exelon®	none
Tacrine	capsule	Cognex®	none
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)and 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. For example, when the benefits and harms related to a drug are being evaluated, the severe side effects associated with tacrine make it an unreasonable choice.
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 (donepezil, galantamine, or rivastigmine) should be considered at the time of diagnosis, taking into account expected therapeutic benefits and potential safety issues. • In patients with moderate to severe AD, treatment with memantine can be considered, alone or in combination with a cholinesterase inhibitor, taking into account expected therapeutic benefits and potential safety issues. • 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.

Clinical Guideline	Recommendation(s)
	• Results of the numerous large placebo-controlled trials of individual cholinesterase inhibitors have suggested similar degrees of efficacy, although tolerability may differ among the medications. Currently available data do not allow a fair, unbiased direct comparison among the cholinesterase inhibitors. There is also no data on whether or how to switch from one cholinesterase inhibitor to another. • Reversible, direct medication-induced hepatotoxicity with hepatocellular injury is a unique property of tacrine. Because of this hepatotoxicity, tacrine is very uncommonly used. Hepatotoxicity has not been associated with donepezil, rivastigmine, or galantamine. • Donepezil, rivastigmine and galantamine are preferred over tacrine because of reversible hepatic toxicity and the requirement that it be given 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**	• For patients with Parkinson's disease (PD) dementia or dementia with Lewy bodies (DLB), rivastigmine is probably effective in improving

Clinical Guideline	Recommendation(s)
Parameter: Evaluation and Treatment of Depression, Psychosis, and Dementia in Parkinson Disease[39] (2006)	cognitive function. However, the magnitude of the benefit is modest and tremor may be exacerbated. Rivastigmine should be considered for the treatment of dementia in PD or DLB. • 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[5-12]

Indication	Parasympathomimetic (Cholinergic) Agents				Central Nervous System Agents, Miscellaneous
	Donepezil	Galantamine	Rivastigmine	Tacrine	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[5-12]

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	90-100	18	Liver (75)	Renal (20) Feces (5)	7
Rivastigmine	Oral: 36-72	40	Liver, extensive Brain, extensive	Renal (>90)	Oral: 1.4-1.7 Transdermal: 3
Tacrine	2.4-36	55	Liver, extensive	Not reported	2-4
Central Nervous System Agents, Miscellaneous					
Memantine	100	45	Liver, partial	Renal (48-50)	60-80

V. Drug Interactions

Significant drug interactions with the Alzheimer's agents are listed in Table 5.

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

Generic Name(s)	Significance Level	Interaction	Mechanism
Tacrine	2	Fluvoxamine	Fluvoxamine may inhibit tacrine metabolism (CYP1A2) resulting in elevated tacrine concentrations and increased pharmacologic and adverse effects of tacrine.

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

VI. Adverse Drug Events

The most common adverse drug events reported with the Alzheimer's agents are listed in Table 6. The use of tacrine is commonly associated with elevations in serum aminotransferase levels, some to levels ordinarily considered to indicate clinically important hepatic injury.[11] Based on data from clinical trials, approximately 50% of patients treated with tacrine can be expected to have at least one ALT/SGPT level above the upper limit of normal; approximately 25% of patients are likely to develop elevations greater than 3 times the upper limit of normal, and about 7% of patients may develop elevations greater than 10 times the upper limit of normal.[11] Serum transaminase levels should be monitored every other week from at least week 4 to week 16 following initiation of treatment, after which monitoring may be decreased to every 3 months.[11]

Table 6. Adverse Drug Events (%) Reported with the Alzheimer's Agents[5-12]

Adverse Events	Parasympathomimetic (Cholinergic) Agents				Central Nervous System Agents, Miscellaneous
	Donepezil	Galantamine	Rivastigmine	Tacrine	Memantine
Cardiovascular					
Angina pectoris	-	-	≥1	-	-
Atrial fibrillation	≥1	-	≥1	-	-
Bradycardia	≥1	2	≥1	-	-
Chest pain	1-2	≥1	≥1	4	-
Electrocardiogram abnormal	≥1	-	-	-	-
Heart failure	≥1	-	≥1	-	≥1
Hemorrhage	2	-	-	-	-
Hot flashes	≥1	-	≥1	-	-
Hypertension	1-3	-	3	≥1	4
Hypotension	≥1	-	≥1	≥1	-
Myocardial infarction	-	-	≥1	-	-
Palpitation	-	-	≥1	-	-
Postural hypotension	-	-	≥1	-	-
Syncope	2	2	3	≥1	≥1
Vasodilation	≥1	-	-	-	-
Central Nervous System					
Abnormal crying	≥1	-	-	-	-
Abnormal dreams	3	-	-	-	-
Abnormal thinking	-	-	-	3	-
Aggression	≥1	-	3	-	≥1
Agitation	≥1	-	≥1	7	≥2
Anxiety	≥1	-	4-5; 3*	3	≥2
Aphasia	≥1	-	-	-	-
Bradykinesia	-	-	≥1	-	-

Adverse Events	Parasympathomimetic (Cholinergic) Agents				Central Nervous System Agents, Miscellaneous
	Donepezil	Galantamine	Rivastigmine	Tacrine	Memantine
Cerebrovascular accident	-	-	-	-	≥1
Confusion	2	-	1-8	7	6
Convulsion	≥1	-	≥1	≥1	-
Delusions	≥1	-	-	-	-
Depression	2-3	7	1-6; 4*	4	≥2
Dizziness	2-8	9	6-21; 2-7*	12	7
Dyskinesia	-	-	≥1	-	-
Emotional lability	2	-	-	-	-
Fatigue	5	5	4-9; 2*	4	2
Gait abnormality	≥1	-	≥1	-	≥2
Hallucination	3	-	4	2	3
Headache	4-10	8	17; 3-4*	11	6
Hostility	3	-	-	2	-
Hyperkinesia	-	-	-	≥1	-
Hypokinesia	-	-	-	-	≥1
Insomnia	5-9	5	3-9; 1-4*	6	≥2
Irritability	≥1	-	-	-	-
Libido increased	≥1	-	-	-	-
Malaise	-	≥1	5	≥1	-
Nervousness	1-3	-	-	≥1	-
Paranoid reaction	-	-	≥1	-	-
Paresthesia	≥1	-	≥1	≥1	-
Parkinson's disease worsening	-	-	3	-	-
Parkinsonism	-	-	2	-	-
Personality disorder	2	-	-	-	-
Restlessness	≥1	-	≥1	-	-
Somnolence	2	4	4-5	4	3
Transient ischemic attack	-	-	≥1	-	≥1
Tremor	≥1	3	4-10; ≥1*	2	-
Vertigo	≥1	-	≥1; 0-2*	≥1	≥1
Wandering	≥1	-	-	-	-
Dermatological					
Diaphoresis	≥1	-	-	≥1	-
Eczema	3	-	-	-	-
Facial/skin flushing	-	-	-	3	-
Pruritus	≥1	-	≥1*	-	-
Rash	≥1	-	≥1	7	≥1
Skin ulcer	≥1	-	-	-	-
Urticaria	≥1	-	-	-	-
Endocrine and Metabolic					
Dehydration	1-2	-	1-2; ≥1*	-	-
Edema	≥1	-	≥1	-	-
Hyperlipemia	2	-	-	-	-
Hypokalemia	-	-	≥1	-	-
Peripheral edema	≥1	-	-	≥1	≥2
Weight decrease	1-3	5-7	3; 3-8*	3	≥1
Gastrointestinal					
Abdominal pain	≥1	5	4-13; 2-4*	8	-
Anorexia	4-8	7-9	6-17; 3-9*	9	≥2
Bloating	≥1	-	-	-	-
Constipation	≥1	-	5; ≥1*	4	5
Diarrhea	10	6-12	7-19; 6-10*	16	≥2
Dyspepsia	≥1	5	1-9	9	-

Adverse Events	Parasympathomimetic (Cholinergic) Agents				Central Nervous System Agents, Miscellaneous
	Donepezil	Galantamine	Rivastigmine	Tacrine	Memantine
Epigastric pain	≥1	-	-	-	-
Fecal incontinence	≥1	-	≥1	-	-
Flatulence	-	≥1	4	4	-
Gastritis	-	-	≥1; ≥1*	-	-
Gastroenteritis	≥1	-	-	-	-
Gastrointestinal bleeding	≥1	-	-	-	-
Nausea	6-11	13-24	29-47; 7-21*	28	≥2
Vomiting	5-8	6-13	17-31; 6-19*	28	3
Genitourinary					
Cystitis	≥1	-	-	-	-
Frequent urination	2	-	-	3	≥1
Hematuria	≥1	3	≥1	-	-
Urinary incontinence	2	≥1	≥1*	3	≥2
Urinary tract infection	≥1	8	7; 2*	3	≥2
Hematologic					
Anemia	≥1	3	≥1; ≥1*	-	≥1
Ecchymosis	4-5	-	-	-	-
Epistaxis	-	-	≥1	-	-
Purpura	-	-	-	2	-
Laboratory Test Abnormalities					
Elevated alkaline phosphatase	≥1	-	-	-	≥1
Elevated creatinine	3	-	-	-	-
Elevated LDH	≥1	-	-	-	-
Elevated transaminases	-	-	-	29	-
Musculoskeletal					
Asthenia	≥1	≥1	2-6; 2-3*	2	-
Arthralgia	-	-	-	≥1	≥2
Arthritis	1-2	-	≥1	≥1	-
Ataxia	≥1	-	≥1	6	≥1
Back pain	3	-	≥1	2	3
Bone fracture	≥1	-	-	≥1	-
Leg cramps	-	-	≥1	-	-
Muscle cramps	6	-	-	-	-
Myalgia	-	-	≥1	9	-
Ocular					
Blurred vision	≥1	-	-	-	-
Cataract	≥1	-	≥1	-	≥1
Conjunctivitis	-	-	-	≥1	≥1
Eye irritation	≥1	-	-	-	-
Respiratory					
Bronchitis	≥1	-	-	≥1	≥2
Cough increased	≥1	-	-	3	4
Dyspnea	≥1	-	≥1	≥1	2
Pharyngitis	≥1	-	-	≥1	-
Pneumonia	≥1	-	≥1*	≥1	≥1
Respiratory tract infection	-	-	-	3	≥2
Rhinitis	-	4	4	8	-
Sinusitis	-	-	-	≥1	-
Other					
Accident	7-13	-	-	-	-
Accidental trauma	-	-	1-10	-	-
Allergy	-	-	≥1	-	-
Chills	-	-	-	≥1	-

Adverse Events	Parasympathomimetic (Cholinergic) Agents				Central Nervous System Agents, Miscellaneous
	Donepezil	Galantamine	Rivastigmine	Tacrine	Memantine
Fall	-	-	≥1*	-	≥2
Fever	2	≥1	≥1	≥1	-
Flu syndrome	≥1	-	3	-	≥2
Infection	1-11	-	-	-	-
Inflicted injury	-	-	-	-	≥2
Influenza	≥1	-	-	-	-
Pain	3-9	-	-	-	3
Tinnitus	-	-	≥1	-	-

*Transdermal patch
✔ Percent not specified
- Event not reported

VII. Dosing and Administration

The usual dosing regimens for the Alzheimer's agents are listed in Table 7.

Table 7. Usual Dosing Regimens for the Alzheimer's Agents[5-12]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Parasympathomimetic (Cholinergic) Agents			
Donepezil	Mild-to-moderate Dementia (Alzheimer's Type): Initial: 5 mg once daily at bedtime Maintenance: 5-10 mg once daily at bedtime Severe Dementia (Alzheimer's Type): Initial: 5 mg once daily at bedtime Maintenance: 10 mg once daily at bedtime	Safety and efficacy in children have not been established.	Orally disintegrating tablet: 5 mg 10 mg Tablet: 5 mg 10 mg
Galantamine	Mild-to-Moderate Dementia (Alzheimer's Type): Initial (IR): 8 mg/day administered twice daily Maintenance (IR): 16-24 mg/day administered twice daily Initial (ER): 8 mg/day administered once daily in the morning Maintenance (ER): 16-24 mg/day administered once daily in the morning	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 Dementia (Alzheimer's Type): Oral: Initial: 1.5 mg twice daily Maintenance: 6-12 mg/day administered 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:

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Mild-to-Moderate Dementia Associated with Parkinson's Disease: Oral Initial: 1.5 mg twice daily Maintenance: 3-12 mg/day administered twice daily Transdermal patch: Initial: 4.6 mg/24 hours Maintenance: 9.5 mg/24 hours		4.6 mg/24 hours 9.5 mg/24 hours
Tacrine	Mild-to-Moderate Dementia (Alzheimer's Type): Initial: 40 mg/day administered four times daily between meals Maintenance: 80-160 mg/day administered four times daily between meals	Safety and efficacy in children have not been established.	Capsule: 10 mg 20 mg 30 mg 40 mg
Central Nervous System Agents, Miscellaneous			
Memantine	Moderate-to-Severe Dementia (Alzheimer's type): Initial: 5 mg/day administered once daily Maintenance: 20 mg/day administered twice daily	Safety and efficacy in children have not been established.	Solution: 10 mg/5 mL Tablet: 5 mg 5-10 mg dose pack 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 8.

Table 8. 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 Study was a follow-up of patients enrolled in three RCT and two OL trials	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.
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 donepezil.
Winblad et al.[24] (2006)	DB, OL, PC	N=286	Primary: GBS	Primary: The GBS total scores indicate that both the continuous-treatment group

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
RCT Donepezil 10 mg/day vs placebo OL Donepezil 5 mg daily for 28 days, then 10 mg/day per clinician's judgment	Patients 40 to 90 years of age with a probable or possible diagnosis of Alzheimer's disease	52-week RCT with a 2-year open-label extension phase	Secondary: MMSE, GDS, PDS, NPI	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.
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 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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The IADL change from baseline at 6 months was 1.01, at 12 months 2.19, and at 36 months 6.18.
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.
Burns et al.[50] (2007) Donepezil 5-10 mg/day Study was a continuation of a 24-week RCT trial	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-

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				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.
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)	DB, MC, PC, RCT	N=343	Primary: SIB and CIBIC-	Primary: Donepezil was more efficacious when compared to placebo on SIB score

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Donepezil 10 mg/day vs placebo	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)	24 weeks	Plus Secondary: ADCS-ADL-sev, NPI, MMSE, CBQ, RUSP	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 vs placebo	RCT, MC, DB, PG, PC 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=302 24 weeks	Primary: SIB and CIBIC-Plus Secondary: ADCS-ADL-sev and BEHAVE-AD	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. 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).

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				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).
Homma et al.[80] (2009) Donepezil 10 mg/day Study was a continuation of a 24-week RCT trial (Homma et al.[61])	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,

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				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.
Birks et al.[21] (2006) Donepezil 5-10 mg/day vs placebo	MA Patients with Alzheimer's disease	N=5,796 (24 RCT) 12-60 weeks	Primary: ADAS-Cog, MMSE, CIBIC-Plus, ADL, withdrawals and adverse events	Primary: A significant difference was seen on the ADAS-Cog scale for patients treated with donepezil 5 mg at 24 weeks (WMD -2.02 points, 95% CI: -2.77 to -1.26, P<0.00001) and 10 mg at 24 weeks (WMD –2.81 points, 95% CI: –3.55 to –2.06, P<0.00001). A significant difference was seen on the MMSE for patients treated with donepezil 10 mg/day as compared to placebo at 52 weeks (WMD 1.84 points, 95% CI: 0.53 to 3.15, P=0.006). Global Clinical State, CIBIC-Plus scores showed significant benefit in patients treated with donepezil 5 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.
Wilcock et al.[51] (2003) Donepezil 10 mg/day	MC, PG, RCT Patients with Alzheimer's disease	N=182 52 weeks	Primary: BrADL Secondary: MMSE, ADAS-Cog, NPI	Primary: BrADL total score showed no significant difference between treatment groups in mean change from baseline to week 52. Secondary: Galantamine patients' scores on the MMSE at week 52 did not differ

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs galantamine 24 mg/day				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 galantamine 16-24	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 subjects). Discontinuation due to adverse effects was lower in those patients on donepezil (3%) vs rivastigmine (17%; P=0.01) and vs galantamine (21%; P=0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/day vs rivastigmine 6-12 mg/day				
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
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.
Birks et al.[59] (2006) Donepezil 10 mg/day, galantamine 24 mg/day, or rivastigmine 6-12 mg/day 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). 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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). No significant difference between treatment groups for serious adverse events was noted.
Raskind et al.[29] (2004)	OL Patients with mild-	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Galantamine 12 mg twice daily	to-moderate Alzheimer's disease			smaller cognitive decline (approximately 50%) than that predicted for the placebo group. Patients discontinuing galantamine therapy before 36 months had declined at a similar rate before discontinuation as those completing 36 months of treatment. Almost 80% of patients who received galantamine for 36 months seemed to demonstrate cognitive benefits compared with those predicted for untreated patients.
Rockwood et al.[41] (2008) Galantamine 12 mg twice daily Study was a continuation of a 36-month OL trial (Raskind et al.[29])	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).
Cummings et al.[30] (2004) Galantamine 8, 16, or 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				caregiver distress.
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.
Dunbar et al.[33] (2006) Galantamine IR 8-16 or 24 mg/day vs galantamine ER 8-16 or 24 mg/day vs placebo	Post-hoc analysis, DB, MC, PC, RCT 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.
Loy et al.[31] (2006)	MA	N=6,805 (10 RCT)	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.
Brodaty et al.[34] (2005) Galantamine IR 8-16 or 24 mg/day vs galantamine ER 8-16 or 24 mg/day vs placebo	AC, DB, MC, PC, PG, 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). 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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.
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. 70% of PP patients had an increased score at the 6-month assessment as compared to baseline with an overall 91% response rate. 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.
Burns et al.[70] (2009) Galantamine 12 mg twice daily 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				In the LOCF analysis, the mean SIB score in the galantamine group increased to 69.3 points. In the placebo group, the mean SIB score decreased by 3.2 points. The between-group least squares mean difference was 5.02 points (95% CI 2.17 to 7.86; P=0.0006). In the LOCF analysis, the mean total seven-item MDS-ADL self-performance score in the galantamine group worsened at endpoint to 13.1 points and to 14.0 points in the placebo group. Changes from baseline in the seven-item MDS-ADL self-performance score were 1.3 points and 1.7 points, respectively. The between-group least squares mean difference was –0.50 (95% CI, –1.39 to 0.39; P=0.394). Significant between-group differences were seen in the galantamine group for memory (P=0.006), praxis (P=0.010), and visuospatial ability (P=0.002). There were no significant differences in language (P=0.064) or attention (P=0.075). Scores for all eleven-item MDS-ADL self-performance subscales worsened in both treatment arms. The deterioration in the subscale score for locomotion on unit was significantly less in the galantamine group (P=0.021). During the study, 88% of patients who received galantamine and 89% who received placebo had at least one adverse event. The most common adverse events in both treatment groups were urinary tract infections, vomiting, diarrhea, nausea, and falls.
Bakchine et al.[81] (2007) Memantine 20 mg/day vs placebo	RCT, DB, PC, MC Patients ≥50 years of age with mild-to-moderate Alzheimer's disease (MMSE score 11-23)	N=470 24 weeks	Primary: ADAS-cog total score and CIBIC-Plus Secondary: NPI and ADCS-ADL_{23}	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 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;

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				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.
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 plus placebo	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).

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vs donepezil plus placebo				Patients receiving memantine showed significantly less cognitive decline in SIB scores compared to patients receiving placebo. Therapy with memantine-donepezil resulted in sustained cognitive performance above baseline compared 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 plus placebo	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).
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).

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Winblad et al.[37] (2007) Memantine 20 mg/day vs placebo	MA Patients with moderate-to-severe Alzheimer's disease	N=1,826 (4 RCT) 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 placebo	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).
Winblad et al.[36] (1999) Memantine 10 mg/day vs placebo	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 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.
McShane et al.[62] (2006)	MA Patients with mild-	N=3,731 (15 RCT)	Primary: CIBIC-Plus, SIB, ADAS-Cog,	Primary: Significant improvement at 6 months was seen for patients with mild-to-moderate dementia treated with memantine on the ADAS-Cog scale

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Memantine 10-30 mg/day vs placebo	to-moderate or moderate-to-severe Alzheimer's disease; patients with mild-to-moderate vascular dementia	Variable duration	ADCS-ADL, NPI	(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 subjects with milder AD.
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).

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				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).
Winblad et al.[43] (2007) Rivastigmine patch 9.5 mg/24 hours vs rivastigmine patch 17.4 mg/24 hours vs rivastigmine capsules 12 mg/day vs placebo	RCT, DB, DD, MC, PG 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-drawing Test, Trail Making Test Part A	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 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).
Grossberg et al.[72] (2009) Rivastigmine patch 9.5 mg/24 hours to 17.4 mg/24 hours Study was a continuation of a	OL Patients 50-85 years of age with Alzheimer's disease (MMSE scores 10-20)	N=870 28 weeks (weeks 25-52 of open-label extension)	Primary: Safety and tolerability Secondary: ADAS-cog	Primary: During the first 4 weeks of the open-label extension, patients formerly randomized to rivastigmine treatment (capsule or patch) reported fewer 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
24-week RCT trial (Winblad et al.[43])				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).
Winblad et al.[44] (2007) Rivastigmine patch 9.5 mg/24 hours	RCT, PC Patients 50-85 years of age with Alzheimer's disease (MMSE scores 10-	N=1,195 24 weeks	Primary: ADAS-Cog subscale, ADCS-CGIC	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).

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vs rivastigmine patch 17.4 mg/24 hours vs rivastigmine 6 mg capsules twice daily vs placebo	20)		Secondary: ADCS-ADL, MMSE, NPI, Ten Point Clock-drawing Test, and Trail-making Test part A	Secondary: All rivastigmine groups (patch and capsule) showed statistically significant benefits over placebo on the ADCS-ADL, MMSE and Trail-making Test part A (all P<0.05 vs placebo). Statistically significant treatment effects were not attained on the NPI or Ten Point Clock-drawing Test.
Blesa et al.[45] (2007) Rivastigmine patch 9.5 mg/24 hours vs rivastigmine patch 17.4 mg/24 hours vs rivastigmine 6 mg capsules twice daily vs placebo	RCT, DB, PC Active controls included different size rivastigmine patches and rivastigmine capsules, caregiver preference based on data generated during the IDEAL trial (Winblad et al.)	N=1,059 24 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).
Dantoine et al.[47] (2006)	MC, OL Patients ≥50 years	N=202 <u>Phase 1</u>	Primary: MMSE	Primary: Based on MMSE scores, 46.3% of patients improved or stabilized on rivastigmine monotherapy at the end of Phase 1.

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Rivastigmine 3-12 mg/day Addition of memantine 5-20 mg/day was allowed for non-responders of rivastigmine at the end of week 16	of age with probable Alzheimer's disease (MMSE scores <18 or GDS scores >4), previously treated for at least 6 months with donepezil 5-10mg/day or galantamine 16-24mg/day and considered not stabilized	16 weeks of rivastigmine monotherapy Phase 2 12 weeks of rivastigmine plus memantine	Secondary: MMSE, Mini-Zarit inventory, NPI, Ten-point Clock-drawing Test, D-KEFS verbal fluency test, CGI-C	For those patients previously on donepezil or galantamine, responder rates were also similar (46.6% and 46.4%). At the end of Phase 2 with combination therapy of rivastigmine and memantine, according to MMSE scores, 77.9% of patients improved or stabilized. Patients switching to combination therapy from galantamine responded more significantly than those who switched from donepezil (84.2% vs 72.3%; P=0.047). Secondary: According to CGI-C data, no change or improvement was seen in 76.5% of patients who completed the study at the end of Phase 1. For the 82.6% who worsened from baseline at the end of Phase 1, 81.4% improved or had no change at the end of Phase 2 with the addition of memantine on the CGI-C. At the end of Phase 1, MMSE and NPI showed significant improvements (P<0.001 and P<0.05, respectively) while there was no change from baseline for Ten-point Clock-drawing Test and D-KEFS verbal fluency test scores and the Mini-Zarit interview. At the end of Phase 2, D-KEFS verbal fluency test, Mini-Zarit, and especially MMSE scores showed significant improvement (P<0.05, P<0.001, and P<0.001, respectively).
Birks et al.[85] (2009) Rivastigmine (1-4 mg/day and 6-12 mg/day) vs placebo	MA Patients diagnosed with probable Alzheimer's disease	N=4,775 (9 RCT) Variable duration	Primary: Cognitive function, global impression, activities of daily living, behavioral disturbance, withdrawal rates, and incidence of adverse effects	Primary: Cognitive function 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 1-4mg/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,

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				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 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

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				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 6-12mg/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 6-12mg/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, 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

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				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.
Bullock et al.[86] (2005) Rivastigmine 3-12 mg/day vs donepezil 5-10 mg/day	RCT, DB, MC Patients 50-85 years of age with moderate to moderately-severe Alzheimer's disease (MMSE score 10-20)	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 (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).
Farlow et al.[48] (1992) Tacrine 20 mg/day for 6 weeks vs tacrine 40 mg/day for 6 weeks	DB, PC, PG Patients ≥50 years of age with Alzheimer's disease	N=468 12 weeks	Primary: ADAS, CGI-C, adverse events	Primary: After 12 weeks, dose-related improvement was significant on the ADAS cognitive component (P=0.014), CGI-C (P=0.016), and caregiver-rated CGI-C (P=0.028) for patients given tacrine. Among patients receiving 80 mg/day of tacrine, 51% achieved a four-point or greater improvement of the ADAS cognitive component after 12 weeks of treatment. Reversible asymptomatic transaminase elevations greater than three times normal occurred in 25% of patients.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo for 6 weeks For the remaining 6 weeks, half of the patients received the same treatment and half of the patients doubled their dose.				Other treatment related adverse events included nausea and/or vomiting (8%), diarrhea (5%), abdominal pain (4%), dyspepsia (3%), and rash (3%).
Trinh et al.[57] (2003) Cholinesterase inhibitors (donepezil, eptastigmine*, galantamine metrifonate*, physostigmine patch*, rivastigmine, tacrine, velnacrine*) 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 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 (donepezil, galantamine,	MA Patients with Alzheimer's disease	N=7,954 (16 RCT) 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

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rivastigmine) vs placebo				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).
Hansen et al.[82] (2008) Cholinesterase inhibitors (donepezil, galantamine, rivastigmine)	MA Patients with Alzheimer's disease	26 RCT Variable duration	Primary: Cognition (ADAS-cog), function, behavior (NPI), global assessment of change (CIBIC+ and CGI-C)	Primary: <u>Cognition (14 studies)</u> 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. <u>Function (14 studies)</u> The pooled standardized mean difference between active treatment and placebo was 0.31 (95% CI 0.21 to 0.40) for donepezil, 0.27 (95% CI 0.18 to 0.36) for galantamine, and 0.26 (95% CI 0.11 to 0.40) for rivastigmine. <u>Behavior (7 studies)</u> 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. <u>Global assessment of change (9 studies)</u> 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.
Parkinson's Disease				
Emre et al.[63] (2004) Rivastigmine 3-12 mg/day; average dose 8.6 mg/day	DB, MC, PC, R Patients ≥50 years of age with mild-to-moderate dementia developed 2 years after the diagnosis	N=541 Dose titration over the first 16 weeks with a subsequent assessment	Primary: ADAS-Cog, ADCS-CGIC Secondary: ADCS-ADL, NPI-10, MMSE, CDR	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. 13% of patients in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	of Parkinson's disease according to the clinical diagnostic criteria of the United Kingdom Parkinson's Disease Society Brain Bank and DSM-IV	period of 8 weeks Total of 24 weeks	power of attention tests, D-KEFS verbal fluency test, Ten Point Clock-drawing Test	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).
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). 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. Secondary: Results for MMSE significantly favored patients treated with rivastigmine

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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, PC=placebo controlled, PG=parallel group, PRO=prospective, R=randomized, RCT=randomized controlled trial, RETRO=retrospective, 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=CDR-Sum of the Boxes, 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, DAD=Disability Assessment, D-KEFS=Delis-Kaplan Executive Function System, EXIT-25=Executive Interview, FAST=Functional Assessment Staging, GBS=Gottfries-Bråne-Steen scale, GDS=Global Deterioration Scale, IADL=Instrumental Activity of Daily Living, IDDD= Interview for Deterioration in Daily Functioning Activities in Dementia, MDS-ADL=Minimum Data Set-Activities of Daily Living, MMSE=Mini-Mental Status Exam, 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] A study conducted by 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 a 5-month trial 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] A study conducted by 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 (51.5 hours less per month; P=0.02).[76] There were also fewer patients institutionalized at week 28 in the memantine group compared to placebo (P=0.04).

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 branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage 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 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®	$$$$	N/A
Galantamine	extended-release capsule, solution, tablet	Razadyne®*, Razadyne ER®*	$$$$	$$$$
Rivastigmine	capsule, solution, transdermal patch	Exelon®	$$$$-$$$$$	N/A
Tacrine	capsule	Cognex®	$$$$$	N/A
Central Nervous System Agents, Miscellaneous				
Memantine	solution, tablet	Namenda®	$$$$	N/A

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

X. Conclusions

The cholinesterase inhibitors are all 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 by the FDA 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. Only galantamine is 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] Donepezil, galantamine and rivastigmine are preferred over tacrine due to hepatotoxicity and the dosing frequency.[15-18] Otherwise, 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 very few studies that directly compare the various agents. Most of the trials have compared active treatment to placebo or no treatment. The published studies also differ with regards to design, patient population and treatment duration, which make it difficult to compare the results.

The Alzheimer's agents are generally well tolerated; however, gastrointestinal adverse effects (diarrhea, nausea and vomiting) occur more frequently with the cholinesterase inhibitors. The use of tacrine is commonly associated with elevations in serum aminotransferase levels.[11] Based on data from clinical trials, approximately 50% of

patients treated with tacrine can be expected to have at least one ALT/SGPT level above the upper limit of normal.[11] Serum transaminase levels should be monitored every other week from week 4 to week 16 following the initiation of treatment, after which monitoring may be decreased to every 3 months.[11]

There is insufficient evidence to support that one brand Alzheimer's agent 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 products within the class reviewed, with the exception of tacrine, 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. Tacrine possesses 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 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.

No brand tacrine product is recommended for preferred status, regardless of cost.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Antidepressants
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I. Overview

The antidepressants are used to treat a variety of mental disorders, including anxiety disorders, depressive disorders, eating disorders (bulimia nervosa) and premenstrual dysphoric disorder.[1-42] Anxiety disorders include generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder and social phobia.[43] Antidepressants have also been used to treat nonpsychiatric conditions, such as diabetic peripheral neuropathy, fibromyalgia, nocturnal enuresis and tobacco abuse.[1-42]

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.[19,28-29,31] The SNRIs are potent inhibitors of neuronal norepinephrine and serotonin reuptake.[12-13,20,33-34] The SSRIs inhibit the neuronal uptake of serotonin and have minimal effects on norepinephrine or dopamine neuronal uptake.[9,14-17,24-27,30] 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. Trazodone is thought to selectively inhibit serotonin uptake at the presynaptic neuronal membrane.[1-3] Nefazodone inhibits neuronal uptake of serotonin and norepinephrine, and is a direct antagonist of serotonin (5-HT_2) receptors. It also blocks $alpha_1$-adrenergic receptors, which may be associated with postural hypotension.[1-3] 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.[1-3,10-11,18,23,32] The miscellaneous antidepressants include mirtazapine and bupropion. 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.[22] 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.[22] 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.[5-8]

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 November 2007.

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®	none
Selegiline	transdermal patch	Emsam®	none
Tranylcypromine	tablet	Parnate®*	tranylcypromine
Selective Serotonin- and Norepinephrine-reuptake Inhibitors			
Desvenlafaxine	extended-release tablet	Pristiq®	none
Duloxetine	delayed-release capsule	Cymbalta®	none

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Milnacipran	tablet	Savella®	none
Venlafaxine	extended-release capsule, extended-release tablet, tablet	Effexor®*, Effexor XR®, Venlafaxine ER®	venlafaxine
Selective Serotonin-reuptake Inhibitors			
Citalopram	solution, tablet	Celexa®*	citalopram
Escitalopram	solution, tablet	Lexapro®	Lexapro®
Fluoxetine	capsule, delayed-release capsule, solution, tablet	Prozac®*, Prozac Weekly®, Sarafem®*, Selfemra®*	fluoxetine
Fluvoxamine	extended-release capsule, tablet	Luvox CR®, Luvox®*†	Luvox CR®, fluvoxamine
Olanzapine and fluoxetine	capsule	Symbyax®	none
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	tablet	N/A	trazodone
Tricyclics and Other Norepinephrine-reuptake Inhibitors			
Amitriptyline	tablet	N/A	amitriptyline
Amitriptyline and chlordiazepoxide	tablet	Limbitrol®*	amitriptyline and chlordiazepoxide
Amoxapine	tablet	N/A	amoxapine
Clomipramine	capsule	Anafranil®*	clomipramine
Desipramine	tablet	Norpramin®*	desipramine
Doxepin	capsule, oral concentrate	N/A	doxepin
Imipramine	capsule, tablet	Tofranil®*, Tofranil-PM®*	imipramine
Maprotiline	tablet	N/A	maprotiline
Nortriptyline	capsule, solution	Pamelor®*	nortriptyline
Perphenazine and amitriptyline	tablet	N/A	perphenazine and amitriptyline
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.
†Brand is no longer available.
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)
National Institute for Health and Clinical Excellence (NICE): **Treatment and Management**	<u>Persistent Subthreshold Depressive Symptoms or Mild to Moderate Depression</u> • Do not use antidepressants routinely to treat persistent subthreshold

Clinical Guideline	Recommendation(s)

of Depression in Adults (Update)[48] (2009)	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 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

Clinical Guideline	Recommendation(s)
	may be less well tolerated (venlafaxine, TCA, MAOI). Complex and Severe Depression • 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[46] (2008)**	Treatment of Major Depressive Disorder (MDD) • 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. Treatment of Depression in Patients with Accompanying Symptom Clusters • 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. Treatment of Depression in Selected Patient Populations • Second-generation antidepressants did not differ in efficacy among subgroups and special populations categorized according to age, sex, 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

Clinical Guideline	Recommendation(s)
	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**[47] **(2007)**	<u>All Types of Childhood/Adolescent Depression</u> • 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. <u>Uncomplicated depression/Brief depression/Mild psychosocial impairment</u> • Initial management: education, support, and case management. Reevaluate if no response after 4-6 weeks. <u>Moderate-to-severe depression</u> • 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). • 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. <u>Psychotic depression</u> • SSRIs combined with atypical antipsychotics are the treatment of choice. <u>Seasonal Affective Disorder (SAD)</u> • Bright light therapy is recommended as treatment of SAD in youths. <u>Bipolar disorder</u> • A mood stabilizer such as lithium, valproate, or lamotrigine may be used.
American Psychiatric Association (APA): **Guideline Watch: Practice Guideline for the Treatment of Patients with Major Depressive Disorder, Second Edition**[45] **(2005)**	• A black-box warning for liver toxicity and failure was added to nefazodone, due to an incidence of 3-4 times the baseline. Patients with pre-existing liver failure should not be treated with nefazodone. • Patients with major depressive disorder are at increased risk of suicide. Caution should be used when initiating and treating these patients. • A black-box warning was added to all antidepressants, highlighting the increased risk of suicide and suicidal thoughts, changes in behavior, as well as other safety concerns, when antidepressants are used in children and adolescents. • Escitalopram and duloxetine are new antidepressants approved since the previous guideline. • Escitalopram is approved for the acute and maintenance treatment of major depressive disorder and is comparable in efficacy and tolerability to other antidepressants, including citalopram and

Clinical Guideline	Recommendation(s)
	venlafaxine. • Duloxetine is a selective serotonin- and norepinephrine-reuptake inhibitor (SNRI), approved for the treatment of depression, that has shown comparable efficacy to SSRIs. • A combination product of olanzapine and fluoxetine was approved for the treatment of episodes of bipolar depression. It has been found useful in the treatment of major depression with psychotic features and in treatment-resistant depression.
American Psychiatric Association (APA): **Practice Guideline for the Treatment of Patients with Major Depressive Disorder**[44] **(2000)**	• Treatment of major depressive disorder can be divided into the acute phase (remission is achieved, usually lasting 6-8 weeks), the continuation phase (remission is preserved, usually lasting 16-20 weeks) and the maintenance phase (susceptible patient is protected against recurrence). • Selecting an agent should be driven by anticipated side effects, tolerability, patient preference, and quantity and quality of available clinical data. • The effectiveness of antidepressants is usually comparable within medication classes and comparable between medication classes. • Selection of medication can be influenced by prior positive response, severity of symptoms, sleep and/or appetite disturbances or the anticipation of the requirement for maintenance therapy. • These medications that can be considered first-line therapy for most patients and should be initiated during the acute phase: selective serotonin-reuptake inhibitors (SSRIs), desipramine, nortriptyline, bupropion, and venlafaxine. • Due to the risk of serious side effects, monoamine oxidase inhibitors (MAOIs) should be reserved for patients who are unresponsive to other available medications. • Secondary amine tricyclic antidepressants may not be the best treatment choice for patients with concomitant cardiovascular disease, close-angle glaucoma, urinary retention, or significant prostatic hypertrophy. • All SSRIs have some risk of sexual side effects. • For patients who present with significant psychosocial stressors, intrapsychic conflict, interpersonal difficulties or axis II comorbidity, psychotherapy may be considered as initial monotherapy. • Patients who present with psychosocial issues as well as moderate-to-severe major depressive disorder may benefit from combination psychotherapy and antidepressant medication. • Therapy should be assessed after 4-8 weeks of therapy to judge response to treatment. If there is no response or partial response at this time, a change in therapy should be considered, including changing the dose, changing the antidepressant, adding psychotherapy or electroconvulsive therapy (ECT). • Switching to a different non-MAOI antidepressant within the same class or to one in a different class are both effective strategies. • The antidepressant medication used to induce remission during the acute phase should be continued through the continuation phase, 16-20 weeks after remission, and through the maintenance phase in patients who are at risk for relapse. • Discontinuation of treatment after maintenance phase may be considered by the prescriber and the patient. Attention should be paid to the probability of relapse, detection of symptoms should they return, and the potential for adverse events upon stopping the antidepressant.
American Psychiatric	• Selective serotonin reuptake inhibitors (SSRIs), serotonin-

Clinical Guideline	Recommendation(s)
Association (APA): **Practice Guideline for the Treatment of Patients with Panic Disorder, Second Edition**[83] **(2009)**	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. • 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.
National Institute for Health and Clinical Excellence (NICE):	<u>Panic Disorder General Considerations</u> • Benzodiazepines are associated with a less effective outcome in the

Clinical Guideline	Recommendation(s)
Management of Anxiety (Panic Disorder, With or Without Agoraphobia, and Generalized Anxiety Disorder) in Adults in Primary, Secondary and Community Care[49] (2007)	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) <u>Panic Disorder - Additional Considerations for Pharmacologic Therapy</u> • 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. <u>Generalized Anxiety Disorder General Considerations</u> • If immediate management of generalized anxiety disorder is necessary, any or all of the following should be considered: o Support and information o Problem solving o Benzodiazepines o Sedating antihistamines o Self-help • Benzodiazepines may be used for acute treatment, but they should not usually be used beyond 2 to 4 weeks. • In the longer-term care of individuals with generalized anxiety disorder, any of the following types of intervention should be offered and the preference of the person with generalized anxiety disorder should be taken into account. The interventions which have evidence for the longest duration of effect, in descending order, are: o Psychological therapy o Pharmacological therapy (antidepressant medication) o Self-help <u>Generalized Anxiety Disorder – Additional Considerations for Pharmacologic Therapy</u> • Antidepressants should be the only pharmacological intervention used in the longer-term management of generalized anxiety disorder. • There is an evidence base for the effectiveness of the SSRIs. Paroxetine and venlafaxine ER have marketing authorization for the treatment of generalized anxiety disorder. Unless otherwise indicated, an SSRI should be offered; if one SSRI is not suitable, another SSRI should be offered. • If the patient is showing improvement the medication should be

Clinical Guideline	Recommendation(s)

	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.
	• If there is no improvement after a 12 week course with an SSRI and if a further medication is appropriate, another SSRI may be considered, or another form of therapy may be offered.
	• Before prescribing venlafaxine, practitioners should consider the following:
	  o Take into account the increased likelihood of patients stopping treatment because of side effects compared with equally effective SSRIs.
	  o Ensure pre-existing hypertension is controlled. Venlafaxine should not be prescribed for patients with uncontrolled hypertension.
	  o The dose of venlafaxine should be no higher than 75 mg per day.
	  o Blood pressure should be checked on initiation and regularly during treatment, particularly during dosage titration. For patients who experience a sustained increase in blood pressure, the dose should be reduced or discontinuation considered.
	  o Monitor patients for the signs and symptoms of cardiac dysfunction, particularly in those with known cardiovascular disease, and take appropriate action as necessary.
	  o Venlafaxine should not be prescribed for patients with a high risk of serious cardiac arrhythmias or recent myocardial infarction.

American Academy of Child and Adolescent Psychiatry (AACAP): **Practice Parameter for the Assessment and Treatment of Children and Adolescents with Anxiety Disorders**[74] **(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

Clinical Guideline	Recommendation(s)
	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 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: **Practice Guideline for the Treatment of Patients with Obsessive-Compulsive Disorder**[50] **(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

Clinical Guideline	Recommendation(s)
	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 Dysmorphic Disorder[51] (2005)**	• 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 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[53] (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.

Clinical Guideline	Recommendation(s)
	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)[52] (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 College of Obstetricians and Gynecologists (ACOG): **Practice Bulletin: Premenstrual Syndrome[54] (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.
Expert Guidelines for the Treatment of Severe PMS, PMDD, and Comorbidities: **The Role of SSRIs[55] (2006)**	• Evidence supports the use of SSRIs as first-line therapy for severe PMS and premenstrual dysphoric disorder (PMDD). • Continuous and intermittent dosing of SSRIs appears to be effective. • Continuous dosing may be more effective in patients with comorbid depressive or anxiety disorders and those who experience withdrawal symptoms when abruptly stopping SSRI therapy. • Intermittent dosing may be better for patients who want to limit exposure to SSRIs, have troublesome side effects from SSRI therapy, and who experience symptoms of severe PMS or PMDD during the luteal phase only.
American Psychiatric Association (APA): **Practice Guideline for the Treatment of Patients with Eating Disorders[56] (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.

Clinical Guideline	Recommendation(s)
	• Atypical antipsychotics may be used in patients with severe symptoms. • SSRIs may be considered in patients with bulimia.
American Pain Society (APS): **Guideline for the Management of Fibromyalgia Syndrome Pain in Adults and Children[71] (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.

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[1-42]

Generic Name(s)	Bulimia Nervosa	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		✔	✔								Diabetic peripheral neuropathic pain; Fibromyalgia
Milnacipran											Fibromyalgia
Venlafaxine		✔	✔ †			✔ †				✔ †	
Selective Serotonin-reuptake Inhibitors											
Citalopram		✔									
Escitalopram		✔	✔								
Fluoxetine	✔	✔ ‡			✔	✔		✔			
Fluvoxamine					✔						
Olanzapine and fluoxetine		✔ ‡									
Paroxetine		✔	✔ §		✔ §	✔	✔ §	✔ †		✔	
Serotonin Modulators											
Nefazodone		✔									
Trazodone		✔									
Tricyclics and Other Norepinephrine-reuptake Inhibitors											
Amitriptyline		✔									
Amitriptyline and chlordiazepoxide				✔							
Perphenazine and amitriptyline				✔							

Generic Name(s)	Bulimia Nervosa	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
Amoxapine		✔		✔							
Clomipramine					✔						
Desipramine		✔									
Doxepin		✔		✔							
Imipramine		✔									Pediatric nocturnal enuresis
Maprotiline		✔									
Nortriptyline		✔									
Protriptyline		✔									
Trimipramine		✔									
Antidepressants, Miscellaneous											
Bupropion		✔							✔ †		
Mirtazapine		✔									

†Extended-release formulation only.
§Immediate-release formulation only.
‡Fluoxetine in combination with olanzapine is approved for the treatment of depressive episodes associated with bipolar I disorder and for treatment resistant depression.

IV. Pharmacokinetics

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

Table 4. Pharmacokinetic Parameters of the Antidepressants[1-42]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism	Excretion (%)	Half-Life (hours)
Monoamine Oxidase Inhibitors					
Isocarboxazid	Not reported	Not reported	Hepatic	Renal	Not reported
Phenelzine	Not reported	Not reported	Hepatic	Renal (79)	11
Selegiline	25-30	90	Hepatic	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	Hepatic	Renal (45)	10-11
Duloxetine	30-80	>90	Hepatic	Renal (70) Feces (20)	8-17
Milnacipran	85-90	13	Hepatic	Renal (50-60) Feces (<5)	6-8
Venlafaxine	12.6-45	27-30	Hepatic	Renal (87) Feces (2)	5
Selective Serotonin-reuptake Inhibitors					
Citalopram	80	80	Hepatic	Renal (20) Feces	33-37
Escitalopram	80	56	Hepatic	Renal (8)	22-32
Fluoxetine	100	94	Hepatic	Renal (60) Feces (12)	96-144
Fluvoxamine	53	80	Hepatic	Renal (94)	15.6
Olanzapine and fluoxetine	O: 60 F: 100	93-94	Hepatic	Renal (O: 57, F: 60) Feces (O: 30, F: 12)	O: 30 F: 96-144
Paroxetine	Not reported	95	Hepatic	Renal (65-67) Feces (36-37)	15-22
Sertraline	Not reported	99	Hepatic	Renal (40-45) Feces (40-45)	24
Serotonin Modulators					
Nefazodone	20	>99	Hepatic	Renal (55) Feces (20-30)	1.9-5.3
Trazodone	65	89-95	Hepatic	Renal (70-75) Feces (21)	7-8
Tricyclics and Other Norepinephrine-reuptake Inhibitors					
Amitriptyline	100	90-95	Hepatic	Renal (18)	9-27
Amitriptyline and chlordiazepoxide	100	90-98	Hepatic	Renal (18)	A: 9-27 C: 6.6-48
Amoxapine	18-54	90	Hepatic	Renal (69) Feces (18)	8
Clomipramine	20-78	97	Hepatic	Renal (51-60) Feces (24-32)	19-37
Desipramine	Not reported	Not reported	Hepatic	Renal (70)	14.3-24.7
Doxepin	Not reported	79-84	Hepatic	Bile	16.8
Imipramine	94-96	89	Hepatic	Renal	6-18
Maprotiline	100	88	Hepatic	Renal (70) Feces (30)	27-53

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism	Excretion (%)	Half-Life (hours)
Nortriptyline	60	93-95	Hepatic	Renal, Feces	28-31
Perphenazine and amitriptyline	P: 20 A: 100	P: Not reported A: 90-95	Hepatic	Renal (A:18)	P: 9-12 A: 9-27
Protriptyline	Not reported	Not reported	Hepatic	Renal Feces	54-198
Trimipramine	Not reported	95	Hepatic	Renal	23
Antidepressants, Miscellaneous					
Bupropion	Not reported	84	Hepatic	Renal (87)	14-21
Mirtazapine	50	85	Hepatic	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 hyperthermia, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes. Altered brain monoamine concentrations are possible. Coadministration is contraindicated.
MAOIs	1	Bupropion	Risk of acute bupropion toxicity may be increased, although the exact mechanism is unknown. Coadministration of bupropion and MAOIs are contraindicated.
MAOIs	1	Carbamazepine	A theoretical risk of severe side effects (e.g., hyperpyrexia, hyper-excitability, muscle rigidity, seizures) exists. Coadministration of carbamazepine and a MAOI is contraindicated.
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	Dexmethylphenidate and methylphenidate	There is an increased risk of hypertensive crisis with the coadministration of MAOIs and methylphenidate. The precise mechanism of this interaction is unknown. The use of methylphenidate is contraindicated in patients receiving concomitant MAOI therapy.
MAOIs	1	Dextromethorphan	Hyperpyrexia, abnormal muscle movement, hypotension, coma, and death

Generic Name(s)	Significance Level	Interaction	Mechanism
			have been associated with the coadministration of these agents. Due to the potential severity of reaction, avoid coadministration.
MAOIs	1	Levodopa	MAOIS may increase the pharmacologic and toxic effects of levodopa; precipitation of a hypertensive crisis is possible. MAOIs may decrease the enzymatic degradation of dopamine and norepinephrine formed from levodopa. The combination should be avoided.
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	1	Mirtazapine	Concomitant administration of mirtazapine and MAOIs may enhance the sympathomimetic effects of mirtazapine. Nausea, dizziness, agitated delirium progressing to generalized hypertonicity, seizures, hyperpyrexia, dyspnea, and cardiovascular instability may occur. The mechanism is unknown.
MAOIs	1	SNRIs/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. Coadministration is contraindicated.
MAOIs	1	Sibutramine	Serotonin syndrome may occur as the serotonergic effects of these agents may be additive. Concomitant administration of these agents is contraindicated.
MAOIs	1	Sympathomimetics	Coadministration of a MAOI and a sympathomimetic agent may cause a hypertensive crisis. The coadministration of these agents should be avoided.
MAOIs	1	Tapentadol	Increased risk of serious or fatal reactions, including hyperthermia, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes. Coadministration is contraindicated.
MAOIs	1	Tricyclic antidepressants	Hyperpyretic crises, convulsions, and death have occurred as a result of this interaction, although the exact mechanism is unclear. Tricyclic antidepressants should not be used within 2 weeks of MAOI therapy.
MAOIs	2	Buspirone	Possible increased risk of adverse effects, including severe hypertension. The mechanism is unknown. Coadministration is not recommended.

Generic Name(s)	Significance Level	Interaction	Mechanism
MAOIs	2	COMT inhibitors	The combination of MAOIs with COMT inhibitors may result in inhibition of the majority of pathways responsible for normal catecholamine metabolism. Excessive sympathetic stimulation may result. Coadministration is not recommended.
MAOIs	2	Insulin	Coadministration of MAOIs may potentiate the hypoglycemic response to insulin and delayed recovery from hypoglycemia. It is believed that this interaction may be the result of stimulation of insulin secretion and inhibition of gluconeogenesis.
MAOIs	2	Linezolid	Adverse effects may be increased with concurrent administration of Linezolid and MAOIs. The mechanism is unknown. Linezolid should be avoided in patients currently receiving MAOIs.
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	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 MAOIs. The mechanism 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. Due to the potential seriousness of the consequences, propoxyphene should be used with caution in patients receiving MAOIs. The use of transdermal selegiline with propoxyphene is contraindicated.
MAOIs	2	Selective 5-HT_1 receptor agonists	Prolonged vasospastic reactions are possible when certain triptans and MAOIs are coadministered. A clear causal relationship has not been established. Clinical significance is not known; the mechanism is unknown. The use of a triptan with a MAOI is not recommended.
MAOIs	2	Sulfonylureas	MAOIs enhance the hypoglycemic action of sulfonylureas. If a patient develops hypoglycemia while taking both medications, dosing adjustments should be made to achieve euglycemia.

Generic Name(s)	Significance Level	Interaction	Mechanism
MAOIs	2	Tryptophan	The combination of MAOIs and tryptophan may produce severe unexpected toxicity (e.g. ocular oscillations, hyperreflexia, behavioral changes). The mechanism is unknown.
Selegiline	2	Contraceptives, oral	Plasma selegiline concentrations may be elevated, causing a loss of selective inhibition of MAO-type B and increasing the risk of selegiline side effects. Oral contraceptives may inhibit the metabolism of selegiline.
Selective Serotonin- and Norepinephrine-reuptake Inhibitors			
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, duloxetine, venlafaxine)	1	Linezolid	Serotonin syndrome may occur, possibly due to excessive accumulation of serotonin. Coadminister linezolid and SRIs with caution.
SNRIs (desvenlafaxine, venlafaxine)	1	Methylene blue	Coadministration of methylene blue and desvenlafaxine may increase the risk of central nervous system toxicity, including serotonin syndrome.
SNRIs (desvenlafaxine, venlafaxine)	1	Metoclopramide	Serotonin syndrome may occur when metoclopramide and desvenlafaxine are coadministered. The mechanism of this interaction is unknown.
SNRIs (duloxetine, venlafaxine)	1	Selective 5-HT_1 receptor agonists	Serotonin syndrome may occur in some patients as a result of rapid accumulation of serotonin in the CNS.
SNRIs (desvenlafaxine, venlafaxine)	1	Sibutramine	A serotonin syndrome may occur as the serotonergic effects of these agents may be additive. Coadministration is not recommended
SNRIs (desvenlafaxine, duloxetine, milnacipran, venlafaxine)	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.
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.
Duloxetine	2	Propafenone	Plasma concentrations of propafenone may be increased by duloxetine due to inhibition of CYP2D6 isoenzymes.

Generic Name(s)	Significance Level	Interaction	Mechanism
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.
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 (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 (desvenlafaxine, venlafaxine)	2	NSAIDs	The toxic effects may be 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 (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 (desvenlafaxine, duloxetine, milnacipran, venlafaxine)	2	Selective 5-HT_1 receptor agonists	Serotonin syndrome may occur in some patients as a result of rapid accumulation of serotonin in the CNS.
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. The combination should be avoided.
SNRIs (desvenlafaxine, venlafaxine)	2	Trazodone	Unexpected toxic effects may occur when trazodone is combined with desvenlafaxine or venlafaxine. The mechanism is unknown.
SNRIs (desvenlafaxine, duloxetine, milnacipran, venlafaxine)	2	Tryptophan	Coadministration may lead to the development of serotonin syndrome. Both agents increase CNS serotonin activity. Coadministration is not recommended.

Generic Name(s)	Significance Level	Interaction	Mechanism
SNRIs (desvenlafaxine, venlafaxine)	2	Warfarin	The risk of bleeding with anticoagulants may be enhanced with the concomitant use of desvenlafaxine or venlafaxine. The mechanism is unknown.
Venlafaxine	2	Azole antifungals (fluconazole, itraconazole, ketoconazole, voriconazole)	Venlafaxine plasma levels may become elevated, which may increase the risk for adverse events. While CYP2D6 is the major pathway for venlafaxine metabolism, CYP3A4 inhibition by azole antifungal agents may be an important factor in poor metabolizers.
Venlafaxine	2	Beta-blockers	Coadministration of venlafaxine and beta-blockers may increase the risk of cardiac and central nervous system toxicity. Inhibition of CYP2D6 isoenzymes by venlafaxine may decrease the metabolism of beta-blockers.
Venlafaxine	2	Cyproheptadine	Decreased pharmacologic effects of venlafaxine may result. Since cyproheptadine is a serotonin antagonist, the interaction may occur at the receptor level.
Venlafaxine	2	Terbinafine	Plasma concentrations and pharmacologic effects of venlafaxine may be increased when coadministered with terbinafine. The potential for adverse effects due to venlafaxine may be increased. Inhibition of CYP2D6-mediated metabolism of venlafaxine by terbinafine is suspected.
Selective Serotonin-reuptake Inhibitors (SSRIs)			
Fluvoxamine	1	Tizanidine	Plasma concentrations and pharmacologic effects of tizanidine may be increased by fluvoxamine. Inhibition of cytochrome P450 1A2 metabolism by fluvoxamine may decrease the metabolic elimination of tizanidine. Coadministration of tizanidine and fluvoxamine is contraindicated.
SSRIs (citalopram, fluoxetine, fluvoxamine, sertraline)	1	Clozapine	Serum clozapine levels may be elevated resulting in increased pharmacologic and toxic effects. Certain SSRIs inhibit clozapine hepatic metabolism, resulting in the need to monitor clozapine serum levels and closely observe the clinical response.
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	1	MAOIs	SSRIs and MAOIs increase central nervous system serotonin activity. Coadministration is not recommended.
SSRIs	1	Methylene blue	Coadministration of methylene blue and SSRIs may increase the risk of central nervous system toxicity, including serotonin syndrome. Consider alternatives

Generic Name(s)	Significance Level	Interaction	Mechanism
			to methylene blue in patients receiving SSRIs.
SSRIs	1	Metoclopramide	Signs of serotonin syndrome with extrapyramidal movements may occur when metoclopramide and SSRIs are coadministered. The mechanism of this interaction is unknown.
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, sertraline)	1	Pimozide	Plasma concentrations of pimozide may be increased by SSRIs. The risk of life-threatening cardiac arrhythmias, including torsades de pointes, may be increased. The mechanism is unknown. Concurrent administration of pimozide with SSRIs is contraindicated.
SSRIs (fluoxetine, paroxetine)	1	Risperidone	Risperidone plasma concentrations may be elevated, increasing the risk of adverse events. Serotonin syndrome may occur. The CYP2D6 inhibition of risperidone metabolism by fluoxetine and paroxetine is suspected as a rapid accumulation of serotonin in the CNS may occur.
SSRIs	1	Sibutramine	Serotonin syndrome may occur, since the serotonergic effects of these agents may be additive. Concomitant administration of these agents is not recommended.
SSRIs (fluoxetine, 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. The concomitant use of CYP2D6 inhibitors with tamoxifen should be avoided if possible.
SSRIs	1	Tramadol	Serotonin syndrome may occur as the serotonergic effects of these agents may be additive.
Fluoxetine	2	Atomoxetine	Plasma concentrations and pharmacologic effects of atomoxetine may be increased by fluoxetine. Inhibition of CYP2D6 isoenzymes by fluoxetine may decrease the metabolic elimination of atomoxetine.
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.

Generic Name(s)	Significance Level	Interaction	Mechanism
Fluvoxamine	2	Alosetron	Plasma concentrations and the potential for adverse effects of alosetron may be increased by fluvoxamine. Inhibition of CYP1A2 by fluvoxamine may decrease the metabolic elimination of alosetron. Concomitant use of this combination is contraindicated.
Fluvoxamine	2	Methadone	Increased serum methadone concentrations may result. Fluvoxamine may inhibit the hepatic metabolism of methadone.
Fluvoxamine	2	Ramelteon	Plasma concentrations of ramelteon may be increased by coadministration of fluvoxamine. Inhibition of CYP1A2 by fluvoxamine may decrease the metabolic elimination of ramelteon.
Fluvoxamine	2	Tacrine	Plasma tacrine concentrations may be elevated, possibly due to the CYP1A2 inhibition of tacrine metabolism by fluvoxamine.
Fluvoxamine	2	Theophylline	Increased theophylline serum concentrations may occur. Fluvoxamine inhibits the hepatic metabolism (CYP1A2) of theophylline, so close monitoring of theophylline levels is warranted when fluvoxamine therapy is started or stopped.
Fluvoxamine	2	Tizanidine	Tizanidine plasma concentrations may be elevated. Inhibition of tizanidine metabolism by fluvoxamine is suspected as a potential mechanism. Coadministration of tizanidine and fluvoxamine is contraindicated.
Olanzapine/fluoxetine	2	Ritonavir	Plasma concentrations and pharmacologic effects of olanzapine/fluoxetine may be decreased by ritonavir. Induction of CYP1A2 isoenzymes by ritonavir may increase the metabolic elimination of olanzapine/fluoxetine. Higher doses of olanzapine/fluoxetine may be needed during concurrent administration of ritonavir.
Paroxetine	2	Phenothiazines	Phenothiazine plasma levels may be elevated due to decreased metabolism of the phenothiazine. Thioridazine is contraindicated in patients receiving paroxetine.
SSRIs	2	Aripiprazole	Plasma concentrations and pharmacologic effects of aripiprazole may be increased by SSRIs. Inhibition of CYP2D6 isoenzymes by SSRIs may decrease the metabolic elimination of aripiprazole.
SSRIs	2	Beta-blockers	Coadministration of SSRIs and beta-blockers may increase the risk of cardiac and CNS toxicity. Inhibition of CYPD6 isoenzymes by SSRIs may decrease the

Generic Name(s)	Significance Level	Interaction	Mechanism
			metabolism of beta-blockers. Close clinical and cardiac monitoring are indicated.
SSRIs (fluoxetine, sertraline)	2	Carbamazepine	Serum carbamazepine levels may be increased. The close monitoring of serum carbamazepine levels during concurrent administration with fluoxetine is recommended. Carbamazepine may decrease the plasma concentrations and pharmacologic effects of sertraline. Induction of hepatic microsomal enzymes by carbamazepine may increase the elimination of sertraline.
SSRIs	2	Cyproheptadine	Decreased pharmacologic effects of SSRIs may result. Since cyproheptadine is a serotonin antagonist, the interaction may occur at the receptor level. If a loss of the antidepressant efficacy occurs, consider discontinuing cyproheptadine therapy.
SSRIs	2	Lithium	Coadministration of lithium and SSRIs may cause CNS toxicity, including serotonin syndrome. Serum lithium concentrations may be elevated due to increased serotonergic neurotransmission.
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	Selective 5-HT_1 receptor agonists	Serotonin syndrome may occur in some patients as a result of rapid accumulation of serotonin in the CNS.

Generic Name(s)	Significance Level	Interaction	Mechanism
SSRIs	2	St. John's wort	Unexpected toxicity may occur when St. John's Wort and SSRIs are coadministered. The mechanism is unknown.
SSRIs (fluoxetine, fluvoxamine, paroxetine)	2	Terbinafine	Plasma concentrations and pharmacologic effects of SSRIs may be increased when coadministered with terbinafine. Inhibition of CYP2D6-mediated metabolism of SSRIs by terbinafine is suspected.
SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline)	2	Trazodone	Unexpected toxic effects may occur when trazodone and SSRIs are coadministered. The mechanism is unknown.
SSRIs (fluoxetine, fluvoxamine, paroxetine, sertraline)	2	TCAs	SSRIs may increase plasma concentrations and toxic effects of TCAs. Inhibition of CYP2D6 isoenzymes by SSRIs may decrease the metabolic elimination of TCAs.
SSRIs	2	Tryptophan	Coadministration of SSRIs with tryptophan may lead to the development of serotonin syndrome. Both agents acutely increase CNS serotonin activity. Coadministration is not recommended.
SSRIs	2	Warfarin	The risk of bleeding with anticoagulants may be potentiated with the concomitant use of SSRIs. Patients are at an increased risk for bleeding. The mechanism is unknown. It is theorized that SSRIs interfere with the release of serotonin by platelets which plays an important role in hemostasis.
Serotonin Modulators			
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. Avoid coadministration of nefazodone and colchicine in patients with hepatic or renal impairment.
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. Avoid coadministration of this combination.
Nefazodone	1	Eplerenone	Elevated eplerenone plasma concentrations may result as nefazodone inhibits the metabolism of eplerenone. Coadministration of eplerenone and nefazodone is contraindicated.
Nefazodone	1	HMG-CoA reductase inhibitors	The risk of rhabdomyolysis and myositis may be increased with certain HMG-CoA

Generic Name(s)	Significance Level	Interaction	Mechanism
		(atorvastatin, lovastatin, simvastatin)	reductase inhibitors. Nefazodone inhibits the metabolism of HMG-CoA reductase inhibitors.
Nefazodone	1	MAO inhibitors	The combination of MAOIs and nefazodone is contraindicated. The therapeutic effects of both drugs may be increased. The mechanism of this interaction is unknown.
Nefazodone	1	Nilotinib	Plasma concentrations and pharmacologic effects of nilotinib may be increased by nefazodone. Inhibition of CYP3A4 isoenzymes by nefazodone may decrease the metabolic elimination of nilotinib. Concomitant use of nilotinib with nefazodone should be avoided.
Nefazodone	1	Pimozide	The risk of life-threatening cardiac arrhythmias may be increased, as nefazodone may inhibit the metabolism (CYP3A4) of pimozide. Coadministration of nefazodone and pimozide is contraindicated.
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. The use of ranolazine with strong inhibitors of CYP3A4 is contraindicated.
Nefazodone	1	Sympathomimetics, inhaled (salmeterol)	The pharmacologic effects of sympathomimetics may be increased by nefazodone. Elevated salmeterol plasma concentrations with cardiovascular toxicity may occur. Inhibition of CYP3A4 isoenzymes by nefazodone may decrease the metabolic elimination of the swallowed portion of a salmeterol dose.
Nefazodone	1	Vasopressin receptor agonists (conivaptan, tolvaptan)	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. Coadministration of vasopressin receptor antagonists and nefazodone is contraindicated.
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 elimination of certain benzodiazepines.

Generic Name(s)	Significance Level	Interaction	Mechanism
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	Carbamazepine	Elevated serum carbamazepine levels with a possible increase in adverse events, or lower nefazodone levels with a possible decrease in efficacy, may occur. Nefazodone may inhibit the hepatic metabolism (CYP3A4) of carbamazepine, while carbamazepine may induce the metabolism of nefazodone. Coadministration of carbamazepine and nefazodone is contraindicated.
Nefazodone	2	Cyclosporine	Cyclosporine concentration may be increased as nefazodone may inhibit the metabolism (CYP3A4) of cyclosporine.
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 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	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	MTOR inhibitors (everolimus, temsirolimus)	Pharmacologic effects of MTOR inhibitors may be increased by nefazodone. Inhibition of CYP34A isoenzymes by nefazodone may decrease the metabolic elimination of MTOR inhibitors. Coadministration of MTOR inhibitors with nefazodone should be avoided.
Nefazodone	2	Muscarinic receptor antagonists (darifenacin, fesoterodine, solifenacin, tolterodine)	Plasma concentrations and pharmacologic effects of muscarinic receptor antagonists may be increased by nefazodone. Inhibition of CYP3A4 by nefazodone may decrease the metabolic elimination of muscarinic receptor antagonists.
Nefazodone	2	Narcotic analgesics	Plasma concentrations and pharmacologic effects of narcotic analgesics may be increased by nefazodone. Inhibition of CYP3A4 metabolism by nefazodone may

Generic Name(s)	Significance Level	Interaction	Mechanism
			decrease the metabolic elimination of narcotic analgesics.
Nefazodone	2	Selective 5-HT_1 receptor agonists	Serotonin syndrome may occur in some patients due to a rapid accumulation of serotonin in the CNS.
Nefazodone	2	Tramadol	Increased risk of seizures is a possibility when tramadol and nefazodone are coadministered. Serotonin syndrome may occur. The mechanism of this interaction is unknown. Use of tramadol with nefazodone is not recommended.
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	Sodium oxybate	Concurrent use of sodium oxybate and trazodone may result in an increase in sleep duration and CNS depression, due to additive effects.
Trazodone	2	SSRIs	Unexpected toxic effects may occur when trazodone and certain SSRIs are coadministered. The mechanism of this interaction is unknown.
Trazodone	2	Warfarin	The hypoprothrombinemic effect of warfarin may be decreased, potentially resulting in suboptimal anticoagulation with possible disease exacerbations occurring. The mechanism of this interaction is unknown.
Tricyclics and Other Norepinephrine-reuptake Inhibitors			
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 interaction is unknown. Clozapine and amitriptyline/ chlordiazepoxide should not be started simultaneously.
Amitriptyline/ chlordiazepoxide	1	Methadone	Potentiation of respiratory and CNS depressant effects of methadone and benzodiazepines may occur.
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.
Maprotiline	1	Furazolidone	Concomitant administration of maprotiline and furazolidone may enhance the sympathomimetic effects of maprotiline. The mechanism is unknown.

Generic Name(s)	Significance Level	Interaction	Mechanism
Maprotiline	1	Methadone	Coadministration of methadone and maprotiline may cause inhibition of cardiac potassium channels and cause significant prolongation of the cardiac QT interval.
Maprotiline	1	Quinolones (gatifloxacin, levofloxacin, moxifloxacin, sparfloxacin)	The risk of life-threatening cardiac arrhythmias may be increased. The exact mechanism is unknown. Levofloxacin should be avoided, while gatifloxacin and moxifloxacin should be used with caution.
Maprotiline	1	Nilotinib	Additive QT prolongation may occur during coadministration of nilotinib and maprotiline. Concomitant use should be avoided.
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 (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 (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. Concomitant use should be avoided.
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.
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.
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

Generic Name(s)	Significance Level	Interaction	Mechanism
			the metabolic elimination of benzodiazepines.
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.
Amitriptyline/ chlordiazepoxide	2	Sodium oxybate	Concurrent use of sodium oxybate and amitriptyline/chlordiazepoxide may result in an additive increase in sleep duration and CNS depression.
Perphenazine/amitriptyline	2	Anticholinergics	The antipsychotic effectiveness of perphenazine/amitriptyline may be decreased by anticholinergics. This combination may cause additive anticholinergic toxicity.
Perphenazine/amitriptyline	2	Levodopa	The pharmacologic effect of levodopa may be decreased when given with perphenazine/amitriptyline. Levodopa increases synaptic dopamine concentrations and enhances stimulation of dopamine receptors. Perphenazine exerts an opposing effect by inhibiting stimulation of dopamine receptors in the brain. Use of levodopa with perphenazine-amitriptyline is not recommended.
Perphenazine/amitriptyline	2	Pergolide	Perphenazine-amitriptyline may decrease the pharmacologic effects of pergolide. The dopamine antagonist effects of perphenazine oppose the pharmacodynamic receptor site effects of pergolide. The use of perphenazine-amitriptyline with pergolide is not recommended.
Tricyclic antidepressants (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)	2	Azole antifungals (fluconazole, itraconazole, ketoconazole, posaconazole)	Serum TCA levels may be elevated resulting in an increase in therapeutic and adverse effects, including cardiac arrhythmias. The inhibition of TCA metabolism (CYP2C9 by fluconazole; CYP3A4 by ketoconazole) is a suspected mechanism for this interaction.
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

Generic Name(s)	Significance Level	Interaction	Mechanism
trimipramine)			bioavailability 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. The combination of clonidine and TCAs should be avoided.
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, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)	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 receptor.
Tricyclic antidepressants (amitriptyline, amoxapine, clomipramine, doxepin, desipramine, 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.
Tricyclic antidepressants	2	Rasagiline	The combination of rasagiline and TCAs may precipitate symptoms of serotonin syndrome. Rasagiline and TCAs increase CNS serotonin activity.
Tricyclic antidepressants	2	Rifamycins (rifabutin, rifampin)	TCA levels may be decreased due to an increase in hepatic metabolism. TCA levels should be monitored when starting, discontinuing, or altering the dose of rifampin.
Tricyclic antidepressants (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, 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).

Generic Name(s)	Significance Level	Interaction	Mechanism
Tricyclic antidepressants (amitriptyline, desipramine, imipramine, nortriptyline)	2	SNRIs	Plasma concentrations of certain TCAs may be increased by SNRIs. Inhibition of CYP2D6 isoenzymes by SNRIs may decrease the metabolic elimination of certain TCAs.
Tricyclic antidepressants (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)	2	Sympathomimetics (dobutamine, epinephrine, phenylephrine)	TCAs potentiate the pressor response of the direct-acting sympathomimetics. The pressor response to the indirect-acting sympathomimetics is decreased by the TCAs. If these agents must be used concurrently, a dosage adjustment of the sympathomimetic may be necessary.
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. Use of tramadol with TCAs is not recommended.
Tricyclic antidepressants (amitriptyline, amoxapine, clomipramine, nortriptyline)	2	Valproic acid and derivatives	Plasma concentrations of TCAs may be increased due to decreased metabolism.
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.
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	Rifampin	Bupropion plasma concentrations may be reduced secondary to increased metabolism of bupropion. In patients receiving bupropion, close monitoring of clinical efficacy is advised when rifampin is coadministered.
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. Caution is advised regarding the concomitant use of tiagabine

Generic Name(s)	Significance Level	Interaction	Mechanism
			with drugs that may lower the seizure threshold.
Mirtazapine	2	Hydantoins (ethotoin, fosphenytoin, phenytoin)	Mirtazapine plasma concentrations may be reduced due to the induction of mirtazapine metabolism (CYP3A4) by hydantoins. In patients receiving mirtazapine, close monitoring of clinical response when starting, stopping, or changing the hydantoin dose is recommended.
Mirtazapine	2	Rasagiline	The combination of rasagiline and mirtazapine may precipitate symptoms of serotonin syndrome, which may be due to an increase in CNS serotonin activity. Monitor patient closely, especially when high doses of mirtazapine are used.

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 – 10.

Table 6a. Adverse Drug Events (%) Reported with the Monoamine Oxidase Inhibitors[1-42]

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

Adverse Events	Isocarboxazid	Phenelzine	Selegiline	Tranylcypromine
Behavior changes	-	-	>1	-
Blurred vision	-	✔	-	✔
Bradykinesia	-	-	>1	-
Chills	2	-	-	✔
Coma	✔	✔	-	-
Confusion	-	-	-	✔
Convulsions	-	✔	-	-
Delirium	-	✔	-	-
Delusions	-	-	<1	-
Depersonalization	-	-	<1	-
Depression	-	-	<1	-
Disorientation	-	-	-	✔
Dizziness	29	✔	-	✔
Drowsiness	4	✔	-	✔
Emotional lability	-	-	<1	-
Euphoria	✔	✔	<1	-
Fatigue	-	✔	-	✔
Fever	-	✔	<1	-
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	-	-	-	✔
Nystagmus	-	✔	-	-
Palilalia	-	✔	-	-
Paranoid reaction	-	-	<1	-
Parasomnia	-	-	>1	-
Paresthesia	2	✔	<1	✔
Restlessness	-	-	-	✔
Schizophrenia precipitation	-	✔	-	-
Sedation	2	-	-	-
Seizure	-	✔	-	-
Sleep disturbance	2-5	✔	-	✔
Tinnitus	-	-	-	✔
Twitching	-	✔	-	✔
Vertigo	-	-	<1	-
Weakness	-	✔	-	✔
Dermatological				
Acne	-	-	≥1	-

Adverse Events	Isocarboxazid	Phenelzine	Selegiline	Tranylcypromine
Alopecia	-	-	-	✔
Application site reaction	-	-	24	-
Bruising	-	-	≥1	-
Cystic acne flare-up	-	-	-	✔
Maculopapular rash	-	-	<1	-
Photosensitivity	✔	-	-	-
Pruritus	-	✔	≥1	✔
Rash	-	✔	4	✔
Scleroderma	-	-	-	✔
Skin benign neoplasm	-	-	<1	-
Skin hypertrophy	-	-	<1	-
Urticaria	-	-	<1	-
Vesiculobullous rash	-	-	<1	-
Endocrine and Metabolic				
Alkaline phosphatase increased	-	-	<1	-
Hepatitis	-	✔ -	-	✔
Hypercholesterolemia	-	-	<1	-
Hyperglycemia	-	-	<1	-
Hypermetabolic syndrome	-	✔	-	✔
Hypernatremia	-	✔	-	-
Hypoglycemic reaction	-	-	<1	-
Hyponatremia	-	-	<1	✔
Jaundice, reversible	-	✔	-	-
Lactate dehydrogenase increased	-	-	<1	-
Liver function tests abnormal	-	-	<1	-
Hepatocellular damage	-	✔	-	-
Serum transaminase elevation	-	✔	-	-
SIADH	✔	✔	-	✔
Weight gain	-	✔	-	-
Weight loss	-	-	5	-
Gastrointestinal				
Anorexia	-	-	≥1	✔
Abdominal pain	-	-	-	✔
Colitis	-	-	<1	-
Constipation	7	✔	<1	✔
Diarrhea	2	-	9	✔
Dry mouth	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	-
Vomiting	≥1	-	≥1	-
Xerostomia	6-9	✔	8	✔
Genitourinary				
Anorgasmia	-	✔	-	-
Dysmenorrhea	-	-	≥1	-
Dysuria	✔	-	-	-

Adverse Events	Isocarboxazid	Phenelzine	Selegiline	Tranylcypromine
Ejaculation disturbances	-	✔	-	✔
Incontinence	✔	-	-	-
Kidney calculus	-	-	<1	-
Libido increased	-	-	<1	-
Pelvic pain	-	-	<1	-
Polyuria	-	-	<1	-
Prostatic hyperplasia	-	-	<1	-
Sexual disturbances	✔	✔	-	-
Sexual side effects	-	-	≤1	-
Urinary frequency	2	-	>1	-
Urinary hesitancy	1	-	-	-
Urinary retention	✔	✔	<1	✔
Urinary tract infection	-	-	≥1	-
Urinary urgency	-	-	<1	-
Urination impaired	-	-	<1	-
Vaginal hemorrhage	-	-	<1	-
Vaginal moniliasis	-	-	<1	-
Hematologic				
Agranulocytosis	-	-	-	✔
Anemia	-	-	-	✔
Hematologic changes	✔	-	-	-
Leukocytosis	-	-	<1	-
Leukopenia	-	✔	<1	✔
Thrombocytopenia	-	-	-	✔
Musculoskeletal				
Generalized spasm	-	-	<1	-
Heavy feeling	2	✔	-	-
Hypertonia	-	-	<1	-
Myalgia	-	-	≥1	-
Myasthenia	-	-	<1	-
Myoclonic jerks/movements	2	✔	<1	✔
Neck pain	-	-	≥1	-
Tenosynovitis	-	-	<1	-
Tremor	4	✔	<1	✔
Respiratory				
Asthma	-	-	<1	-
Bronchitis	-	-	≥1	-
Cough	-	-	≥1	-
Dyspnea	-	-	<1	-
Edema of the glottis	-	✔	-	-
Laryngismus	-	-	<1	-
Pharyngitis	-	-	3	-
Pneumonia	-	-	<1	-
Respiratory depression, transient	-	✔	-	-
Sinusitis	-	-	3	-
Other				
Appetite increased	-	-	<1	-
Bacterial infection	-	-	<1	-
Bilirubinemia	-	-	<1	-
Black tongue	✔	-	-	-
Blurred vision	✔	✔	-	-
Circumoral paresthesia	-	-	<1	-

Adverse Events	Isocarboxazid	Phenelzine	Selegiline	Tranylcypromine
Dehydration	-	-	<1	-
Dental caries	-	-	<1	-
Diaphoresis	2	✔	≥1	✔
Epistaxis	-	-	<1	-
Facial edema	-	-	<1	-
Fungal infection	-	-	<1	-
Glaucoma	-	✔	-	✔
Glossitis	-	-	<1	-
Heat stroke	-	-	<1	-
Hematuria	-	-	<1	-
Hernia	-	-	<1	-
Hyperactive	2	-	-	-
Impaired water secretion	✔	-	-	✔
Lupus-like syndrome	-	✔	-	-
Lymphadenopathy	-	-	<1	-
Moniliasis	-	-	<1	-
Neoplasia	-	-	<1	-
Osteoporosis	-	-	<1	-
Otitis external	-	-	<1	-
Parasitic infection	-	-	<1	-
Periodontal abscess	-	-	<1	-
Salivation increased	-	-	<1	-
Spider telangiectases	✔	-	-	-
Suicide attempt	-	-	<1	-
Sweating	2	✔	-	-
Taste perversion	-	-	≥1	-
Tinnitus	-	-	≥1	✔
Tongue edema	-	-	<1	-
Toxic amblyopia	✔	-	-	-
Toxic delirium	-	✔	-	-
Viral infection	-	-	<1	-
Visual field defect	-	-	<1	-

✔ Percent not specified
- Event not reported

Table 6b. Adverse Drug Events (%) Reported with the Selective Serotonin- and Norepinephrine-reuptake Inhibitors[1-42]

Adverse Events	Desvenlafaxine	Duloxetine	Milnacipran	Venlafaxine
Cardiovascular				
Aneurysm	-	-	-	<1
Angina pectoris	-	-	-	<1
Arrhythmia	-	-	-	<1
Atrial fibrillation	-	<1	-	-
Atrioventricular block	-	-	-	<1
Bigeminy	-	-	-	<1
Blood pressure increased	-	-	3	-
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

Adverse Events	Desvenlafaxine	Duloxetine	Milnacipran	Venlafaxine
Edema	-	-	-	✔
EKG abnormalities	-	-	-	<1
Extrasystoles	-	-	-	<1
Flushing	-	-	3	-
Heart arrest	-	-	-	<1
Heart rate increased	-	-	6	-
Hemorrhage	-	-	-	<1
Hypertension, dose related	<1	-	5	3-13
Hypertensive crisis	-	<1	<1	-
Hypotension	-	-	-	<1
Myocardial infarct	<2	<1	-	<1
Myocardial ischemia	<1	-	-	-
Orthostatic hypotension	<2	<1	-	-
Palpitation	≤3	1-2	7	3
Peripheral edema	-	<1	≥1	-
Postural hypotension	-	-	-	1
Syncope	<2	<1	-	<1
Tachycardia	-	<1	1-2	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	-	-	2	3
Concentration decreased	≤1	-	-	-
Confusion	-	-	<1	2
Deafness	-	-	-	<1
Delusions	-	-	-	<1
Dementia	-	-	-	<1
Depersonalization	<2	-	-	1
Depression	-	-	≥1	1-3
Diplopia	-	<1	-	-
Disorientation	-	<1	-	-
Dizziness	10-13	6-17	10	11-20
Dystonia	-	-	-	<1
Extrapyramidal symptoms	<2	-	-	-
Fatigue	7	2-15	≥1	-
Fever	-	1-3	≥1	✔
Guillain-Barre syndrome	-	-	-	<1
Hallucination	-	-	<1	-
Hostility	-	-	-	<1
Hypoesthesia	-	1	-	-
Headache	-	13	18	25-38
Hypoesthesia	-	1	-	✔
Hypomania	<2	-	-	-
Insomnia	9-12	8-16	12	15-23

Adverse Events	Desvenlafaxine	Duloxetine	Milnacipran	Venlafaxine
Irritability	2	1	≥1	-
Lethargy	-	1	-	-
Loss of consciousness	-	-	<1	<1
Mania	-	<1	-	-
Migraine	-	-	5	✔
Mood swings	-	<1	-	-
Nervousness	-	1	-	6-21
Neuroleptic malignant syndrome	-	-	<1	-
Neuropathy	-	-	-	<1
Neutropenia	-	-	-	<1
Nightmares	-	1	-	-
Paresthesia	≤2	1	-	2-3
Parkinsonism	<1	-	<1	-
Photopsia	-	<1	-	-
Photosensitivity	-	<1	-	-
Restlessness	-	1	-	-
Seizure	-	<1	<1	<1
Sleep disorder	-	1	-	-
Somnolence	≤9	13-20	≥1	12-23
Trismus	-	-	-	✔
Vertigo	-	1	-	✔
Yawning	-	1	-	3-5
Dermatological				
Acne	-	<1	-	-
Alopecia	-	<1	-	-
Bruising	-	-	-	✔
Ecchymosis	-	<1	-	-
Eczema	-	<1	-	-
Erythema	-	<1	-	-
Erythema multiforme	-	-	<1	<1
Exfoliative dermatitis	-	-	-	<1
Hyperhidrosis	-	6-8	9	-
Maculopapular rash	-	-	-	<1
Miliaria	-	-	-	<1
Pruritus	-	3	-	1
Rash	1	4	3	3
Skin atrophy	-	-	-	<1
Stevens-Johnson syndrome	-	<1	<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
Galactorrhea	-	-	<1	-
Hepatic steatosis	-	<1	-	-
Hepatitis	-	<1	<1	<1
Hot flushes	-	2	12	-

Adverse Events	Desvenlafaxine	Duloxetine	Milnacipran	Venlafaxine
Hypercalcinuria	-	-	-	<1
Hyperchlorhydria	-	-	-	<1
Hypercholesterolemia	-	<1	≥1	<15
Hyperglycemia	-	-	-	<1
Hyperkalemia	-	-	-	<1
Hyperlipidemia	-	<1	-	<1
Hyperphosphatemia	-	-	-	<1
Hyperprolactinemia	-	-	>	-
Hyperthyroidism	-	-	-	<1
Hypertriglyceridemia	-	<1	-	-
Hyperuricemia	-	-	-	<1
Hypocholesterolemia	-	-	-	<1
Hypoglycemia	-	1	-	<1
Hypokalemia	-	-	-	<1
Hyponatremia	-	<1	<1	<1
Hypophosphatemia	-	-	-	<1
Hypothyroidism	-	-	-	<1
Jaundice	-	<1	-	<1
Kidney function abnormal	-	-	<1	<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	3	6
Abnormal taste	-	-	≥1	2
Anorexia	5-8	3-5	<1	8-20
Aphthous stomatitis	-	<1	-	-
Appetite decreased	-	3-11	2	-
Appetite increased	-	-	-	✔
Bloody stools	-	<1	-	-
Cholelithiasis	-	-	-	<1
Colitis	-	<1	-	-
Constipation	9-11	5-15	16	8-15
Diarrhea	9-11	7-13	≥1	6-8
Diverticulitis	-	<1	-	-
Dyspepsia	-	4-5	≥1	7
Dysphagia	-	<1	-	-
Eructation	-	<1	-	-
Esophageal stenosis	-	<1	-	-
Flatulence	-	-	≥1	3-4
Gastric emptying impaired	-	<1	-	-
Gastric irritation	-	<1	-	-
Gastric ulcer	-	<1	-	<1
Gastritis	-	1	-	-
GERD	-	-	≥1	-
Hematemesis	-	-	-	<1
Intestinal obstruction	-	-	-	<1
Irritable bowel syndrome	-	<1	-	-

Adverse Events	Desvenlafaxine	Duloxetine	Milnacipran	Venlafaxine
Loose stools	-	2-3	-	-
Melena	-	<1	-	-
Nausea	22-26	14-30	37	21-58
Vomiting	≤4	1-6	7	3-6
Xerostomia	11-17	5-18	5	12-22
Genitourinary			-	
Crystalluria	-	-	-	<1
Cystitis	-	-	≥1	-
Dysuria	-	1	≥2	-
Ejaculation abnormality	≤1	1-4	≥2	2-19
Erectile dysfunction	3-6	1-5	≥2	-
Impotence	-	-	-	4-10
Libido decreased	4-5	2-4	≥2	3-9
Menstrual abnormalities	-	-	-	<1
Micturition urgency	-	<1	-	-
Nocturia	-	<1	-	-
Pollakiuria	-	1-5	-	-
Prostatic disorder	-	-	≥2	✔
Proteinuria	6-8	-	-	-
Pyelonephritis	-	-	-	<1
Pyuria	-	-	-	<1
Scrotal/testicular pain or swelling	-	-	≥2	-
Urinary frequency	-	-	-	3
Urinary hesitation	-	-	≥2	-
Urinary retention	-	<1	≥2	1
Urinary symptoms	≤1	1	-	-
Urinary tract infection	-	-	≥1	-
Urination impaired	-	-	≥2	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
Neutropenia	-	-	<1	-
Pancytopenia	-	-	-	<1
Thrombocytopenia	-	<1	<1	<1
Thrombophlebitis	-	-	-	<1
Musculoskeletal				
Arthralgia	-	-	-	✔
Dysarthria	-	<1	-	-
Extrapyramidal symptoms	-	-	-	<1
Falling	-	-	≥1	-
Hypertonia	-	-	-	3
Malaise	-	<1	-	-
Muscle cramp	-	4-5	-	-

Adverse Events	Desvenlafaxine	Duloxetine	Milnacipran	Venlafaxine
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	<1
Rheumatoid arthritis	-	-	-	<1
Rigors	-	1	-	-
Tendon rupture	-	-	-	<1
Tremor	≤3	3-4	2	4-10
Weakness	≤2	2-8	-	8-19
Respiratory				
Asthma	-	-	-	<1
Atelectasis	-	-	-	<1
Cough	-	3-6	-	✔
Dyspnea	-	-	2	✔
Epistaxis	<2	-	-	-
Nasopharyngitis	-	7-9	-	-
Pharyngitis	-	-	-	7
Pharyngolaryngeal pain	-	1-6	-	-
Pleurisy	-	-	-	<1
Pneumonia	-	-	-	<1
Sinusitis	-	-	-	2
Upper respiratory infection	-	7	-	-
Other				
Anaphylactic reaction	-	<1	-	<1
Angioneurotic edema	-	<1	-	-
Arteritis	-	-	-	<1
Bacteremia	-	-	-	<1
Basophilia	-	-	-	<1
Blurred/abnormal vision	-	1-3	-	4-6
Bruxism	-	<1	-	-
Carcinoma	-	-	-	<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

Adverse Events	Desvenlafaxine	Duloxetine	Milnacipran	Venlafaxine
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	≥1	-
Oropharyngeal edema	-	<1	-	-
Phlebitis	-	<1	-	-
Retinal detachment	-	<1	-	-
Serotonin syndrome	-	-	<1	<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[1-42]

Adverse Events	Citalopram	Escitalopram	Fluoxetine	Fluvoxamine	Olanzapine/ Fluoxetine	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	<1
Cardiomyopathy	-	-	-	<1	-	-	-
Cerebrovascular accident	-	<1	<1	<1	-	<1	-
Chest pain	<1	<1	✔	3	-	3	>10
Chest tightness	-	<1	-	-	-	<1	-
Congestive heart failure	-	-	<1	<1	-	<1	-
Coronary artery disease	-	-	-	<1	-	-	-
ECG abnormal	-	<1	-	<1	-	-	-
Edema	<1	<1	<1	≤ 1-	3	-	-
Hemorrhage	-	-	✔	<1	-	-	-
Hypertension	<1	<1	✔	1-2	-	≥ 1	-
Myocardial infarct	-	-	<1	<1	-	<1	-
Orthostatic hypotension	-	<1	-	≤ 1-	✔	<1	-
Palpitation	-	<1	✔	-	-	2-3	>10
Pericarditis	-	-	-	<1	-	-	-
Peripheral edema	-	-	-	-	9	-	-
Postural hypotension	1-10	-	<1	-	-	-	-
Pulmonary hypertension	-	-	<1	-	-	-	<1
QT_c prolongation	<1	<1	<1	-	<1	-	<1
Supraventricular extrasystoles	-	-	-	<1	-	-	-
Syncope	-	<1	<1	≤ 1	-	-	-
Tachycardia	1-10	<1	<1	≤ 1	<1	≥ 1	-
Vasculitis	-	<1	<1	<1	-	<1	<1
Vasodilation	-	-	1-5	2	≥ 1	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	-
Abnormal gait	-	<1	-	-	-	-	-
Abnormal thinking	-	-	2	3	2	-	-
Aggression	-	<1	-	-	-	-	>2
Agitation	3<10	<1	✔	2-3	-	3-5	>10
Akathisia	-	<1	-	-	-	-	-

Adverse Events	Citalopram	Escitalopram	Fluoxetine	Fluvoxamine	Olanzapine/ Fluoxetine	Paroxetine	Sertraline
Akinesia	-	-	-	<1	-	<1	-
Amnesia	✔	<1	✔	✔	≥ 1	2	-
Anxiety	4	<1	6-15	5-8	-	5	>10
Apathy	-	<1	-	1-3	-	-	-
Aphasia	-	-	-	-	-	<1	-
Asthenia	-	-	-	14	-	-	-
Ataxia	-	-	-	<1	<1	-	-
Auditory hallucination	-	<1	-	-	-	-	-
Blindness	-	-	-	-	-	-	<1
Blurred vision	-	1-10	-	-	-	-	-
Chills	-	-	✔	2	≥ 1	2	-
CNS stimulation	-	-	-	2	-	-	-
Concentration impaired	✔	1-10	-	-	5	3-4	-
Confusion	✔	<1	✔	-	-	1	-
Deafness	-	-	-	-	-	<1	-
Delirium	<1	<1	-	-	-	<1	-
Depersonalization	-	<1	-	-	-	≤3	-
Depression	✔	<1	-	2	✔	-	-
Dizziness	-	5	9	11-15	-	6-14	>10
Dyskinesias	<1	<1	<1	<1	✔	<1	-
Dystonia	-	-	-	<1	<1	<1	<1
Emotional lability	-	<1	✔	-	-	>1	-
Euphoria	-	-	<1	-	-	-	-
Excitability	-	<1	-	-	-	-	-
Extrapyramidal symptoms	-	-	<1	<1	-	<1	<1
Fatigue	5	5-8	-	-	12	-	>10
Fever	2	<1	2	-	2	-	-
Guillain-Barre syndrome	-	-	-	-	-	<1	-
Hallucinations	-	<1	<1	<1	-	<1	<1
Headache	-	24	21	22-35	-	17-18	>10
Hiccup	-	-	<1	-	-	-	-
Hyperkinesia	-	-	✔	✔	-	-	>2
Hyperreflexia	-	<1	-	-	-	-	-
Hypersomnia	-	-	-	-	5	-	-
Hypertonia	-	-	-	2	-	-	1-10
Hypoesthesia	-	<1	-	-	-	-	1-10
Hypokinesia	-	-	-	✔	<1	-	-
Hypomania	-	-	-	<1	-	-	-
Impaired cognition	-	-	-	-	✔	-	-
Insomnia	>10	9-12	10-33	21-35	-	11-24	>10

Adverse Events	Citalopram	Escitalopram	Fluoxetine	Fluvoxamine	Olanzapine/ Fluoxetine	Paroxetine	Sertraline
Irritability	-	<1	-	-	-	-	-
Lethargy	-	3	-	-	3	-	-
Lightheadedness	-	<1	-	-	-	-	-
Malaise	-	<1	<1	✔	-	-	1-10
Mania	-	-	-	✔	✔	-	-
Meningitis	-	-	-	-	-	<1	-
Migraine	✔	<1	<1	-	-	<1	-
Nervousness	-	-	8-14	10-12	2	4-9	1-10
Neuralgia	-	-	-	<1	-	-	-
Neuropathy	-	-	-	<1	-	<1	-
Neurosis	-	-	-	2	-	-	-
Nystagmus	-	<1	-	-	-	-	-
Optic neuritis	-	-	<1	-	-	-	<1
Panic reaction	-	<1	-	-	-	-	-
Paralysis	-	-	-	<1	-	-	-
Paresthesia	✔	2	-	3	-	4	1-10
Parkinsonism	-	<1	-	-	-	-	-
Psychiatric disturbances	-	<1	-	✔	-	-	<1
Seizure	-	✔	-	<1	✔	<1	-
Somnolence	>10	6-13	5-17	22-27	8-14	15-24	>10
Tardive dyskinesia	-	<1	-	<1	-	-	-
Tetany	-	-	-	-	-	<1	-
Tremors	-	-	-	4	-	-	>10
Vertigo	-	<1	-	-	-	>1	-
Yawning	<10	2	<11	2-5	-	2-4	1-10
Dermatological							
Acne	-	-	<1	2	-	-	-
Alopecia	-	-	<1	-	-	-	-
Angioedema	-	-	-	<1	-	<1	<1
Bruising	-	-	<1	4	-	<1	-
Bullous eruption	-	-	-	<1	-	-	-
Cellulitis	-	-	-	-	-	<1	-
Ecchymosis	-	<1	-	-	≥ 1	<1	-
Eczema	<1	-	-	-	-	-	-
Epidermal necrolysis	<1	<1	<1	-	-	<1	-
Erythema multiforme	<1	<1	<1	-	-	<1	-
Erythema nodosum	-	-	<1	-	-	-	-
Exfoliative dermatitis	-	-	<1	-	<1	<1	-
Photosensitivity	<1	-	<1	-	≥ 1	-	<1
Pruritus	✔	-	4	-	-	>1	-

Adverse Events	Citalopram	Escitalopram	Fluoxetine	Fluvoxamine	Olanzapine/ Fluoxetine	Paroxetine	Sertraline
Rash	✔	<1	2-6	-	-	2-3	>10
Stevens-Johnson syndrome	-	-	<1	<1	-	-	<1
Urticaria	<1	-	-	-	-	-	-
Endocrine and Metabolic							
Albuminuria	-	-	<1	-	-	-	-
Alkaline phosphatase increased	-	-	-	-	-	<1	-
Bicarbonate decreased	-	-	-	-	14	-	-
Bilirubin increased	-	<1	-	-	15	<1	<1
BUN increased	-	-	-	-	-	<1	-
Cholecystitis	-	-	-	<1	-	-	-
Cholelithiasis	-	-	<1	<1	-	<1	-
Cholestatic jaundice	-	-	<1	-	-	-	-
Creatinine elevated	-	-	-	-	<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	-
Hyperglycemia	-	<1	-	<1	✔	<1	<1
Hyperprolactinemia	-	-	<1	-	28	-	<1
Hyperthyroidism	-	-	-	-	-	<1	-
Hypoalbuminemia	-	-	-	-	3	-	-
Hypoglycemia	-	<1	-	<1	-	<1	-
Hypokalemia	-	<1	-	<1	-	-	-
Hyponatremia	<1	-	<1	<1	✔	-	-
Hypophosphatemia	-	-	-	-	2	-	-
Hypothyroidism	-	-	-	<1	-	<1	<1
Jaundice	-	-	<1	<1	-	<1	<1
SIADH	<1	<1	-	-	-	-	<1
Transaminase elevation	-	-	-	-	3	<1	<1
Uric acid levels increased	-	-	-	-	3	-	-
Weight gain	✔	<1	✔	✔	✔	>1	1-10
Weight loss	✔	<1	2	1-2	≥1	-	-
Gastrointestinal							
Abdominal cramps	-	1-10	-	-	-	-	-

Adverse Events	Citalopram	Escitalopram	Fluoxetine	Fluvoxamine	Olanzapine/ Fluoxetine	Paroxetine	Sertraline
Abdominal pain	3	2	-	5	2	4	<1
Abnormal taste	✔	<1	✔	2-3	≥1	2	-
Anorexia	4	-	4-17	6-14	-	5-9	>10
Aphthous stomatitis	-	-	<1	-	-	<1	-
Appetite decreased	-	3	-	4	-	5-9	-
Appetite increased	-	1-10	✔	-	20	2-4	1-10
Carbohydrate craving	-	<1	-	-	-	-	-
Cholelithiasis	-	-	<1	-	-	-	-
Colitis	-	-	<1	<1	-	<1	-
Constipation	-	3-5	5	4-10	-	5-16	1-10
Diarrhea	8	8	8-18	11-18	≥ 1	9-12	>10
Dyspepsia	5	-	6-10	8-10	-	2-5	1-10
Dysphagia	-	<1	<1	2	-	<1	-
Esophagitis	-	-	<1	-	-	-	-
Flatulence	✔	2	3	4	3	4	1-10
Gastritis	-	-	<1	-	-	-	-
Gastroenteritis	-	<1	-	-	-	<1	-
Gastroesophageal reflux	-	<1	-	-	-	-	-
GI bleeding	-	-	-	<1	<1	-	-
GI ulcer	-	-	<1	-	-	<1	-
Gingivitis	-	-	-	2	-	-	-
Glossitis	-	-	<1	-	-	-	-
Heartburn	-	<1	-	-	-	-	-
Hematemesis	-	-	-	<1	-	<1	-
Indigestion	-	3	-	10	-	-	-
Intestinal obstruction	-	-	-	<1	<1	<1	-
Melena	-	-	<1	-	-	-	-
Nausea	>10	15	12-29	34-40	-	19-26	>10
Pancreatitis	<1	<1	<1	<1	<1	<1	<1
Vomiting	4	1-10	3	4-6	-	2-3	1-10
Xerostomia	>10	6-9	4-12	10-14	15	9-18	>10
Genitourinary							
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	>10
Erectile dysfunction	-	-	-	-	2	-	-
Hematuria	-	-	-	<1	-	-	-
Impotence	3	2-3	<7	2	-	2-9	1-10
Libido decreased	1-4	3-7	1-11	2-10	-	3-15	>10

Adverse Events	Citalopram	Escitalopram	Fluoxetine	Fluvoxamine	Olanzapine/ Fluoxetine	Paroxetine	Sertraline
Menstrual cramps	-	1-10	-	-	-	-	-
Menstrual disorder	3	<1	<1- 2	3	≥ 1	5	-
Micturition disorders	✔	-	-	-	-	-	<1
Priapism	<1	<1	<1	-	-	-	<1
Sexual dysfunction	✔	-	-	2-4	✔	-	-
Urinary frequency	-	<1	✔	2-3	≥ 1	2-3	-
Urinary incontinence	<1	-	-	-	≥ 1	-	>2
Urinary retention	<1	-	-	1	-	-	-
Urinary tract infection	-	<1	-	2	<1	2	-
Hematologic							
Agranulocytosis	-	-	-	<1	-	-	<1
Anemia	-	<1	<1	<1	<1	<1	-
Aplastic anemia	-	<1	<1	-	-	-	<1
Blood dyscrasias	-	-	-	-	-	<1	-
Hemoglobin increased	-	-	-	-	3	-	-
Hemolytic anemia	<1	<1	<1	-	-	-	-
Increased bleeding	-	-	-	-	-	<1	<1
Ketosis	-	-	-	-	-	<1	-
Leukocytosis	<1	-	-	<1	-	-	-
Leukopenia	-	-	-	<1	-	-	<1
Liver enzymes increased	<1	-	<1	1-2	-	-	-
Lymphadenopathy	-	-	-	<1	-	<1	-
Lymphocytopenia	-	-	-	-	2	-	-
Pancytopenia	-	-	<1	-	-	<1	-
Platelet count abnormalities	-	-	-	-	-	<1	-
Porphyria	-	-	-	<1	-	-	-
Prothrombin decreased	-	<1	-	-	-	-	-
Purpura	<1	<1	<1	<1	<1	-	>2
Thrombosis	-	<1	-	-	-	<1	-
Thrombocytopenia	-	<1	<1	<1	<1	-	<1
Thrombocytopenic purpura	-	-	<1	-	-	-	-
Musculoskeletal							
Arthralgia	2	<1	-	-	4	>1	-
Arthritis	-	-	<1	-	-	<1	-
Back pain	-	-	-	-	-	3	1-10
Bursitis	-	-	<1	-	-	-	-
Choreoathetosis	-	<1	-	-	-	-	-
Limb pain	-	1-10	-	-	-	-	-
Muscle contractions	-	<1	-	2	-	-	-
Muscle cramp	-	<1	<1	-	-	-	-

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

Adverse Events	Citalopram	Escitalopram	Fluoxetine	Fluvoxamine	Olanzapine/ Fluoxetine	Paroxetine	Sertraline
Cataract	-	-	<1	-	-	<1	<1
Dehydration	-	-	<1	-	-	<1	-
Diaphoresis	>10	4-5	2-8	6-7	-	5-14	>10
Ear ache	-	<1	✔	-	-	-	-
Flu-like syndrome	-	5	3-10	3	-	-	-
Gout	-	-	<1	-	-	-	-
Gum hyperplasia	-	-	-	-	-	-	<1
Infection	-	-	-	-	2	5-6	-
Lupus-like syndrome	-	-	<1	-	-	-	<1
Oculogyric crisis	-	-	-	-	-	-	<1
Pain	-	-	<1	10	2-3	-	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	-
Thirst	<1	<1	≥ 2	-	-	-	-
Tinnitus	-	<1	✔	-	-	>1	1-10
Tooth disorder	-	2	-	2-3	-	-	-
Vasculitis	-	-	<1	-	-	-	-
Visual difficulty	-	<1	2	-	-	2-4	1-10
Withdrawal syndrome	<1	<1	-	-	-	-	-

✔ Percent not specified
- Event not reported

Table 6d. Adverse Drug Events (%) Reported with the Serotonin Modulators[1-42]

Adverse Events	Nefazodone	Trazodone
Cardiovascular		
Atrioventricular block	<1	-
Bradycardia	1-10	<1
Edema	-	1-10
Hypertension	-	1-10
Hypotension	1-10	1-10
Peripheral edema	1-10	-
Postural hypotension	1-10	-
Syncope	-	1-10
Tachycardia	-	<1
Vasodilation	1-10	-
Central Nervous System		
Abnormal dreams	1-10	-
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
Drowsiness	>10	-
Fatigue	-	1-10
Fever	1-10	-
Hallucinations	<1	-
Headache	>10	>10
Incoordination	1-10	1-10
Insomnia	>10	-
Lightheadedness	1-10	-
Memory impairment	1-10	-
Paresthesia	1-10	-
Psychomotor retardation	1-10	-
Sedation	-	>10
Seizure	<1	<1
Speech impairment	-	<1
Dermatological		
Alopecia	-	<1
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	
Liver function tests abnormal	<1	-
Prolactin increased	<1	-
Weight gain	-	1-10
Weight loss	-	1-10
Gastrointestinal		

Adverse Events	Nefazodone	Trazodone
Abnormal taste	1-10	-
Appetite increased	1-10	-
Constipation	>10	1-10
Diarrhea	1-10	1-10
Dyspepsia	1-10	-
Gastroenteritis	1-10	-
Nausea	>10	>10
Vomiting	1-10	-
Xerostomia	>10	>10
Genitourinary		
Impotence	1-10	-
Libido decreased	1-10	-
Priapism	<1	<1
Urinary frequency	1-10	-
Urinary retention	1-10	<1
Hematologic		
Hematocrit decreased	1-10	-
Leukopenia	<1	-
Thrombocytopenia	<1	-
Musculoskeletal		
Arthralgia	1-10	-
Extrapyramidal symptoms	-	<1
Hypertonia	1-10	-
Myalgia	-	1-10
Neck rigidity	1-10	-
Rhabdomyolysis	<1	-
Tremor	1-10	1-10
Weakness	>10	-
Respiratory		
Bronchitis	1-10	-
Cough	1-10	-
Dyspnea	1-10	-
Nasal congestion	-	1-10
Pharyngitis	1-10	-
Other		
Allergic reaction	<1	<1
Angioedema	<1	-
Blurred/abnormal vision	7-9	>10
Breast pain	1-10	-
Eye pain	1-10	-
Flu syndrome	1-10	-
Infection	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[1-42]

Adverse Events	Amitrip-tyline	Amitriptyline/ Chlordiazepoxide	Amox-apine	Clomip-ramine	Desip-ramine	Doxepin	Imip-ramine	Mapro-tiline	Nortrip-tyline	Perphenazine/ Amitriptyline	Protrip-tyline	Trimip-ramine
Cardiovascular												
Aneurysm	-	-	-	<1	-	-	-	-	-	-	-	-
Arrhythmia	✔	✔	-	<1	✔	-	✔	<1	✔	✔	✔	✔
Atrial flutter	-	-	-	<1	-	-	-	-	-	-	-	-
AV conduction changes	✔	✔	-	-	-	-	-	-	-	✔	-	-
Bradycardia	-	-	-	<1	-	-	-	-	-	✔	-	-
Bundle branch block	-	-	-	<1	-	-	-	-	-	-	-	-
Cardiac arrest	-	-	-	-	-	-	-	-	-	✔	-	-
Cardiomyopathy	✔	✔	-	-	-	-	-	-	-	✔	-	-
Cerebral hemorrhage	-	-	-	<1	-	-	-	-	-	-	-	-
Chest pain	-	-	-	4	-	-	-	-	-	-	-	-
Chills	-	-	-	2	-	-	-	-	-	-	-	-
Congestive heart failure	-	-	-	-	-	-	✔	-	-	-	-	-
Cyanosis	-	-	-	<1	-	-	-	-	-	-	-	-
ECG changes	✔	✔	-	<1	-	-	✔	-	-	✔	-	-
Edema	-	-	1-10	-	✔	-	-	-	-	-	-	-
Encephalopathy	-	-	-	<1	-	-	-	-	-	-	-	-
Extrasystole	-	-	-	<1	-	-	-	-	-	-	-	-
Heart block	✔	✔	-	<1	-	-	✔	<1	✔	✔	✔	✔
Hypertension	✔	✔	<1	-	✔	✔	✔	<1	✔	✔	✔	✔
Hypotension	-	1-10	-	1-10	✔	✔	-	<1	-	✔	✔	✔
Myocardial infarction	✔	✔	-	<1	✔	-	✔	-	✔	✔	✔	✔
Myocardial ischemia	-	-	-	<1	-	-	-	-	-	-	-	-
Orthostatic hypotension	✔	✔	-	-	-	-	✔	-	✔	✔	-	-
Palpitations	✔	✔	-	1-10	✔	-	✔	-	✔	✔	✔	✔
Peripheral ischemia	-	-	-	<1	-	-	-	-	-	-	-	-
Stroke	✔	✔	-	-	✔	-	✔	-	-	✔	✔	✔
Syncope	✔	✔	-	-	-	-	-	-	-	✔	-	-
Tachycardia	✔	✔	-	1-10	✔	✔	✔	-	✔	✔	✔	✔
Vasospasm	-	-	-	<1	-	-	-	-	-	-	-	-
Central Nervous System												
Abnormal dreaming	-	-	-	3	-	-	-	-	-	-	-	-
Aggressiveness	-	-	-	2	-	-	-	-	-	-	-	-
Agitation	-	-	-	3	✔	-	✔	1-10	✔	-	✔	✔
Akathisia	-	1-10	-	-	-	-	-	<1	-	-	-	-
Anxiety	✔	✔	1-10	9	✔	-	✔	1-10	✔	✔	✔	✔
Aphasia	-	-	-	<1	-	-	-	-	-	-	-	-
Apraxia	-	-	-	<1	-	-	-	-	-	-	-	-

Adverse Events	Amitrip-tyline	Amitriptyline/ Chlordiazepoxide	Amox-apine	Clomip-ramine	Desip-ramine	Doxepin	Imip-ramine	Mapro-tiline	Nortrip-tyline	Perphenazine/ Amitriptyline	Protrip-tyline	Trimip-ramine
Ataxia	✔	>10	1-10	<1	✔	✔	-	<1	✔	✔	✔	-
Catalepsy	-	-	-	<1	-	-	-	-	-	-	-	-
Confusion	-	1-10	-	3	-	-	-	-	✔	-	✔	-
Cerebral edema	-	-	-	-	-	-	-	-	-	✔	-	-
Cognitive function (impaired)	✔	✔	-	-	-	-	-	-	-	✔	-	-
Coma	✔	✔	-	<1	-	-	-	-	-	✔	-	-
Confusion	✔	1-10	1-10	3	✔	✔	✔	<1	-	✔	-	✔
Coordination impairment	✔	✔	<1	5	✔	-	✔	-	✔	✔	✔	✔
Deafness	-	-	-	<1	-	-	-	-	-	-	-	-
Delirium	-	-	-	<1	✔	-	-	-	✔	-	✔	✔
Delusions	-	-	-	<1	-	-	✔	<1	✔	-	✔	✔
Depersonalization	-	-	-	2	-	-	-	-	-	-	-	-
Depression	-	-	-	5	-	-	-	-	-	-	-	-
Disinhibition	-	1-10	-	-	-	-	-	-	-	-	-	-
Disorientation	✔	✔	-	-	✔	✔	✔	<1	✔	✔	-	-
Dizziness	✔	1-10	1-10	54	✔	✔	✔	1-10	-	✔	✔	-
Drowsiness	-	>10	>10	>10	✔	✔	✔	>10	-	✔	✔	✔
Dysarthria	-	>10	-	-	-	-	-	<1	-	-	-	-
Dyskinesia	-	-	-	<1	-	-	-	-	-	-	-	-
Dysphagia	-	-	-	-	-	-	-	<1	-	-	-	-
Dysphonia	-	-	-	<1	-	-	-	-	-	-	-	-
Dystonia	-	-	-	<1	-	-	-	-	-	-	-	-
Emotional lability	-	-	-	2	-	-	-	-	-	-	-	-
Excitement	-	-	1-10	-	-	-	-	-	-	-	-	-
Extrapyramidal symptoms	✔	✔	<1	<1	✔	✔	✔	<1	✔	✔	✔	✔
Fatigue	✔	>10	-	39	✔	-	✔	1-10	-	✔	✔	-
Fever	✔	✔	-	4	✔	-	-	-	-	✔	-	-
Flushing	-	-	-	8	✔	-	-	-	-	-	-	-
Hallucinations	✔	✔	-	<1	✔	-	✔	<1	✔	✔	✔	✔
Hangover effect	-	-	-	-	-	-	-	-	-	-	✔	-
Headache	✔	✔	1-10	28-52	✔	✔	✔	1-10	-	✔	-	✔
Hemiparesis	-	-	-	<1	-	-	-	-	-	-	-	-
Hostility	-	-	-	<1	-	-	-	-	-	-	-	-
Hyperactivity	-	-	-	-	-	-	-	-	-	✔	-	-
Hyperesthesia	-	-	-	<1	-	-	-	-	-	-	-	-
Hyperkinesia	-	-	-	<1	-	-	-	-	-	-	-	-
Hyperreflexia	-	-	-	<1	-	-	-	-	-	-	-	-
Hypertonia	-	-	-	4	-	-	-	-	-	-	-	-
Hypoesthesia	-	-	-	<1	-	-	-	-	-	-	-	-

Adverse Events	Amitrip-tyline	Amitriptyline/ Chlordiazepoxide	Amox-apine	Clomip-ramine	Desip-ramine	Doxepin	Imip-ramine	Mapro-tiline	Nortrip-tyline	Perphenazine/ Amitriptyline	Protrip-tyline	Trimip-ramine
Hypokinesia	-	-	-	<1	-	-	-	-	-	-	-	-
Hypomania	-	-	-	-	✔	-	-	-	✔	-	✔	-
Ideation	-	-	-	<1	-	-	-	-	-	-	-	-
Insomnia	✔	✔	1-10	11-25	✔	-	✔	1-10	✔	✔	✔	✔
Irritability	-	>10	-	-	-	-	-	-	-	-	-	-
Lightheadedness	-	>10	-	-	-	-	-	-	-	-	-	-
Malaise	-	-	-	>10	-	-	-	-	-	-	-	-
Mania	-	-	-	<1	-	-	-	<1	-	-	-	-
Memory impairment	-	>10	-	9	-	-	-	-	-	-	-	-
Migraine	-	-	-	3	-	-	-	-	-	-	-	-
Nervousness	-	-	1-10	4-18	✔	-	-	1-10	-	-	-	✔
Neuralgia	-	-	-	<1	-	-	-	-	-	-	-	-
Neuropathy	-	-	-	<1	-	-	-	-	-	-	-	-
Nightmares	✔	✔	-	-	-	-	✔	-	✔	✔	✔	✔
Oculogyric crisis	-	-	-	<1	-	-	-	-	-	-	-	-
Oculomotor nerve paralysis	-	-	-	<1	-	-	-	-	-	-	-	-
Panic	-	-	-	1	-	-	-	-	✔	-	✔	-
Paradoxical excitement	-	-	-	-	-	-	-	-	-	✔	-	-
Paranoia	-	-	-	<1	-	-	-	-	-	-	-	-
Paresis	-	-	-	9	-	-	-	-	-	-	-	-
Paresthesia	-	-	-	2	-	-	-	-	-	-	-	-
Parkinsonian syndrome	-	-	-	-	✔	-	-	-	-	-	-	-
Psychosis exacerbation	-	-	-	<1	✔	-	✔	-	✔	-	✔	✔
Restlessness	✔	✔	1-10	-	✔	-	✔	-	✔	✔	✔	✔
Sedation	✔	✔	-	-	-	-	-	-	-	✔	-	-
Sensory disturbance	-	-	-	<1	-	-	-	-	-	-	-	-
Seizure	✔	✔	<1	<1	✔	✔	✔	<1	✔	✔	✔	✔
Somnolence	✔	✔	-	-	-	-	-	-	-	✔	-	-
Speech disorder	-	-	-	3	-	-	-	-	-	-	-	-
Stupor	-	-	-	<1	-	-	-	-	-	-	-	-
Syncope	-	-	<1	-	-	-	-	<1	-	-	-	-
Twitching	-	-	-	7	-	-	-	-	-	-	-	-
Yawning	-	-	-	3	-	-	-	-	-	-	-	-
Dermatological												
Acne	-	-	-	2	-	-	-	-	-	-	-	-
Alopecia	✔	✔	-	<1	✔	✔	<1	-	✔	✔	✔	-
Cellulitis	-	-	-	<1	-	-	-	-	-	-	-	-
Cheilitis	-	-	-	<1	-	-	-	-	-	-	-	-
Dermatitis	-	1-10	-	2	-	-	-	-	-	-	-	-

Adverse Events	Amitrip-tyline	Amitriptyline/ Chlordiazepoxide	Amox-apine	Clomip-ramine	Desip-ramine	Doxepin	Imip-ramine	Mapro-tiline	Nortrip-tyline	Perphenazine/ Amitriptyline	Protrip-tyline	Trimip-ramine
Dry skin	-	-	-	2	-	-	-	-	-	-	-	-
Petechiae	-	-	-	-	✔	-	<1	-	✔	-	✔	✔
Photosensitivity	✔	<1	<1	<1	✔	✔	<1	<1	✔	✔	✔	✔
Pruritus	-	-	-	1-6	✔	✔	<1	-	✔	-	✔	✔
Rash	✔	>10	1-10	1-8	✔	✔	<1	<1	✔	✔	✔	✔
Skin discoloration	-	-	-	-	-	-	-	-	-	✔	-	-
Skin ulceration	-	-	-	<1	-	-	-	-	-	-	-	-
Urticaria	✔	✔	-	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	-	-	-	-	-	-	-	-	-	✔	-	-
Prolactin levels increased	-	-	1-10	-	-	-	-	-	-	-	-	-
SIADH	✔	✔	<1	<1	✔	✔	✔	-	✔	✔	✔	✔
Gastrointestinal												
Abdominal pain/cramps	-	-	-	11	✔	-	✔	-	✔	✔	-	-
Anorexia	✔	✔	-	12-22	✔	✔	✔	-	✔	✔	✔	✔
Appetite decreased	-	>10	-	11	-	-	-	-	-	-	-	-
Appetite increased	-	>10	-	>10	-	-	-	-	-	-	✔	✔
Black tongue	✔	✔	-	-	✔	-	✔	-	✔	✔	-	-
Blood in stool	-	-	-	<1	-	-	-	-	-	-	-	-
Chronic enteritis	-	-	-	<1	-	-	-	-	-	-	-	-
Constipation	✔	✔	>10	22-47	✔	✔	✔	1-10	✔	✔	✔	✔
Diarrhea	✔	✔	<1	7-13	✔	✔	✔	-	✔	✔	✔	✔
Dysphagia	-	-	-	2	-	-	-	-	-	-	-	-
Dyspepsia	-	-	-	13-22	✔	-	-	-	-	-	-	-
Esophageal sphincter tone decrease	-	-	-	-	✔	✔	-	-	-	-	✔	✔
Esophagitis	-	-	-	1	-	-	-	-	-	-	-	-
Flatulence	-	-	-	8	-	-	-	-	-	-	-	-
Gastric/peptic ulcer	-	-	-	<1	-	-	-	-	-	-	-	-
Indigestion	-	-	-	-	-	✔	-	-	-	-	✔	✔

Adverse Events	Amitrip-tyline	Amitriptyline/ Chlordiazepoxide	Amox-apine	Clomip-ramine	Desip-ramine	Doxepin	Imip-ramine	Mapro-tiline	Nortrip-tyline	Perphenazine/ Amitriptyline	Protrip-tyline	Trimip-ramine
Intestinal obstruction	-	-	-	<1	-	-	-	-	-	-	-	-
Irritable bowel syndrome	-	-	-	<1	-	-	-	-	-	-	-	-
Nausea	✔	✔	1-10	9-33	✔	✔	✔	1-10	✔	✔	✔	✔
Paralytic ileus	✔	✔	-	<1	✔	-	✔	-	-	✔	-	-
Reflux	-	-	-	<1	-	-	-	-	-	-	-	-
Salivation decreased	-	>10	-	-	-	-	-	-	-	-	-	-
Salivation increased	-	1-10	-	-	-	-	-	-	-	✔	-	-
Stomatitis	✔	✔	-	-	✔	✔	✔	-	-	✔	-	-
Taste changes	✔	✔	-	8	✔	✔	✔	-	✔	✔	✔	✔
Tongue ulceration	-	-	-	<1	-	-	-	-	-	-	-	-
Vomiting	✔	✔	<1	7	✔	✔	✔	<1	✔	✔	✔	✔
Weight gain	✔	>10	-	>10	✔	✔	✔	-	✔	✔	✔	✔
Weight loss	-	>10	-	-	✔	-	✔	-	✔	-	✔	-
Xerostomia	✔	>10	>10	63-84	✔	✔	✔	>10	✔	✔	✔	✔
Genitourinary												
Albuminuria	-	-	-	<1	-	-	-	-	-	-	-	-
Amenorrhea	-	-	-	-	-	-	-	-	-	✔	-	-
Cervical dysplasia	-	-	-	<1	-	-	-	-	-	-	-	-
Dysuria	-	-	-	2	-	-	-	-	-	-	-	-
Ejaculation failure	-	-	-	42	-	-	-	-	-	-	-	-
Ejaculatory dysfunction	-	-	-	-	-	-	-	-	-	✔	-	-
Epididymitis	-	-	-	<1	-	-	-	-	-	-	-	-
Hematuria	-	-	-	<1	-	-	-	-	-	-	-	-
Impotence	-	-	<1	20	✔	-	✔	<1	✔	-	✔	-
Incontinence	-	1-10	-	<1	-	-	-	-	-	-	-	-
Leucorrhea	-	-	-	2	-	-	-	-	-	-	-	-
Micturition disorder/difficulty	-	>10	-	4-14	-	-	-	<1	✔	-	✔	-
Micturition frequency	-	-	-	5	-	-	-	-	-	-	-	-
Polyuria	-	-	-	-	✔	-	-	-	-	✔	-	-
Pyelonephritis	-	-	-	<1	-	-	-	-	-	-	-	-
Renal calculus	-	-	-	<1	-	-	-	-	-	-	-	-
Renal cyst	-	-	-	<1	-	-	-	-	-	-	-	-
Sexual dysfunction	-	1-10	-	-	✔	-	-	-	✔	-	-	✔
Testicular edema	-	-	<1	-	✔	✔	✔	-	✔	-	✔	✔
Urinary retention	✔	✔	<1	2	✔	✔	✔	<1	✔	✔	✔	✔
Urinary tract infection	-	-	-	2-6	-	-	-	-	-	-	-	-
Vaginal hemorrhage	-	-	-	<1	-	-	-	-	-	-	-	-
Vaginitis	-	-	-	2	-	-	-	-	-	-	-	-
Hematologic												

Adverse Events	Amitrip-tyline	Amitriptyline/ Chlordiazepoxide	Amox-apine	Clomip-ramine	Desip-ramine	Doxepin	Imip-ramine	Mapro-tiline	Nortrip-tyline	Perphenazine/ Amitriptyline	Protrip-tyline	Trimip-ramine
Agranulocytosis	-	-	<1	-	✔	✔	<1	-	✔	✔	✔	✔
Aphasia	-	-	-	<1	-	-	-	-	-	-	-	-
Aphasia	-	-	-	<1	-	-	-	-	-	-	-	-
Bone marrow depression	✔	✔	-	<1	-	-	-	-	-	✔	-	-
Eosinophilia	✔	✔	-	-	✔	✔	<1	-	✔	✔	✔	✔
Hemolytic anemia	-	-	-	-	-	-	-	-	-	✔	-	-
Hemoptysis	-	-	-	<1	-	-	-	-	-	-	-	-
Leukemoid reaction	-	-	-	<1	-	-	-	-	-	-	-	-
Leukopenia	-	-	<1	-	-	✔	-	-	-	✔	✔	-
Lymphadenopathy	-	-	-	<1	-	-	-	-	-	-	-	-
Lymphoma-like disorder	-	-	-	<1	-	-	-	-	-	-	-	-
Pancytopenia	-	-	-	-	-	-	-	-	-	✔	-	-
Purpura	✔	✔	-	3	✔	✔	<1	-	✔	✔	✔	✔
Thrombocytopenia	-	-	-	-	✔	✔	<1	-	✔	-	✔	✔
Thrombophlebitis	-	-	-	<1	-	-	-	-	-	-	-	-
Hepatic												
Cholestatic jaundice	-	-	-	-	✔	-	<1	-	✔	✔	✔	✔
Hepatitis	-	-	-	<1	✔	-	-	-	-	-	-	-
Liver enzymes increased	-	-	-	-	✔	-	<1	-	✔	-	✔	✔
Neuromuscular and skeletal												
Arthralgia	-	-	-	3	-	-	-	-	-	-	-	-
Back pain	-	-	-	6	-	-	-	-	-	-	-	-
Choreoathetosis	-	-	-	<1	-	-	-	-	-	-	-	-
Muscle cramps	-	1-10	-	-	-	-	-	-	-	-	-	-
Myalgia	-	-	-	13	-	-	-	-	-	-	-	-
Myoclonus	-	-	-	2-13	-	-	-	-	-	-	-	-
Myositis	-	-	-	<1	-	-	-	-	-	-	-	-
Neuroleptic malignant syndrome	✔	✔	<1	-	-	-	-	-	-	✔	-	-
Numbness	✔	✔	<1	-	✔	✔	✔	-	✔	✔	✔	✔
Paresthesia	✔	✔	<1	1-10	✔	✔	✔	-	✔	✔	-	✔
Peripheral neuropathy	✔	✔	-	-	✔	-	✔	-	✔	✔	-	✔
Rigidity	-	1-10	-	-	-	-	-	-	-	-	-	-
Tardive dyskinesia	-	-	<1	-	-	✔	-	-	-	-	-	-
Tingling	-	-	-	-	✔	-	✔	-	✔	-	✔	✔
Torticollis	-	-	-	<1	-	-	-	-	-	-	-	-
Tremor	✔	1-10	1-10	54	✔	✔	✔	1-10	✔	✔	✔	✔
Weakness	✔	✔	1-10	-	✔	✔	✔	1-10	-	✔	✔	-
Ocular												

Adverse Events	Amitrip-tyline	Amitriptyline/ Chlordiazepoxide	Amox-apine	Clomip-ramine	Desip-ramine	Doxepin	Imip-ramine	Mapro-tiline	Nortrip-tyline	Perphenazine/ Amitriptyline	Protrip-tyline	Trimip-ramine
Accommodation disturbances	-	-	-	<1	✔	-	✔	<1	✔	-	-	✔
Blepharitis	-	-	-	<1	-	-	-	-	-	-	-	-
Blurred vision	✔	✔	1-10	1-10	✔	✔	✔	1-10	✔	✔	✔	✔
Conjunctival hemorrhage	-	-	-	<1	-	-	-	-	-	-	-	-
Conjunctivitis	-	-	-	1	-	-	-	-	-	-	-	-
Cornea and lens changes	-	-	-	-	-	-	-	-	-	✔	-	-
Exophthalmos	-	-	-	<1	-	-	-	-	-	-	-	-
Eye pain	-	-	-	1-10	-	-	-	-	✔	-	✔	✔
Glaucoma,	-	-	-	<1	-	-	-	-	-	-	-	-
Intraocular pressure increased	✔	✔	<1	-	✔	-	-	-	-	✔	✔	✔
Keratitis	-	-	-	<1	-	-	-	-	-	-	-	-
Lacrimation abnormal	-	-	-	3	-	-	-	-	-	-	-	-
Mydriasis	✔	✔	<1	2	✔	-	✔	-	✔	✔	-	✔
Scleritis	-	-	-	<1	-	-	-	-	-	-	-	-
Strabismus	-	-	-	<1	-	-	-	-	-	-	-	-
Otic												
Hyperacusis	-	-	-	<1	-	-	-	-	-	-	-	-
Tinnitus	✔	1-10	<1	6	✔	✔	✔	<1	✔	✔	✔	✔
Respiratory												
Bronchitis	-	-	-	<1	-	-	-	-	-	-	-	-
Bronchospasm	-	-	-	2-7	-	-	-	-	-	-	-	-
Cough	-	-	-	6	-	-	-	-	-	-	-	-
Hypo/hyperventilation	-	-	-	<1	-	-	-	-	-	-	-	-
Epistaxis	-	-	-	2	-	-	-	-	-	-	-	-
Nasal congestion	-	1-10	-	-	-	-	-	-	-	✔	-	-
Pharyngitis	-	-	-	14	-	-	-	-	-	-	-	-
Pneumonia	-	-	-	<1	-	-	-	-	-	-	-	-
Rhinitis	-	-	-	12	-	-	-	-	-	-	-	-
Sinusitis	-	-	-	6	-	-	-	-	-	-	-	-
Other												
Allergic reactions	-	-	<1	-	✔	✔	-	-	✔	-	✔	✔
Dehydration	-	-	-	<1	-	-	-	-	-	-	-	-
Diaphoresis	✔	✔	1-10	9-29	✔	✔	✔	-	✔	✔	✔	-
Diplopia	-	-	-	<1	-	-	-	-	-	-	-	-
Endometrial hyperplasia	-	-	-	<1	-	-	-	-	-	-	-	-
Endometriosis	-	-	-	<1	-	-	-	-	-	-	-	-
Ovarian cyst	-	-	-	<1	-	-	-	-	-	-	-	-
Pain	-	-	-	3	-	-	-	-	-	-	-	-
Parosmia	-	-	-	<1	-	-	-	-	-	-	-	-

Adverse Events	Amitrip-tyline	Amitriptyline/ Chlordiazepoxide	Amox-apine	Clomip-ramine	Desip-ramine	Doxepin	Imip-ramine	Mapro-tiline	Nortrip-tyline	Perphenazine/ Amitriptyline	Protrip-tyline	Trimip-ramine
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[1-42]

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

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

Adverse Events	Bupropion	Mirtazapine
Nausea	1-18	-
Pancreatitis	✔	-
Stomach ulcer	✔	-
Vomiting	2-4	✔
Xerostomia	17-26	25
Genitourinary		
Cystitis	✔	-
Dyspareunia	✔	-
Ejaculation abnormality	✔	-
Impotence	✔	-
Libido decreased	3	-
Libido increased	✔	-
Menopause	✔	-
Menstrual complaints	2-5	-
Painful erection	✔	-
Prostate disorder	✔	-
Salpingitis	✔	-
Urinary frequency	2-5	2
Urinary incontinence	✔	-
Urinary retention	✔	-
Urinary tract infection	<1	-
Urinary urgency	<2	-
Vaginal hemorrhage	<2	-
Vaginitis	✔	-
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	✔	-
Rhabdomyolysis	✔	-
Rigidity	✔	-
Tardive dyskinesia	✔	-
Tremor	3-6	2
Twitching	1-2	-
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	✔	-
Allergic reaction	✔	-
Amblyopia	2	-
Angioedema	✔	-
Auditory disturbance	5	-
Bruxism	✔	-
Deafness	✔	-
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	✔	-
Lymphadenopathy	✔	<1
Mouth ulcers	✔	-
Mydriasis	✔	-
Phlebitis	✔	-
Salivation increased	✔	-
Sciatica	✔	-
Stomatitis	✔	-
Suicidal ideation	✔	-
Thirst	✔	<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, milnacipran, mirtazapine, nortriptyline, olanzapine/fluoxetine, paroxetine, phenelzine, protriptyline, tranylcypromine, trazodone, trimipramine, venlafaxine are not approved for use in pediatric patients. Clomipramine and fluvoxamine 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. Milnacipran is not approved for use in the treatment of MDD. 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. Sertraline is not approved for use in children, except for patients with obsessive compulsive disorder (OCD).

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.

Table 10. Boxed Warning for Olanzapine/Fluoxetine[1]

WARNING
Increased mortality in elderly patients with dementia-related psychosis: Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was approximately 4.5% compared with a rate of approximately 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (CV) (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug, as opposed to some characteristic(s) of the patients, is not clear. Olanzapine/fluoxetine is not approved for the treatment of patients with dementia-related psychosis.

VII. Dosing and Administration

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

Table 11. Usual Dosing Regimens for the Antidepressants[1-42]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Monoamine Oxidase Inhibitors			
Isocarboxazid	Depression: Tablet: 10 mg two to three times per day up to a maximum 60 mg per day; reduce dose to 10-20 mg/day in divided doses when condition improves Elderly: refer to adult dosing	Safety and efficacy in children have not been established.	Tablet: 10 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Phenelzine	Depression: Tablet: 15 mg three 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 Elderly: initial, 7.5 mg/day; increase by 7.5-15 mg/day every three to four days as tolerated; usual therapeutic dose: 15-60 mg/day in three to four divided doses	Safety and efficacy in children have not been established.	Tablet: 15 mg
Selegiline	Depression: Patch: initial, 6 mg/24 hours once daily; may titrate based on clinical response in increments of 3 mg/day every two weeks up to a maximum of 12 mg/24 hours Elderly: refer to adult dosing	Safety and efficacy in children have not been established.	Transdermal patch: 6 mg/24 hours 9 mg/24 hours 12 mg/24 hours
Tranylcypromine	Depression: Tablet: 10 mg twice daily; increase by 10 mg increments at one to three week intervals; maximum: 60 mg/day; usual effective dose: 30 mg/day Elderly: refer to adult dosing	Safety and efficacy in children have not been established.	Tablet: 10 mg
Selective Serotonin- and Norepinephrine-reuptake Inhibitors			
Desvenlafaxine	Depression: Tablet: 50mg once daily Elderly: refer to adult dosing	Safety and efficacy in children have not been established.	Tablet (ER): 50 mg 100 mg
Duloxetine	Depression: Capsule: initial, 40-60 mg/day; dose may be divided or given as a single daily dose of 60 mg; maximum dose: 60 mg/day Diabetic Peripheral Neuropathic Pain: Capsule: 60 mg once daily; lower initial doses may be considered in patients where tolerability is a concern and/or renal impairment is present Fibromyalgia: Capsule: 30 mg once daily for 1 week, then increase to 60 mg/day as tolerated	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
	Generalized Anxiety Disorder: Capsule: initial, 30-60 mg/day as a single daily dose; patients initiated at 30 mg/day should be titrated to 60 mg/day after one week; maximum dose: 120 mg/day; note: doses >60 mg/day have not been demonstrated to be more effective than 60 mg/day Elderly: refer to adult dosing		
Milnacipran	Fibromyalgia: Day 1: 12.5 mg once Days 2-3: 12.5 mg twice daily Days 4-7: 25 mg twice daily >7 days: 50 mg twice daily; may be increased to 200 mg/day based on individual patient response	Safety and efficacy in children have not been established.	Tablet: 12.5 mg 25 mg 50 mg 100 mg Tablet, dose pack: 12.5-25-50 mg
Venlafaxine	Depression: Tablet: 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 (SR): 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 (SR): 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 (SR): 37.5 mg once daily for 1 week; may increase to 75 mg daily, with subsequent weekly increases of 75 mg/day	Safety and efficacy in children have not been established.	Capsule (ER): 37.5 mg 75 mg 150 mg Tablet: 25 mg 37.5 mg 50 mg 75 mg 100 mg Tablet (ER): 37.5 mg 75 mg 150 mg 225 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Social Anxiety Disorder: Capsule (SR): 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 4 days as tolerated; maximum: 225 mg/day Tablet (SR): 75 mg once daily with food; there is no evidence that doses >75 mg/day offer any additional benefit Elderly: refer to adult dosing		
Selective Serotonin-reuptake Inhibitors			
Citalopram	Depression: Oral: 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 Elderly: initial, 10-20 mg once daily; increase dose to 40 mg/day only in nonresponders	Safety and efficacy in children have not been established.	Solution: 10 mg/5 ml Tablet: 10 mg 20 mg 40 mg
Escitalopram	Depression/Generalized Anxiety Disorder: Oral: initial, 10 mg/day; dose may be increased to 20 mg/day after at least one week Elderly: initial, 5-10 mg/day; doses may be increased by 5-10 mg/day after at least one week	Depression: Children ≥ 12 years: 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/day in the morning (lower doses of 5-10 mg/day have been used for initial treatment); may increase after several weeks by 20 mg/day increments; usual dose: 60mg/day; maximum: 80 mg/day; doses >20 mg may be given once daily or divided twice daily	Depression: Children 8-18 years: 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: Children 7-18 years: 10 mg/day; in adolescents and	Capsule (DR): 90 mg Capsule: 10 mg 20 mg 40 mg Solution: 20 mg/5 ml Tablet:

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Depression: Capsule/tablet/solution (IR): 20 mg/day in the morning (lower doses of 5-10 mg/day have been used for initial treatment); may increase after several weeks by 20 mg/day increments; usual dose range: 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 Elderly: some patients may require an initial dose of 10 mg/day with dosage increases of 10 mg and 20 mg every several weeks as tolerated Depressive Episodes 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/day in the morning (lower doses of 5-10 mg/day have been used for initial treatment); may increase after several weeks by 20 mg/day increments; usual dose range: 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 one week, increase to 20 mg/day; may increase after several weeks; doses >60 mg/day	higher-weight children, dose may be increased to 20 mg/day after two weeks; range: 10-60 mg/day	10 mg 15 mg 20 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	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 at four- to seven-day intervals; usual dose range: 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 two divided doses Capsule (SR): 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 (SR): 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 Elderly: reduce dose and titrate slowly	Obsessive-Compulsive Disorder: Children 8-17 years: initial, 25 mg at bedtime; adjust in 25 mg increments at four- to seven-day intervals, as tolerated; range: 50-200 mg/day	Capsule (ER): 100 mg 150 mg Tablet: 25 mg 50 mg 100 mg
Olanzapine and fluoxetine	Depression Associated with Bipolar I Disorder: Initial: 6-25 mg once daily in the evening; dosing range: olanzapine 6-12 mg and fluoxetine 25-50 mg Treatment Resistant Depression: Initial: 6-25 mg once daily in the evening; dosing range: olanzapine 6-18 mg and fluoxetine 25-50 mg Elderly: refer to adult dosing;	Safety and efficacy in children have not been established.	Capsule: 3-25 mg 6-25 mg 6-50 mg 12-25 mg 12-50 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	safety and efficacy have not been established in patients >65 years of age		
Paroxetine	Depression: Tablet/suspension (IR): initial, 20 mg once daily, preferably in the morning; increase by 10 mg/day increments at intervals of at least one week; maximum dose: 50 mg/day Tablet (SR): 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 Elderly: Tablet/suspension (IR): initial, 10 mg/day; increase if needed by 10 mg/day increments at intervals of at least one week; maximum dose: 40 mg/day Elderly: Tablet (SR): initial, 12.5 mg/day; increase if needed by 12.5 mg/day increments at intervals of at lease one week; maximum dose: 50 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	Safety and efficacy in children have not been established.	Suspension: 10 mg/5 ml Tablet: 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
	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 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: Oral (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: Oral (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 and Obsessive-Compulsive Disorder: Oral: 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: Children 6-12 years: initial, 25 mg once daily Children 13-17 years: initial, 50 mg once daily	Concentrate, oral: 20 mg/ml Tablet: 25 mg 50 mg 100 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Elderly: initial, 25 mg/day in the morning; increase by 25 mg/day increments every two to three days if tolerated to 50-100 mg/day; additional increases may be necessary; maximum: 200 mg/day Panic Disorder, Posttraumatic Stress Disorder, Social Anxiety Disorder: Oral: initial, 25 mg once daily; increased after one week to 50 mg once daily Elderly: refer to adult dosing Premenstrual Dysphoric Disorder: Oral: 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	May increase daily dose, at intervals of not less than one week; maximum: 200 mg/day; if somnolence is noted, give at bedtime	
Serotonin Modulators			
Nefazodone	Depression: Tablet: 200 mg/day, administered in two divided doses initially, with a range of 300-600 mg/day in two divided doses thereafter Elderly: initial, 50 mg twice daily; increase dose to 100 mg twice daily in two weeks; usual maintenance dose: 200-400 mg/day	Safety and efficacy in children have not been established.	Tablet: 50 mg 100 mg 150 mg 200 mg 250 mg
Trazodone	Depression: Tablet: initial, 150 mg/day in three divided doses; dose may be increased by 50 mg/day every three-seven days; maximum: 600 mg/day Elderly: initial, 25-50 mg at bedtime with 25-50 mg/day dose increase every three days for inpatients and weekly for	Safety and efficacy in children have not been established.	Tablet: 50 mg 100 mg 150 mg 300 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	outpatients; usual dose: 75-150 mg/day		
Tricyclics and Other Norepinephrine-reuptake Inhibitors			
Amitriptyline	Depression: Tablet: 50-150 mg/day single dose at bedtime or in divided doses; dose may be gradually increased up to 300 mg/day Elderly: initial, 10-25 mg at bedtime; dose should be increased in 10-25 mg increments every week if tolerated; dose range: 25-150 mg/day	Depression: Children >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
Amitriptyline and chlordiazepoxide	Depression and Anxiety: Tablet: initial, three to four tablets in divided doses; may be increased to six tablets per day as required; some patients respond to smaller doses and can be maintained on two tablets Elderly: refer to adult dosing	Safety and efficacy in children have not been established.	Tablet: 12.5-5 mg 25-10 mg
Amoxapine	Depression: Tablet: initial, 25 mg two to three times/day; if tolerated, dosage may be increased to 100 mg two to three times/day; may be given in a single bedtime dose when dosage <300 mg/day; maximum daily dose: 600 mg (inpatients) and 400 mg (outpatients) Elderly: initial, 25 mg at bedtime increased by 25 mg weekly for outpatients and every three days for inpatients if tolerated; usual dose: 50-150 mg/day, but doses up to 300 mg may be necessary	Depression: Children >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: Capsule: initial, 25 mg/day and gradually increase, as tolerated, to 100 mg/day the first two weeks; may then be increased to a total of 250 mg/day maximum	Obsessive-Compulsive Disorder: Children >10 years: initial, 25 mg/day and gradually increase, as tolerated, to a maximum of 3 mg/kg/day or 200 mg/day, whichever is smaller	Capsule: 25 mg 50 mg 75 mg
Desipramine	Depression: Tablet: initial, 75 mg/day in divided does; increase gradually to 150-200 mg/day	Depression: Children >12 years of age: initial, 25-50 mg/day; gradually increase to 100	Tablet: 10 mg 25 mg 50 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	in divided or single dose; maximum: 300 mg/day Elderly: initial, 10-25 mg/day; increase by 10-25 mg every three days for inpatients and every week for outpatients if tolerated; usual maintenance dose: 75-100 mg/day, but doses up to 150 mg/day may be necessary	mg/day in single or divided doses; maximum: 150 mg/day	75 mg 100 mg 150 mg
Doxepin	Depression/Anxiety: Oral: initial, 25-150 mg/day at bedtime or in two to three divided doses; may gradually increase up to 300 mg/day; single dose should not exceed 150 mg; select patients may respond to 25-50 mg/day Elderly: initial, 10-25 mg at bedtime; increase by 10-25 mg every three days for inpatients and weekly for outpatients if tolerated, rarely does the maximum dose required exceed 75 mg/day; a single bedtime dose is recommended	Depression/Anxiety: Children >12 years of age: 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 Oral concentrate: 10 mg/ml
Imipramine	Depression: 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 Elderly: Tablet: initial, 10-25 mg at bedtime; increase by 10-25 mg every three days for inpatients and weekly for outpatients if tolerated, average daily dose to achieve a therapeutic concentration: 100 mg/day; range: 50-150 mg/day; capsules may be used if total daily dosage is ≥75 mg.	Depression: Adolescents: Tablet: initial, 30-40 mg/day; increase gradually; maximum: 100 mg/day in single or divided doses Enuresis: Children ≥6 years: 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) The safety and efficacy of Tofranil-PM® have not been established in children. In adolescents, Tofranil-PM® may be used when total daily dosage is ≥75 mg.	Capsule: 75 mg 100 mg 125 mg 150 mg Tablet: 10 mg 25 mg 50 mg
Maprotiline	Depression and Anxiety: Tablet: initial, 75 mg/day; increase by 25 mg every two	Safety and efficacy in children have not been established.	Tablet: 25 mg 50 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	weeks up to 150-225 mg/day; given in three divided doses or in a single daily dose Elderly: initial, 25 mg at bedtime, increase by 25 mg every three days for inpatients and weekly for outpatients if tolerated; usual maintenance dose: 50-75 mg/day, higher doses may be necessary in nonresponders		75 mg
Nortriptyline	Depression: Oral: 25 mg three to four times/day up to 150 mg/day Elderly: Oral: initial, 30-50 mg/day, given as a single daily dose or in divided doses	Safety and efficacy in children have not been established.	Capsule: 10 mg 25 mg 50 mg 75 mg Solution: 10 mg/5 ml
Perphenazine and amitriptyline	Depression/Anxiety: Tablet: one tablet two to four times per day Elderly: refer to adult dosing	Safety and efficacy in children have not been established.	Tablet: 2-10 mg 2-25 mg 4-10 mg 4-25 mg 4-50 mg
Protriptyline	Depression: Tablet: 15-60 mg/day in three to four divided doses Elderly: Tablet: initial, 5-10 mg/day; increase dose every three to seven days by 5-10 mg; usual dose: 15-20 mg/day	Depression: Adolescents: 15-20 mg per day in three divided doses	Tablet: 5 mg 10 mg
Trimipramine	Depression: Capsule: 50-150 mg/day as a single bedtime dose; maximum: 200 mg/day for outpatients and 300 mg/day for inpatients Elderly: initial, 25 mg at bedtime; increase by 25 mg/day every three days for inpatients and weekly for outpatients, as tolerated; maximum: 100 mg/day	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 (IR): initial, 100 mg twice daily; maximum: 450 mg/day Tablet (SR): initial, 150 mg/day in the morning; may increase to 150 mg twice	Safety and efficacy in children have not been established.	Tablet: 75 mg 100 mg Tablet (SR): 100 mg 150 mg 200 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	daily by day four if tolerated; target dose: 300 mg/day given as 150 mg twice daily; maximum dose: 400 mg/day given as 200 mg twice daily Tablet, hydrochloride (SR 24H): 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 Tablet, hydrobromide (SR 24H): initial, 174 mg/day in the morning; may increase as early as day four to 348 mg/day; maximum dose: 522 mg/day Elderly: initial (IR) 37.5 mg twice daily or (SR) 100 mg/day; increase by 37.5-100 mg every three to four days as tolerated <u>Seasonal Affective Disorder:</u> Tablet (SR): initial, 150 mg/day in the morning; if tolerated, may increase after one week to 300 mg/day <u>Smoking Cessation:</u> Tablet (IR): initial, 150mg once daily for three days; increase to 150 mg twice daily; treatment should continue for seven to twelve weeks Elderly: refer to adult dosing		Tablet (ER): 150 mg 174 mg 300 mg 348 mg 522 mg
Mirtazapine	<u>Depression:</u> Oral: 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 Elderly: initial, 7.5 mg/day at bedtime; increase by 7.5-15 mg/day every one to two weeks; usual dose: 15-30 mg/day	Safety and efficacy in children have not been established.	Orally disintegrating tablet: 15 mg 30 mg 45 mg Tablet: 7.5 mg 15 mg 30 mg 45 mg

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

VIII. Effectiveness

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

Table 12. Comparative Clinical Trials with the Antidepressants

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Depression				
Weihs et al.[96] (2000) Bupropion SR tablets 100-300 mg/day vs paroxetine 10-40 mg/day	DB, MC, RCT Elderly (≥60 years) outpatients 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.[97] (1997) Bupropion SR tablets 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.
Hewett et al.[73] (2009) Bupropion ER 150 mg/day for 4 weeks, then 300 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	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs venlafaxine ER 75 mg/day for 4 weeks, then 150 mg/day vs placebo			score (observed cases - OC), MADRS subscore, percentage of MADRS responders and remitters at week 8; CGI-I score at week 8; CGI-S score and HAMA total score at weeks 1, 2, 4, 6 and 8	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 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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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).
Clayton et al.[119] (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.
Rocca et al.[98] (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.[64] (2009)	RCT, DB, PC (Pooled analysis)	N=3,023 (9 RCT)	Primary: HAM-D_{17} total score	Primary: Decreases in HAM-D_{17} total scores (LOCF) were significantly greater compared with placebo for the overall nine-study desvenlafaxine group

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Desvenlafaxine 50-400 mg/day vs placebo	Patients ≥18 years of age with major depressive disorder	8 weeks	Secondary: MADRS total score, HAM-D_6 total score, CGI-I and CGI-S scales, and rates of response and remission	(-11.2 for desvenlafaxine vs -9.4 for placebo; P<0.001). 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).
Archarya et al.[93] (2006) Duloxetine 40-120 mg daily vs placebo	MA Patients with major depressive disorder	N=2,996 (12 RCT) 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).
Nierenberg et al.[122] (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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Pigott et al.[69] (2007) Acute Phase Duloxetine 60 mg/day vs escitalopram 10 mg/day vs placebo Extension Phase Duloxetine 60-120 mg/day vs escitalopram 10-20 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: $HAMD_{17}$, 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 $HAMD_{17}$ total score and the $HAMD_{17}$ Maier, anxiety/somatization, and retardation/ somatization subscales. The only $HAMD_{17}$ subscale with a significant drug difference was the $HAMD_{17}$ 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%, escitalopram 75%; P=0.44).
Goldstein et al.[123] (2004) Duloxetine 20-40 mg twice daily vs paroxetine 20 mg daily vs	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				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.[128] (2006) Duloxetine 40 mg twice daily vs duloxetine 60 mg twice daily vs paroxetine 20 mg daily vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with major depressive disorder	N=392 8 months	Primary: Mean change from baseline in HAMD-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 HAMD-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 HAMD-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%).
Van Baardewijk et al.[99] (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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Vis et al.[124] (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 RCT) 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.[80] (2008) Duloxetine 60-120 mg/day vs venlafaxine ER 75-225 mg/day	RCT, DB, MC (pooled analysis) Patients >18 years of age with major depressive disorder	N=667 (2 RCT) 12 weeks	Primary: Global benefit–risk ([GBR] defined as remission at endpoint using the 17-item Hamilton Depression Rating Scale [$HAMD_{17}$] ≤7) Secondary: Efficacy	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 $HAMD_{17}$ total scores were not different between the duloxetine and venlafaxine treatment groups. Comparisons of mean change from baseline to endpoint on secondary efficacy measures ($HAMD_{17}$ item 1, $HAMD_{17}$ 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%,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				51.7% and 67.4% for the venlafaxine-treated group, respectively (P=0.309).
Moore et al.[100] (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.[102] (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.[121] (2002) Escitalopram 10 mg daily vs escitalopram 20 mg daily vs citalopram 40 mg	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	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
daily vs placebo			HAM-D, CGI-S, CGI-I, HAMA, QOL, and CES-D	Response to treatment was observed in 50% of escitalopram 10 mg, 51.2% of escitalopram 20 mg, and 45.6% of citalopram 40 mg groups; the difference in response rate was significantly greater than that of placebo group (P<0.01) but not statistically different among the three active groups. There were no significant differences in the mean change of CGI-I, HAM-D, and CGI-S scores from baseline to endpoint between the escitalopram 20 mg daily and citalopram 40 mg daily groups (P=0.09). All three treatment groups exhibited significantly improved HAM-D depressed mood scores from baseline to endpoint (P≤0.01). Patients randomized to the escitalopram 10 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Yevtushenko et al.[71] (2007) Escitalopram 10 mg/day vs citalopram 10 mg/day vs citalopram 20 mg/day	RCT, DB, MC, AC Patients 25-45 years of age with major depressive disorder	N=330 6 weeks	Primary: MADRS total score Secondary: MADRS total score in severely depressed patients, MADRS core depression subscale score, CGI-S and CGI-I scores, proportions of patients classified as responders and remitters	Primary: The mean changes in MADRS total score were significantly greater in patients receiving escitalopram than citalopram 10 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.[101] (2006) Escitalopram 10-20 mg daily	MA Outpatients with major depressive disorder	N=1,321 (3 RCT) 8 weeks	Primary: MADRS, response rate Secondary: CGI-I, CGI-S,	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

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vs citalopram 20-40 mg daily			HAMD	difference between escitalopram and placebo (P=0.0010) and escitalopram and citalopram (P=0.0012) became greater the more severely depressed the patient was at baseline. Secondary: Similar results were seen in the secondary outcomes.
Gorman et al.[103] (2002) Escitalopram 10-20 mg daily vs citalopram 20-40 mg daily	MA Outpatients with major depressive disorder	N=1,321 (3 RCT) 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.[120] (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 RCT) 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Wade et al.[72] (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 $HAMD_{17}$ (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.[105] (2007) Escitalopram 10-20 mg daily vs duloxetine 60 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 forward approach (LOCF)	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 groups in the observed case (OC) analysis (P=0.79).
Boulenger et al.[106] (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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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.[108] (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.[127] (2002) Fluoxetine 20 mg daily vs sertraline 50 mg daily vs paroxetine 20 mg daily	DB, MC, RCT Patients ≥18 years of age with depression	N=284 10-16 weeks	Primary: HAM-D-17 scores Secondary: Improvement in insomnia/sleep disturbances	Primary: As indicated by baseline-to-endpoint improvement on the HAM-D-17, there were no statistically significant differences between fluoxetine, sertraline, and paroxetine on all outcome measures (P=0.365). Secondary: Insomnia improvement when using the sleep disturbance factor was similar in all patients with no significant difference between groups (P=0.868).
Thase et al.[109] (2002) Imipramine (IMI) (mean dosage, 221	DB, SC Patients with chronic major depression who	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/day) vs sertraline (mean dosage, 163 mg/day)	failed to respond to 12 weeks of treatment with either imipramine or sertraline			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.[110] (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). 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.[111] (1998) Mirtazapine 15-60 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

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vs fluoxetine 20-40 mg/day				mirtazapine. No other assessment endpoints were statistically different between the two groups at week 6.
Blier et al.[76] (2009) Mirtazapine 30 mg at bedtime (may be increased to 45 mg after 4 weeks) vs paroxetine 20 mg in the morning (may be increased to 30 mg after 4 weeks) vs mirtazapine 30 mg/day plus paroxetine 20 mg/day for 6 weeks After 6 weeks, non-responders on monotherapy had the second trial drug added to their current regimen. Non-responders on combination therapy had the	RCT, DB Patients with major depressive disorder	N=61 8 weeks	Primary: MADRS, $HAMD_{17}$, 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 $HAMD_{17}$ in the combination group at day 35 (P=0.02) when compared to mirtazapine (P=0.005), and at day 42 (P=0.007) when compared to both drugs alone (mirtazapine: P=0.002; paroxetine: P=0.04). Statistical significance was achieved on the CGI in the combination group at day 35 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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
dosage of both drugs increased by 50%.				
Behke et al.[112] (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.[113] (2001) Mirtazapine 15-60 mg/day vs venlafaxine 75-375 mg/day	DB, MC, RCT Hospitalized patients with severe depressive episode with melancholic features	N=157 8 weeks	Primary: HAM-D, MADRS Secondary: Adverse effects	Primary: 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). 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.[94] (1998) Nefazodone 200 mg twice daily	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs 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.
Corya et al.[88] (2006) Olanzapine 1-12 mg/day and fluoxetine 5-50 mg/day (OFC) vs olanzapine 6-12 mg/day vs fluoxetine 25-50 mg/day vs venlafaxine 75-375 mg/day	RCT, DB Patients ≥18 years of age with treatment-resistant depression, with historic failure on a selective serotonin reuptake inhibitor (SSRI) and prospective failure on open-label venlafaxine	N=483 12 weeks	Primary: MADRS Secondary: CGI-Depression, HAMA, Brief Psychiatric Rating Scale (BPRS)	Primary: For the primary efficacy measure of baseline to endpoint mean change in the MADRS, the OFC group was significantly more effective than the olanzapine group only (-14.1 vs. -7.7, P<0.001). Secondary: For the secondary efficacy measures of baseline to endpoint mean change in CGI-Depression, HAMA, and BPRS, the OFC group was significantly more effective than the olanzapine group (P<0.001, P=0.015, P=0.008, respectively). The OFC group was significantly more effective than fluoxetine for HAMA only (P=0.039). Clinical response rates at endpoint were: OFC 43.3%; olanzapine 25.4%; fluoxetine 33.9%; venlafaxine 50.0%, and low–dose OFC 36.4% (overall, P=0.04; OFC vs olanzapine, P=0.017; OFC vs other treatments, P=NS). Remission rates at endpoint were: OFC 29.9%; olanzapine 13.6%; fluoxetine 17.9%; venlafaxine 22.4%, and low-dose OFC 20.0% (overall, P=0.05; OFC vs olanzapine, P=0.013; OFC vs other treatments, P=NS).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Thase et al.[87] (2007) Olanzapine 6-18 mg/day and fluoxetine 50 mg/day (OFC) vs fluoxetine 50 mg/day vs olanzapine 6-18 mg/day	RCT, DB Patients 18-65 years of age with major depressive disorder who failed to achieve a satisfactory response to an antidepressant after at least 6 weeks of therapy occurring with the current episode of MDD	N=605 (2 RCT) 8 weeks	Primary: Mean change in MADRS total score Secondary: MADRS response and remission, time to response, time to remission, onset of action, CGI-S, HAMA, SDS, SF-36	Primary: There was no significant difference in the mean change in MADRS total score in Study 1 between the treatment groups (OFC, -11.0; fluoxetine, -9.4 [P=0.253]; olanzapine, -10.5 [P=0.739]. In Study 2, there was a significantly greater improvement in MADRS total score with OFC (-14.5) compared to fluoxetine (-8.6; P<0.001) and olanzapine (-7.0; P<0.001). Secondary: Rates of clinical response were not different among the treatment groups in Study 1 (OFC, 36.6%; fluoxetine, 29.4%; olanzapine, 35.8%; overall, P=0.496). Study 2 response rates were significantly better with OFC (44.3%) compared to fluoxetine (29.7%) and olanzapine (16.7%; overall, P<0.001). Remission rates were not different among the treatment groups in Study 1 (OFC, 23.8%; fluoxetine, 17.6%; olanzapine, 18.9%; overall, P=0.522). Study 2 remission rates were significantly better with OFC (30.9%) compared to fluoxetine (15.8%) and olanzapine (10.8%; overall, P=0.001). The time required for 25% of patients to achieve response was 30 days for the OFC group, 55 days for the fluoxetine group (P=0.004) and 53 days for the olanzapine group (P=0.002). The time required for 25% of patients to achieve remission was 52 days for the OFC group and 71 days for the fluoxetine group (P=0.003). The olanzapine group did not have enough remitters to yield 25th percentile time to remission results. There was no significant difference in CGI-S (OFC vs fluoxetine, P=0.384; OFC vs olanzapine, P=0.722) or HAMA (OFC vs fluoxetine, P=0.656; OFC vs olanzapine, P=0.399) among the treatment groups in Study 1. OFC was significantly better on CGI-S (OFC vs fluoxetine, P=0.004; OFC vs olanzapine, P<0.001) and HAMA (OFC vs fluoxetine, P=0.001; OFC vs olanzapine, P<0.001) among the treatment groups in Study 2.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				On the SDS (both studies combined), OFC patients showed significantly greater endpoint improvement (mean=-1.6) than the fluoxetine (mean=-1.1; P=0.027) and olanzapine groups (mean=-0.9; P=0.005). Individual study results were not reported. On the SF-36, the OFC group had a greater endpoint improvement than the olanzapine group on all subscales except vitality. The OFC group had greater endpoint improvement than fluoxetine on the bodily pain and social functioning subscales.
Dunner et al.[95] (2005) Paroxetine CR 12.5-62.5 mg vs placebo	DB, PC, RCT (Pooled analysis) Adults with major depressive disorder	N=303 (4 RCT) 8-12 weeks	Primary: Changes in depressive symptoms according to HAMD-17 and CGI-I, patients achieving remission	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 (HAMD-17 treatment difference, -1.89 [95% CI: –2.91 to –0.87; P<0.001]). The odds of CGI-Improvement response were also significantly higher for patients receiving paroxetine CR than those receiving placebo, regardless of baseline depressive symptomatology (severe MDD: OR, 2.42 [95% CI: 1.50 to 3.91; P<0.001]; nonsevere MDD: OR, 1.63 [95% CI: 1.21 to 2.19; P<0.002]).
Birkenhager et al.[114] (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.[115] (2005)	DB, RCT Patients >59 years	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Sertraline 150 mg daily vs fluvoxamine 200 mg daily	of age with major depressive disorder			treatment groups (P=0.12).
Lenox-Smith et al.[83] (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.[116] (2004) Venlafaxine ER 225 mg/day vs escitalopram 20 mg/day	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$10) rates at endpoint were 41.2% for escitalopram and 36.7% for venlafaxine ER. Response ($\geq$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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Venlafaxine ER had a higher incidence of discontinuation due to adverse events (16% vs 4.1%; P<0.01).
Nemeroff et al.[125] (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.[126] (1999) Venlafaxine ER 75-225 mg/day vs fluoxetine 20-60 mg/day vs placebo	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 investigational sites.
Benkert et al.[117] (1996) Venlafaxine 150-375 mg/day vs	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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
imipramine 200 mg/day				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.[84] (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.[63] (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 the current depressive episode	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. 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).
Cipriani et al.[66] (2009) New-generation	MA Patients with major depressive disorder	N=25,928 (117 RCT) 6-12 weeks	Primary: Response (defined as the proportion of patients who	Primary: <u>Direct Comparisons</u> Efficacy favored escitalopram over citalopram; citalopram over reboxetine and paroxetine; mirtazapine over fluoxetine and venlafaxine; sertraline

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
antidepressants (bupropion, citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, milnacipran, mirtazapine, paroxetine, reboxetine, sertraline, venlafaxine)		(acute treatment)	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	over fluoxetine; and venlafaxine over fluoxetine and fluvoxamine. For dropouts, fluoxetine was better tolerated than reboxetine and citalopram than sertraline. <u>Multiple-treatments Meta-analyses</u> 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, 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%),

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				fluvoxamine (0.4%), paroxetine (0.2%), and reboxetine (0.1%).
Moncrieff et al.[90] (2004) Antidepressants vs placebo	MA Patients with major depressive disorder	N=751 (9 RCT) 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.[91] (2002) Antidepressants vs placebo	MA Adult outpatients with major depressive disorder	N=not specified (75 RCT) 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 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.[92] (2003) Antidepressants vs placebo	MA Studies evaluating relapse prevention of depression	N=4,410 (31 RCT) 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.[129] (1995) Phenelzine (PHZ)	MA Patients with major depressive disorder	Review of Medline and Psychological abstracts from	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%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs isocarboxazid (ISO) vs tranylcypromine (TRP) vs placebo		1959-1992		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.[130] (2005) Fluoxetine, sertraline, nortriptyline, amitriptyline, venlafaxine, imipramine, nefazodone, citalopram, desipramine, paroxetine, pramipexole, fluvoxamine, trazodone, bupropion, clomipramine, duloxetine, mirtazapine, doxepin	MA Patients with major depressive disorder	N=9,311 (132 RCT) Variable duration	Primary: Number of patients who responded to treatment (HAM-D, MADRS) Secondary: Tolerability	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 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.[118] (1997) Mirtazapine up to	MA Patients with major depressive disorder	N=580 (4 RCT) 6 weeks	Primary: HAM-D, HDRS, responder rate (percentages of	Primary: Compared to placebo, both mirtazapine and amitriptyline therapy significantly improved patient HDRS, MADRS, and CGI scores from baseline (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
35 mg daily vs amitriptyline up to 280 mg daily vs placebo up to 7 capsules daily			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 scale, anxiety/ somatization factor, sleep disturbance factor, melancholia factor, tolerability	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). 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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.[131] (2002) Continuation of an SSRI vs discontinuation of an SSRI vs switching of an SSRI	RETRO Adult patients diagnosed with a depressive disorder, taking an SSRI for at least 6 months were interviewed over the phone; prescribing physicians were asked to complete a survey	N=137,401 6 months	Primary: Patient-physician communication about therapy duration and adverse effects, therapy discontinuation or switching of medication within 3 months of SSRI use, BDI-FS, depression symptoms	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; 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.[132] (2000) Tricyclic antidepressants	MA Patients with major depressive disorder	N=10,706 (102 RCT) 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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(TCAs) vs Selective serotonin-reuptake inhibitors (SSRIs)				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.[133] (2003) Tricyclic antidepressants (TCAs) vs Selective serotonin-reuptake inhibitors (SSRIs)	MA Patients with major depressive disorder	N=2,951 (11 RCT) 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: 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.[134] (1997) Tricyclic antidepressants (TCAs) vs Selective serotonin-reuptake inhibitors (SSRIs)	MA Patients with major depressive disorder	N=not specified (34 RCT) 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 subjects 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.
Fibromyalgia				
Arnold et al.[67] (2009)	RCT, MC, DB, PC (pooled analysis)	N=1,332 (4 RCT)	Primary: Pain severity (BPI)	Primary: In both depressed and nondepressed patients, significantly more

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Duloxetine 60-120 mg/day vs placebo	Outpatients ≥18 years of age with fibromyalgia and a score of ≥4 on the average pain severity item of the Brief Pain Inventory (BPI)	12-15 weeks	Secondary: BPI pain interference items, Fibromyalgia Impact Questionnaire (FIQ), CGI-S, Patient Global Impression of Improvement scale (PGI-I), HAMD, Short-Form Health Survey (SF-36), Sheehan Disability Scale (SDS), Multidimensional Fatigue Inventory (MFI)	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, 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 $HAMD_{17}$ total score from baseline to endpoint was significantly greater

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				for duloxetine-treated patients compared with placebo-treated patients. In patients without MDD, the mean improvement on the $HAMD_{17}$ 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.[70] (2008) Duloxetine 20 mg/day vs duloxetine 60 mg/day vs duloxetine 120 mg/day vs placebo	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 Impressions-Severity (CGI-S), tender-point pain assessments, Multidimensional Fatigue Inventory (MFI), $HAMD_{17}$, Sheehan Disability Scale (SDS), Short-Form Health Survey (SF-36), EuroQoL Questionnaire-5	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 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),

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Dimensions (EQ-5D)	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 placebo (21.6%). In patients diagnosed with MDD at study entry, LS mean changes in $HAMD_{17}$ 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.
Clauw et al.[75] (2008) Milnacipran 100 mg daily	RCT, DB, MC, PC Patients 18-70 years of age with fibromyalgia	N=1,207 15 weeks	Primary: Fibromyalgia (FM) composite responder rate and FM pain composite responder rate	Primary: A greater proportion of patients treated with milnacipran (either dose) met all criteria for an FM composite response compared with those who received placebo (milnacipran 100 mg/d, P=0.01; milnacipran 200 mg/d, P=0.02).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs milnacipran 200 mg daily vs placebo			Secondary: Time-weighted averages and response rates of the individual components of the composite responder analyses, weekly averages of PED morning-recall and real-time pain scores, PED weekly recall pain scores	A greater proportion of patients treated with milnacipran (either dose) met all criteria for an FM pain composite response (milnacipran 100 mg/d, P=0.03; milnacipran 200 mg/d, P=0.004). Secondary: There were significant differences between both milnacipran doses and placebo for the time-weighted averages of the weekly mean PED morning-recall pain scores (P<0.001) and PGIC scores (P<0.001). Time-weighted averages of SF-36 PCS scores indicated significant improvement with milnacipran 100 mg/d (P<0.001). Compared with placebo, both doses of milnacipran were associated with a greater mean change in pain scores from baseline (100 mg/d: P=0.03; 200 mg/d: P=0.002) and pain response (100 mg/d: P=0.009; 200 mg/d: P<0.001). The PGIC response rate favored milnacipran, with odds ratios of 1.94 (95% CI, 1.37-2.74) for milnacipran 100 mg/d and 2.19 (95% CI, 1.55-3.11) for milnacipran 200 mg/d (OC analysis). The overall difference was significant for both milnacipran doses compared with placebo (milnacipran 100 mg/d, P=0.001; milnacipran 200 mg/d, P<0.001).
Mease et al.[82] (2009) Milnacipran 100 mg/day vs milnacipran 200 mg/day vs placebo	RCT, DB, MC, PC Patients 18-70 years of age with fibromyalgia	N=888 27 weeks	Primary: Fibromyalgia (FM) composite responder rate and FM pain composite responder rate at weeks 15 and 27 Secondary: Pain severity, patient global impression of change (PGIC); physical function (SF-36 PCS); mental function	Primary: At week 15, more patients treated with milnacipran 100 mg/day (19.6%) and 200 mg/day (19.3%) met criteria as FM responders compared to placebo (12.1%; P=0.028 and P=0.017, respectively). More patients treated with milnacipran 100 mg/day (27.2%) and 200 mg/day (26.8%) met criteria as FM pain responders compared to placebo (19.3%; P=0.056 and P=0.032, respectively). At week 27, more patients treated with milnacipran 100 mg/day (18.3%) and 200 mg/day (18.1%) met criteria as FM responders compared to placebo (13.0%; P=0.245 and P=0.105, respectively). More patients treated with milnacipran 100 mg/day (25.9%) and 200 mg/day (25.6%) met criteria as FM pain responders compared to placebo (18.4%; P=0.072 and P=0.034, respectively). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			(SF-36 MCS); impact of disease [Fibromyalgia Impact Questionnaire (FIQ)]; fatigue [Multidimensional Fatigue Inventory (MFI)]; severity of depressive symptoms (BDI); sleep quality [Medical Outcomes Study (MOS)-Sleep Problems Index scale]; general health-related quality of life (SF-36 domain scores, FIQ, Multidimensional Health Assessment Questionnaire); self-reported cognitive impairments [Multiple Ability Self-report Questionnaire (MASQ)]	For pain severity, there were significant improvements at weeks 15 and 27 in patients receiving milnacipran 200 mg/day compared to placebo (15 weeks: P=0.006, P=0.009, P=0.019 for weekly average of 24-hour morning recall pain scores, weekly average of real-time pain scores, and weekly recall pain scores, respectively; 27 weeks: P=0.01 and P=0.013 for weekly averages of 24-h recall and real-time pain scores, respectively). Pain improvements were similar between milnacipran 200 mg/day and 100 mg/day. Patients receiving milnacipran reported greater overall improvements on the PGIC at week 15 compared to placebo (milnacipran 200 mg/day, P<0.001; milnacipran 100 mg/day, P=0.009. PGIC scores for patients on milnacipran 200 mg/day were significantly improved over patients on placebo at 27 weeks (P<0.001). Improvements with milnacipran 200 mg/day were seen at week 15 in the SF-36 domains of physical functioning (P=0.026), bodily pain (P=0.003), and mental health (P=0.008) compared to placebo. At week 27, both doses of milnacipran showed improvements in the SF-36 domains of bodily pain (milnacipran 200 mg/day, P=0.004; milnacipran 100 mg/day, P=0.043) and mental health (milnacipran 200 mg/day, P=0.015; milnacipran 100 mg/day, P=0.007). Treatment with milnacipran 200 mg/day reduced fatigue compared to placebo as measured by the MFI total score (15 weeks, P=0.016; 27 weeks, P=0.035). Changes in the MASQ total scores were improved for patients on milnacipran 200 mg/day compared to placebo (15 weeks, P=0.025; 27 weeks, P=0.016). No significant difference was found with regards to quality or quantity of sleep as measured by the MOS-Sleep Problems Indices.
Generalized Anxiety Disorder (GAD)				
Hartford et al.[68] (2007)	RCT, DB, MC, PC Outpatients ≥18	N=487 10 weeks	Primary: HAMA total score	Primary: Patients receiving duloxetine or venlafaxine ER experienced greater improvements in anxiety symptom severity (as measured by HAMA)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Duloxetine 60-120 mg/day vs venlafaxine ER 75-225 mg/day vs placebo	years of age with generalized anxiety disorder		Secondary: HAMA psychic anxiety factor score, somatic anxiety factor score, mood item, and tension item; HADS anxiety and depression subscales scores; CGI-I, Patient Global Impression of Improvement (PGI-I) rating scales; Sheehan Disability Scale impairment scores (SDS)	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 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.[74] (2009) Duloxetine 20	RCT, DB, MC, PC Outpatients ≥18 years of age with	N=581 10 weeks	Primary: HAMA total score Secondary:	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/day vs duloxetine 60–120 mg/day vs venlafaxine ER 75–225 mg/day vs placebo	generalized anxiety disorder		HAMA psychic and somatic factor scores, Sheehan Disability Scale (SDS), HADS, CGI-I and Patient Global Impression Improvement (PGI-I)	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 -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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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.[135] (2005) Escitalopram 10-20 mg daily	MC, OL Patients who completed an 8-week, DB, PC, lead-in and were diagnosed with GAD were eligible to enter extension trial	N=526 24 weeks	Primary: CGI-I, HAMA core ≤7 Secondary: Safety	Primary: Ninety two percent of the patients were considered responders. Secondary: Adverse events led to study withdrawal in 9.9% of patents. The most frequent adverse events leading to study withdrawal were ejaculations disorder (1.6%), insomnia (1.3%), and nausea (1%). Serious adverse events were reported by 2.1% of patients, including 1 completed suicide.
Goodman et al.[136] (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).
Bose et al.[73] (2008) Escitalopram 10-	RCT, DB, PC Outpatients 18-65 years of age with	N=404 8 weeks	Primary: Change from baseline to week 8 in the HAMA total	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
20 mg/day vs venlafaxine ER 75-225 mg/day vs placebo	generalized anxiety disorder		score Secondary: HAMA psychic anxiety subscale, CGI-I, CGI-S, VAS, Hospital Anxiety and Depression Scale (HAD), QoL, Sheehan Disability Scale (SDS)	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).
Dahl et al.[137] (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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Bielski et al.[138] (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%). 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).
Ball et al.[139] (2005) Paroxetine 10-40 mg daily vs sertraline 25-100 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 Impressions scale Secondary: Improvement in IU-GAM	Primary: Both sertraline and paroxetine groups displayed significant reductions in HAMA scores from baseline to end of treatment (P<0.001). The mean percent reduction in HAMA scores was 57.3% for the paroxetine group and 55.9% for the sertraline group. The percent of treatment responders was 68% in the paroxetine group and 61% in the sertraline group. 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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Schmitt et al.[140] (2005) Venlafaxine, paroxetine, imipramine, trazodone, diazepam, sertraline	MA Patients with generalized anxiety disorder	N=2,238 8-28 weeks	Primary: Absence of treatment response Secondary: Acceptability of the treatment as measured by the number of people dropping out during the trial	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 (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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Obsessive-compulsive Disorder (OCD)				
Alaghband-Rad et al.[59] (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.[141] (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.[143] (1997) Fluvoxamine 100-300 mg daily vs	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-BOCS obsessions: P=0.000; Y-BOCS compulsions: P=0.000; Y-BOCS

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
paroxetine 20-60 mg daily vs citalopram 20-60 mg daily				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.[142] (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.[146] (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 ($P \leq 0.05$).
Dannon et al.[66] (2007)	OL	N=200	Primary: Panic Self-	Primary: Following 52 weeks of therapy, the clinical improvements observed were

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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	Questionnaire (PSQ), CGI-I	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.[147] (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.[144] (2007) Nefazodone 300-600 mg daily vs	DB, MC, PC, PG, 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
placebo				
Sheehan et al.[145] (2005) Paroxetine CR 25-75 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.
Bandelow et al.[148] (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).
Ballenger et al.[149] (1998) Paroxetine 10 mg daily vs paroxetine 20 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-	Primary: The percent of subjects 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 subjects 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs paroxetine 40 mg daily			Asberg Depression Rating Scale	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-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.
Pollack et al.[85] (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 75 mg, 41.0%; paroxetine 40 mg, 39.3%) than in the placebo group (26.8%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Posttraumatic Stress Disorder (PTSD)				
Davidson et al.[150] (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.[104] (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.[89] (2005) Paroxetine CR 12.5 mg daily or 25 mg daily	DB, MC, PC, RCT Patients aged 18-45 years who had regular menstrual cycles with PMDD	N=47 3 menstrual cycles	Primary: VAS-Mood Secondary: VAS-Total	Primary: A statistically significant difference was observed in favor of paroxetine CR 25 mg versus placebo on the VAS-Mood (P<0.001) and for paroxetine CR 12.5 mg versus placebo (P=0.013). Secondary: Paroxetine CR demonstrated greater mean reduction in VAS-Total scores

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				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.[88] (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.[87] (2007) Duloxetine vs placebo	MA Randomized, double-blind, placebo-controlled clinical trials of patients diagnosed with either an MDD, diabetic peripheral	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 of ECG abnormality or vital sign changes between patients ≥65 years of age and a younger population.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	neuropathy, fibromyalgia, generalized anxiety disorder, or lower urinary tract infection			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.[86] (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.[85] (2000) SSRIs, MAOIs, benzodiazepines, beta blockers, buspirone, gabapentin, olanzapine	MA 36 randomized controlled trials for social anxiety disorders 25 trials were short term (≤14 weeks or less); 7 trials had maintenance	N=5,264 (36 RCT) 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; 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	component; 8 trials had a relapse component; trials were completed prior to 2003			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), 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, GSP=Generalized Social Phobia, HAMA=Hamilton Rating Scale for Anxiety, HAM-D=Hamilton Rating Scale for Depression, IES= Impact of Event Scale, ITT-Intent-to-Treat Analysis, IU-GAM= Indiana University Generalized Anxiety Measurement Scale, 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, NIMH-OC=National Institute of Mental Health-Obsessive-Compulsive Scale, PAS=Panic and Agoraphobia Scale, PMTS=Premenstrual Tension Scale, PTSD=Posttraumatic Stress Disorder, QoL=Quality of Life, Q-LES-Q=Quality of Life, Enjoyment, and Satisfaction Questionnaire, SSRIs=Selective Serotonin-reuptake Inhibitors, VAS=Visual Analog Scale, 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.[84] 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.[75] 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 branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage 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 Antidepressants

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

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
	release tablet, tablet			
Selective Serotonin-reuptake Inhibitors				
Citalopram	solution, tablet	Celexa®*	$$$$	$
Escitalopram	solution, tablet	Lexapro®	$$$	N/A
Fluoxetine	capsule, delayed-release capsule, solution, tablet	Prozac®*, Prozac Weekly®, Sarafem®*, Selfemra®*	$$$-$$$$$	$-$$$
Fluvoxamine	extended-release capsule, tablet	Luvox CR®, Luvox®*†	$$$$	$$
Olanzapine and fluoxetine	capsule	Symbyax®	$$$$$	N/A
Paroxetine	extended-release tablet, suspension, tablet	Paxil®*, Paxil CR®*, Pexeva®	$$$-$$$$$	$-$$$
Sertraline	oral concentrate, tablet	Zoloft®*	$$$$	$
Serotonin Modulators				
Nefazodone	tablet	N/A	N/A	$-$$
Trazodone	tablet	N/A	N/A	$
Tricyclics and Other Norepinephrine-reuptake Inhibitors				
Amitriptyline	tablet	N/A	N/A	$
Amitriptyline and chlordiazepoxide	tablet	Limbitrol®*	$$$$	$-$$$
Amoxapine	tablet	N/A	N/A	$-$$
Clomipramine	capsule	Anafranil®*	$$$$$	$
Desipramine	tablet	Norpramin®*	$$$-$$$$	$-$$
Doxepin	capsule, oral concentrate	N/A	N/A	$
Imipramine	capsule, tablet	Tofranil®*, Tofranil-PM®*	$$$$$	$-$$$$$
Maprotiline	tablet	N/A	N/A	$$
Nortriptyline	capsule, solution	Pamelor®*	$$$$$	$
Perphenazine and amitriptyline	tablet	N/A	N/A	$
Protriptyline	tablet	Vivactil®*	$$$$$	$$$-$$$$$
Trimipramine	capsule	Surmontil®*	$$$$$	$$$$
Antidepressants, Miscellaneous				
Bupropion	extended-release tablet, sustained-release tablet, tablet	Aplenzin®, Wellbutrin®*, Wellbutrin SR®*, Wellbutrin XL®*	$$$$-$$$$$	$-$$$$
Mirtazapine	orally disintegrating tablet, tablet	Remeron®*	$$$	$-$$$

*Generic is available in at least one dosage form or strength.
†Brand is no longer available.
N/A=Not available

X. Conclusions

The antidepressants are used to treat a variety of mental disorders, including anxiety disorders, eating disorders (bulimia nervosa), mood disorders and premenstrual dysphoric disorder.[1-42] Some agents are also approved for the treatment of nonpsychiatric conditions, such as diabetic peripheral neuropathy, fibromyalgia, nocturnal enuresis and tobacco abuse.[1-42] 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.

There are a variety of published clinical trials which directly compare the efficacy and safety of the antidepressants in patients with major depressive disorder. Many studies have demonstrated similar efficacy among the antidepressants.[60,69,72-73,83-84,96-98,102,108,110-117,121-122,125,127] The available guidelines do not give preference to one particular agent over another.[44,46,48] Rather, the selection of an antidepressant should be based on adverse events, tolerability and patient preference.[44,46]

Several of the 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.[83] 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.[49] SSRIs are also recommended for the initial treatment of obsessive-compulsive disorder.[50-51] 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.[59,66,68,73-74,85,136-137,139-143,145-148] Guidelines do not give preference to one agent over another.[49-53,83] The choice of treatment should be based on safety, adverse events, drug interactions, prior response to treatment and comorbid conditions.[50,83]

The SSRIs are recommended as initial therapy for the treatment of premenstrual dysphoric disorder, either given intermittently or continuously.[54-55] Studies have demonstrated efficacy in reducing both physical and behavioral symptoms.[55,88-89] Duloxetine and milnacipran are approved for the treatment of fibromyalgia and have been shown to relieve pain to a greater extent than placebo.[67,70,75,82] The American Pain Society recommends the use of TCAs or SSRIs as one of several initial treatment options for patients with fibromyalgia.[71] It should be noted that these guidelines were published in 2005 and they do not provide recommendations regarding the use of SNRIs.

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.[1-42] 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. Serious neuropsychiatric events, including depression, suicidal ideation, suicide attempt and completed suicide have been reported in patients taking bupropion for smoking cessation.[1] Cases of life-threatening hepatic failure have been reported in patients treated with nefazodone.[1] 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. Guidelines recommend that the MAOIs be reserved for patients who are not responding to other treatment options.[44] Selegiline is available in a transdermal formulation and the clinical data for the 6 mg/24 hours strength indicate that a modified diet is not required at this dose.[29] However, data are limited for the 9 mg/24 hours and 12 mg/24 hours strengths. Patients receiving these doses should follow the dietary modifications required for patients taking MAOIs.[29]

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 products 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.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Cerebral Stimulants/Agents Used for ADHD
Amphetamines, AHFS Class 282004
Anorexigenic Agents and Respiratory and Cerebral Stimulants, Miscellaneous AHFS Class 282092
Central Nervous System Agents, Miscellaneous, AHFS Class 289200
February 10, 2010

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 agents that are approved by the FDA for the treatment of ADHD. This includes cerebral stimulants (amphetamines and methylphenidate derivatives) and atomoxetine. The stimulants are available in a variety of dosage forms, which primarily differ in their release mechanism and duration of action. Although the exact mechanism in ADHD is unknown, 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.[1-17] Due to their potential for abuse, the stimulants are classified as Schedule II controlled substances. Atomoxetine is a selective norepinephrine reuptake inhibitor and it is not a controlled substance.[18]

The cerebral stimulants are also used to treat a variety of sleep disorders.[1-21] 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 FDA-approved to improve wakefulness in adult patients with excessive sleepiness associated with narcolepsy, OSA and shift work sleep disorder.[1-3,19-21] 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.[19-20] As a result, these agents are classified as Schedule IV controlled substances.

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 November 2007.

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)
Amphetamines			
Amphetamine aspartate, amphetamine sulfate, and dextroamphetamine	extended-release capsule, tablet	Adderall®*, Adderall XR®*	Adderall XR®*, amphetamine aspartate, amphetamine sulfate, and dextroamphetamine
Dextroamphetamine	sustained-release	Dexedrine®*†, Procentra®	Dexedrine®*†,

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
	capsule, solution, tablet		dextroamphetamine
Lisdexamfetamine	capsule	Vyvanse®	Vyvanse®
Methamphetamine	tablet	Desoxyn®	none
Anorexigenic Agents and Respiratory and Cerebral Stimulants, Miscellaneous			
Armodafinil	tablet	Nuvigil®	none
Dexmethylphenidate	extended-release capsule, tablet	Focalin®*, Focalin XR®	Focalin®*, Focalin XR®, dexmethylphenidate
Methylphenidate	chewable tablet, extended-release capsule, extended-release tablet (osmotic release), sustained-release tablet, solution, tablet, transdermal patch	Concerta®, Daytrana®, Metadate CD®, Metadate ER®*, Methylin®*, Ritalin®*, Ritalin LA®, Ritalin-SR®*	Concerta®, Ritalin®*, methylphenidate, methylphenidate SR
Modafinil	tablet	Provigil®	none
Central Nervous System Agents, Miscellaneous			
Atomoxetine	capsule	Strattera®	none

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

Table 2. Cerebral Stimulants/Agents Used for ADHD Classified by Duration of Action[1-20,23]

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

†Sustained-release formulation

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 Child and Adolescent Psychiatry	• Initial pharmacologic therapy should be with an agent approved by the FDA for the treatment of ADHD. This includes dextroamphetamine,

Clinical Guideline	Recommendation(s)
(AACAP): **Practice Parameter for the Assessment and Treatment of Children and Adolescents With Attention-Deficit/Hyperactivity Disorder**[24] **(2007)**	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 be individualized.
Institute for Clinical Systems Improvement (ICSI): **Diagnosis and Management of Attention Deficit Hyperactivity Disorder in Primary Care for School-Age Children and Adolescents**[25] **(2007)**	First-Line Medication Trials • Stimulant medications are considered first-line therapy in children. The four types of psychostimulant medications are methylphenidate, dexmethylphenidate, dextroamphetamine and amphetamine salts. • Response to one stimulant does not predict response with other stimulant agents. • Atomoxetine may be considered a first-line agent in patients for whom stimulants may not be an 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. Alternative Medications • When adequate stimulant and atomoxetine trials are unsuccessful (due to either poor response or side effects in spite of adjustment), or if

Clinical Guideline	Recommendation(s)
	associated comorbidity, alternative medication trials may be considered. • Second-line medications for ADHD therapy include tricyclic antidepressants (imipramine, desipramine), alpha adrenergic agonist (clonidine) and a non-tricyclic antidepressant (bupropion).
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 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.
British Association of Psychopharmacology: **Evidence-Based Guidelines for the Management of Attention Deficit Hyperactivity Disorder in Adolescents in Transition to**	<u>Treatment Recommendations for Children</u> • 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.

Clinical Guideline	Recommendation(s)
Adult Services and in Adults[28] (2006)	• 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 Pediatrics (AAP): **Clinical Practice Guideline: Treatment of the School-Aged Child With Attention-Deficit Hyperactivity Disorder[26] (2001)**	General Information
	• Upon diagnosis, the clinician should recommend stimulant medications. The three types of stimulants that are recommended are methylphenidate, dextroamphetamine and mixed amphetamine salts.
	• Behavior therapy may be utilized to improve outcomes in children with ADHD.
	Treatment Goals
	• The primary goal of treatment is to maximize function. Desired results include:
	  o Improvements in relationships with parents, siblings, teachers, and peers
	  o Decreased disruptive behaviors
	  o Improved academic performance, in volume of work, efficiency, completion, and accuracy
	  o Increased independence in self-care or homework
	  o Improved self-esteem
	  o Enhanced safety in the community, such as crossing streets or riding bicycles
	Medication Trials
	• At least 80% of children will respond to one of the stimulants if they are tried in a systematic way. Children who fail to show positive effects or who experience intolerable side effects on one stimulant medication should be tried on another stimulant medication. The reasons for this recommendation include:
	  o Most children who fail to respond to one medication may respond to an alternative stimulant.
	  o Numerous crossover trials indicate efficacy of different stimulants in the same child.
	  o Idiosyncratic response to one medication does not dictate a similar response to another.
	• Children who fail 2 stimulant medications can be tried on a third stimulant medication for the same reason.
	• When the selected regimen has not met targeted outcomes, clinicians should evaluate the original diagnosis, use of all appropriate

Clinical Guideline	Recommendation(s)
	treatments, adherence to the treatment plan, and presence of coexisting conditions. • If a child fails treatment with at least 3 stimulants, second-line treatments may be considered; these include tricyclic antidepressants, clonidine, and bupropion.
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 anticataplectics have little effect on alertness. However, some compounds act on both symptoms. Compounds should be selected depending on the diagnosis and the targeted symptoms. Co-administration 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. • 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)**	<u>Weight Reduction</u> • 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. <u>Pharmacologic Agents</u> • 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. <u>Supplemental Oxygen</u> • Oxygen supplementation is not recommended as a primary treatment for OSA. <u>Medical Therapies Intended to Improve Nasal Patency</u>

Clinical Guideline	Recommendation(s)
	• 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]

Generic Name(s)	ADHD	Narcolepsy	Exogenous Obesity	Obstructive Sleep Apnea	Shift Work Sleep Disorder
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	✔				

†Immediate-release formulation.
‡Sustained-release formulation.
§Extended-release formulation.

IV. Pharmacokinetics

The pharmacokinetic parameters of the cerebral stimulants/agents used for ADHD are listed in Table 5. Transdermal methylphenidate should be applied to the skin 2 hours before the desired therapeutic effect. The recommended application time is 9 hours per day. The patch may be removed earlier than 9 hours if a shorter duration of effect is preferred, or if late day adverse events occur. However, methylphenidate plasma concentrations persist after patch removal, resulting in a mean elimination half-life between 3-4 hours.[12]

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

Generic Name(s)	Onset (hours)	Duration (hours)	Protein Binding (%)	Bioavailability (%)	Metabolism	Excretion (%)	Half-Life (hours)
Amphetamines							
Amphetamine aspartate, amphetamine sulfate, and dextroamphetamine	1-3†	IR: 4-6 XR: 10-12	20†	Well absorbed†	Liver, extensive†	Renal (67-73)†	7-31†
Dextroamphetamine	2-3	IR: 4-6 SR: 6-8	Not reported	Well absorbed	Liver, extensive	Renal (17-73)	10-12
Lisdexamfetamine	Not reported	10	Not reported	Rapid	Liver, Intestinal	Renal (96) Feces (0.3)	<1
Methamphetamine	Not reported	Not reported	Not reported	Rapid	Liver	Renal (62)	4-5
Anorexigenic Agents and Respiratory and Cerebral Stimulants, Miscellaneous							
Armodafinil	Not reported	Not reported	60	Rapid	Liver	Renal	15
Dexmethylphenidate	1	IR: 5-6 XR: 12	12-15	22-25	Liver	Renal (90)	3
Methylphenidate	IR: 0.5-1 SR: 4-7 ER: 1-2 XR: 0.5-1 Transdermal: 2	IR: 3-5 SR: 3-8 ER: 10-12 XR: 8-12 Transdermal: 10-12	10-33	10-52	Liver	Renal (67-97)	3-4
Modafinil	Not reported	Not reported	60	Rapid	Liver, extensive	Renal (80) Feces (1)	7.5-15
Central Nervous System Agents, Miscellaneous							
Atomoxetine	1 week	Not reported	98	63-94	Liver	Renal Feces (<17)	4-22

ER=extended-release (osmotic), IR=immediate-release, SR=sustained-release, 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
Amphetamines			
Amphetamines	1	Furazolidone	Toxicity of amphetamines may be increased by furazolidone. Headache, hyperpyrexia, and elevated blood pressure (possibly hypertensive crisis and intracranial hemorrhage) 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 (possible hypertensive crisis and intracranial hemorrhage) 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			
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

Generic Name(s)	Significance Level	Interaction	Mechanism
			sometimes fatal reactions have occurred. Pharmacologic effects of atomoxetine and MAOIs may be additive.
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.

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 – 8. The boxed warning for the cerebral stimulants/agents used for ADHD are listed in Tables 9 – 12. 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 is not a controlled substance.[18] Clinical studies demonstrated that atomoxetine was not associated with a pattern of response that suggested stimulant or euphoriant properties.[18] There was also no evidence of rebound or withdrawal symptoms upon discontinuation.

Table 7. Adverse Drug Events (%) Reported with the Cerebral Stimulants/Agents Used for ADHD (Amphetamines)[1-20]

Adverse Events	Amphetamine Aspartate/ Amphetamine Sulfate / Dextroamphetamine	Dextroamphetamine	Lisdexamfetamine	Methamphetamine
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	-
Anxiety	8*	-	6	-
Depression	-	-	✔	-
Dizziness	2-7*	✔	5	✔
Dyskinesia	✔ †	✔	✔	-
Dysphoria	✔ †	✔	✔	✔
Euphoria	✔ †	✔	✔	✔
Fever	5*	-	2	-
Headache	✔ †, 26*	✔	12	✔
Insomnia	12-27*	✔	4-27	✔
Irritability	-	-	10	-

Adverse Events	Amphetamine Aspartate/ Amphetamine Sulfate / Dextroamphetamine	Dextroamphetamine	Lisdexamfetamine	Methamphetamine
Labile affect	-	-	3	-
Mania	-	✔	-	-
Nervousness	6*	-	-	-
Overstimulation	✔ †	✔	✔	✔
Psychotic episodes	✔ †	✔	✔	✔
Restlessness	✔ †	✔	3	✔
Seizures	✔ *	-	✔	-
Somnolence	2-4*	-	2	-
Speech disorder	2-4*	-	-	-
Stroke	✔ *	-	✔	-
Tourette's exacerbation	✔ †	✔	✔	✔
Dermatological				
Diaphoresis	2-4*	-	-	-
Hyperhidrosis	-	-	3	-
Angioedema	-	-	✔	-
Photosensitivity	2-4*	-	-	-
Rash	✔ †	✔	3	✔
Stevens-Johnson syndrome	-	-	✔	-
Toxic epidermal necrolysis	-	-	✔	-
Urticaria	✔ †	✔	✔	✔
Endocrine and Metabolic				
Dysmenorrhea	2-4*	-	-	-
Growth suppression	-	-	-	✔
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*	-	-	-
Other GI disturbances	-	✔	-	✔
Nausea	2-8*	-	6-7	✔
Tooth disorder	2-4*	-	-	-
Unpleasant taste	✔	✔	✔	✔

Adverse Events	Amphetamine Aspartate/ Amphetamine Sulfate / Dextroamphetamine	Dextroamphetamine	Lisdexamfetamine	Methamphetamine
Vomiting	2-7*	-	9	✔
Weight loss	4-11*	✔	9	✔
Genitourinary				
Changes in libido	2-4*	✔	✔	✔
Impotence	2-4*	✔	✔	✔
Urinary tract infection	5*	-	-	-
Musculoskeletal				
Tic exacerbation	✔ †	✔	2	✔
Tremor	✔ †	✔	2	✔
Twitching	2-4*	-	-	-
Weakness	2-6*	-	-	-
Respiratory				
Dyspnea	2-4*	-	2	-
Other				
Anaphylaxis	-	-	✔	-
Hypersensitivity reactions	-	-	✔	-
Infection	2-4*	-	-	-
Tolerance/withdrawal symptoms	-	-	-	✔

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

Table 8. Adverse Drug Events (%) Reported with the Cerebral Stimulants/Agents Used for ADHD (Miscellaneous Agents)[1-20]

Adverse Events	Anorexigenic Agents and Respiratory and Cerebral Stimulants, Miscellaneous				Central Nervous System Agents, Miscellaneous
	Armodafinil	Dexmethylphenidate	Methylphenidate	Modafinil	Atomoxetine
Cardiovascular					
Angina	-	✔	✔	-	-
Cardiac arrhythmia	-	✔	✔	-	-
Cerebral arteritis	-	✔	✔	-	-
Cerebral occlusion	-	✔	✔	-	-
Chest pain	-	-	✔	3	-
Diastolic BP increased	-	-	-	-	≤ 4
Edema	-	-	-	1	-
Flushing	-	-	-	-	≥ 2

Adverse Events	Anorexigenic Agents and Respiratory and Cerebral Stimulants, Miscellaneous				Central Nervous System Agents, Miscellaneous
	Armodafinil	Dexmethylphenidate	Methylphenidate	Modafinil	Atomoxetine
Hypotension	-	✔	✔	-	-
Hypertension	-	✔	✔	3	1-9
Orthostatic hypotension	-	-	-	-	<2
Myocardial infarction	-	-	✔	-	-
Palpitations	2	✔	✔	2	3
Pulse increase/decrease	1	✔	✔	-	-
QT prolongation	-	-	-	-	<1
Raynaud's phenomenon	-	-	✔	-	✔
Stroke	-	-	-	-	✔
Sudden death	-	✔	-	-	-
Systolic BP increased	✔	-	-	-	4-5
Tachycardia	-	3	✔	2	2-3
Vasodilation	-	-	-	2	-
Central Nervous System					
Abnormal dreams	-	-	-	-	4
Aggressive behavior	-	✔	✔	-	✔
Agitation	1	-	-	1	✔
Akathisia	-	-	-	-	✔
Anxiety	4	5-6	-	5	✔
Attention disturbance	1	-	-	-	-
Chills	-	-	-	-	3
Crying	-	-	-	-	2
Depression	1-3	✔	✔	2	-
Dizziness	5	6	✔	5	5-6
Drowsiness	-	✔	✔	-	-
Dyskinesia	-	✔	✔	1	-
Early morning awakening	-	-	-	-	<2
Emotional instability	-	-	6†	-	-
Fatigue/lethargy	2	-	-	-	6-9
Fever	1	5	✔	-	3
Hallucinations	-	-	✔ †	-	-
Headache	14-23	25-26	✔, 28†	34	2-19
Hostility	-	-	-	-	✔
Hyperkinesia	-	-	-	1	-
Hypertonia	-	-	-	1	-

Adverse Events	Anorexigenic Agents and Respiratory and Cerebral Stimulants, Miscellaneous				Central Nervous System Agents, Miscellaneous
	Armodafinil	Dexmethylphenidate	Methylphenidate	Modafinil	Atomoxetine
Insomnia	4-6	✔	✔, 13-30†	5	2-15
Irritability	-	-	-	-	≤ 6
Jittery feeling	-	12	-	-	2
Labile affect	-	-	✔	-	-
Mania	-	-	✔	✔	✔
Migraine	1	-	-	-	-
Mood swings	-	-	-	-	1-2
Nervousness	1	✔	✔	7	-
Neuroleptic malignant syndrome	-	✔	✔	-	-
Overstimulation	-	-	-	1	-
Panic disorder	-	-	-	-	✔
Paresthesia	1	-	✔	2	4
Psychotic episodes	-	-	-	✔	-
Restlessness	-	12	-	-	-
Rigors	-	-	-	-	3
Seizures	--	-	✔ †	-	-
Sleep disturbance	-	-	-	-	3
Somnolence	-	-	-	2	4-11
Suicidal ideation	-	-	-	-	✔
Syncope	-	-	-	-	✔
Tic	-	-	3†	-	-
Tourette's exacerbation	-	✔	✔	-	-
Toxic psychosis	-	✔	✔	-	-
Vertigo	-	-	-	1	-
Dermatological					
Alopecia	-	-	✔	-	-
Application site reaction	-	-	✔ †	-	-
Dermatitis	1	-	-	-	2-4
Diaphoresis	-	-	-	1	2
Erythema	-	-	✔	-	-
Erythema multiforme	-	✔	✔	✔ -	-
Exfoliative dermatitis	-	✔	✔	-	-
Flushing	-	-	-	-	2
Hair loss	-	✔	✔	-	-
Herpes simplex	-	-	-	1	-

Adverse Events	Anorexigenic Agents and Respiratory and Cerebral Stimulants, Miscellaneous				Central Nervous System Agents, Miscellaneous
	Armodafinil	Dexmethylphenidate	Methylphenidate	Modafinil	Atomoxetine
Hyperhidrosis	1	-	✔	-	4
Rash	1-4	✔	✔	-1	2
Stevens-Johnson syndrome	-	-	-	✔	-
Toxic epidermal necrolysis	-	-	✔	-	-
Urticaria	-	✔	✔	-	✔
Endocrine and Metabolic					
Dysmenorrhea	-	-	✔	-	6
Growth suppression	-	-	✔	-	-
Hot flushes	-	-	-	-	8
Menstrual disturbances	-	-	-	-	2-3
Gastrointestinal					
Abdominal pain	2	15	✔	-	7-18
Anorexia	1	6	✔, 5-46†	4	<3
Appetite decreased	1	30	✔, 26†	-	11-16
Bruxism	-	-	✔	-	-
Constipation	1	-	✔	2	1-9
Diarrhea	4	-	✔	6	4
Dry mouth	2-7	7	✔	4	4-21
Dyspepsia	2	5-8	✔	5	4-6
Flatulence	-	-	-	1	2
Mouth ulceration	-	-	-	1	-
Nausea	-	9	✔, 12†	11	7-21
Stomach cramps	-	✔	-	-	-
Thirst	-	-	-	1	-
Unpleasant taste	-	-	-	1	-
Vomiting	1	-	✔, 10†	-	3-11
Weight loss	-	✔	✔, 9†	-	2-3
Genitourinary					
Abnormal urine	-	-	-	1	-
Dysuria	-	-	-	-	3
Ejaculatory disturbance	-	-	-	-	3
Erectile disturbance	-	-	✔	-	9
Hematuria	-	-	-	1	-
Impotence	-	-	-	-	3
Libido decreased	-	-	✔	-	4

Adverse Events	Anorexigenic Agents and Respiratory and Cerebral Stimulants, Miscellaneous				Central Nervous System Agents, Miscellaneous
	Armodafinil	Dexmethylphenidate	Methylphenidate	Modafinil	Atomoxetine
Orgasm abnormal	-	-	-	-	2
Polyuria	1	-	-	-	-
Prostatitis	-	-	-	-	2
Pyuria	-	-	-	1	-
Urinary retention	-	-	-	-	7
Hematologic					
Agranulocytosis	-	-	-	✔	-
Anemia	-	✔	✔	-	-
Eosinophilia	-	-	-	1	-
Leukopenia	-	✔	✔	-	-
Pancytopenia	✔	-	✔	-	-
Thrombocytopenic purpura	-	✔	✔	-	-
Hepatic					
Abnormal liver function tests	✔	✔	✔	2	-
Hepatic coma	-	✔	✔	-	-
Hepatotoxicity	-	-	-	-	✔
Jaundice	-	-	-	-	✔
Musculoskeletal					
Arthralgia	-	✔	✔	-	-
Back pain	-	-	-	6	-
Tic	-	-	✔, 7†	-	-
Tremor	1	-	-	1	2
Ocular					
Abnormal vision	-	-	-	1	-
Accommodation difficulties	-	✔	✔	1	-
Amblyopia	-	-	-	1	-
Blurred vision	-	✔	✔	1	-
Dry eyes	-	-	✔	-	-
Eye pain	-	-	-	1	-
Mydriasis	-	-	✔	-	<2
Respiratory					
Cough	-	-	✔	-	11
Dyspnea	1	-	✔	-	-
Epistaxis	-	-	-	1	-
Lung disorder	-	-	-	2	-

Adverse Events	Anorexigenic Agents and Respiratory and Cerebral Stimulants, Miscellaneous				Central Nervous System Agents, Miscellaneous
	Armodafinil	Dexmethylphenidate	Methylphenidate	Modafinil	Atomoxetine
Nasal congestion	-	-	✔, 6†	-	-
Nasopharyngitis	-	-	✔, 5†	-	-
Pharyngitis	-	-	✔	4	-
Pharyngolaryngeal pain	-	4	✔	-	-
Respiratory tract infection	-	-	✔	-	-
Rhinitis	-	-	✔	7	-
Rhinorrhea	-	-	-	-	4
Sinus headache	-	-	-	-	3
Sinusitis	-	-	✔	-	6
Other					
Accidental injury	-	-	✔	-	-
Allergic contact sensitization	-	-	✔ †	-	✔
Anaphylaxis	✔	-	✔ †	✔	-
Ear infection	-	-	-	-	3
Flu-like syndrome	1	-	-	4	✔
Hypersensitivity reactions	-	✔	✔	✔	<1
Influenza	-	-	-	-	3
Necrotizing vasculitis	-	✔	✔	-	-
Pain	1	-	-	-	-
Thirst	1	-	-	-	-
Viral infection	-	-	28†	-	-

†Transdermal formulation
✔ Percent not specified
- Event not reported

Table 9. 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 10. 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 11. 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 12. 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.

VII. Dosing and Administration

The usual dosing regimens for the cerebral stimulants/agents used for ADHD are listed in Table 13.

Table 13. Usual Dosing Regimens for the Cerebral Stimulants/Agents Used for ADHD[1-20]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Amphetamines			
Amphetamine aspartate, amphetamine sulfate, and dextroamphetamine	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. ADHD (Capsule XR): 20 mg daily; may titrate at weekly intervals to appropriate efficacy and tolerability as indicated 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.	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. ADHD (Capsule XR): 6-12 years of age: 5-10 mg once daily; may increase dose by 5-10 mg daily at weekly intervals 13-17 years of age: 10 mg once daily; may increase to 20 mg daily after one week if ADHD symptoms not adequately controlled 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.	Capsule (XR): 5 mg 10 mg 15 mg 20 mg 25 mg 30 mg Tablet: 5 mg 7.5 mg 10 mg 12.5 mg 15 mg 20 mg 30 mg
Dextroamphetamine	ADHD (IR): 5 mg once or twice daily; may increase daily dose in 5 mg increments at weekly intervals until optimal response	ADHD (IR): 3-5 years of age: 2.5 mg once daily; may increase by 2.5 mg daily at weekly intervals until optimal	Capsule (SR): 5 mg 10 mg 15 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	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 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.	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; 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.	Solution (IR): 5 mg/5 ml Tablet (IR): 5 mg 10 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
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
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: 150mg 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 (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 methylphenidate ADHD (Capsule XR): Methylphenidate naïve patients: 10 mg once daily; may increase by 10 mg increments at weekly intervals Patients already using methylphenidate: initiate dexmethylphenidate at half	Children ≥6 years of age: 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 methylphenidate ADHD (Capsule XR): Methylphenidate naïve patients: 5 mg once daily; may increase by 5 mg increments at weekly intervals	Capsule (XR): 5 mg 10 mg 15 mg 20 mg Tablet: 2.5 mg 5 mg 10 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	(1/2) the current total daily dose of racemic methylphenidate Patients already using dexmethylphenidate immediate-release tablets: switch to the same daily dose	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	
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 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. Tablet ER Osmotic (Concerta®): Initial, 18-36 mg once daily; may increase in 18 mg increments at weekly intervals 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	Children ≥6 years of age: 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, 5 mg twice daily; 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. Tablet ER Osmotic (Concerta®): Initial, 18 mg once daily; may increase in 18 mg increments at weekly intervals 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	Capsule (ER): 10 mg 20 mg 30 mg 40 mg 50 mg 60 mg Solution: 5 mg/5 ml 10 mg/5 ml Tablet (IR): 5 mg 10 mg 20 mg Tablet, chewable (IR): 2.5 mg 5 mg 10 mg Tablet (ER osmotic): 18 mg 27 mg 36 mg 54 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
	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. 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.	needed and remove 9 hours after application. Narcolepsy: Solution (Methylin®), Tablet (Ritalin®, Methylin®): Initial, 5 mg twice daily; 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 Administer either as a single daily dose in the morning or as evenly divided doses in the morning and late afternoon or early evening.	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 Administer either as a single daily dose in the morning or as evenly divided doses in the morning and late afternoon or early evening.	Capsule: 10 mg 18 mg 25 mg 40 mg 60 mg 80 mg 100 mg

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

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the cerebral stimulants/agents used for ADHD are summarized in Table 14.

Table 14. 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%) subjects 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 RCT) 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, PG, 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.
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 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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Greenhill et al.[49] (2006) DXM-XR (Focalin XR®) 5-30 mg daily vs placebo	DB, MC, PC, PG, 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, FXD, MC, PG, 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 with improvement ≥30% 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). 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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.
Biederman et al.[51] (2007) LDX (Vyvanse®) 30-70 mg daily vs placebo	DB, FD, MC, PC, PG, 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 (Vyvanse®) 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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.
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).
Wolraich et al.[73] (2001) MPH-ER (Concerta®) 18-54 mg daily vs	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	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
MPH-IR 5-15 mg three times daily vs placebo			parents), CGI-I scores (investigators), global assessment of efficacy (parents and teachers)	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 three times daily vs placebo	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.
Gau et al.[70] (2006) MPH-ER (Concerta®) 18-36 mg daily vs	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
MPH-IR 5-10 mg three times daily				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 vs placebo	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).
Swanson et al.[77] (2004) MPH-ER (Concerta®) 18-54 mg daily vs MPH-XR (Metadate CD®)	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	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
20-60 mg daily vs placebo	MPH in doses of 10-60 mg daily			
Silva et al.[79] (2005) MPH-ER (Concerta®) 18 mg vs MPH-ER (Concerta®) 36 mg vs methylphenidate extended-release (ER-MPH) 20 mg vs methylphenidate extended-release (ER-MPH) 40 mg vs placebo All medications were dosed once per study day (6	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
consecutive Saturdays). Subjects continued their regular ADHD medications on Sunday through Thursday of the study weeks, with no medications allowed on Friday				
Efron et al.[69] (1997) MPH-IR 0.3 mg/kg/dose twice daily vs DEX-IR 0.15 mg/kg/dose twice daily Patients received 1 drug for 2 weeks then crossed over to the other stimulant for 2 weeks.	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).
Pelham et al.[78] (1990) MPH-IR 10 mg twice daily vs	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	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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
MPH-SR (Ritalin SR®) 20 mg daily vs DEX-SR (Dexedrine®) 10 mg daily vs pemoline 56.25 mg daily vs placebo			continuous performance task	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).
Greenhill et al.[54] (2002) MPH-XR (Metadate CD®) 20-60 mg daily vs placebo	DB, MC, PC, PG, 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)	RCT, OL (first 5 weeks) then DB, PC	N=80	Primary: Evaluate time	Primary: Mean SKAMP-D scores were improved with MTS vs placebo (mean

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Methylphenidate transdermal system (MTS) 10-27 mg daily vs placebo transdermal system (PTS)	Children 6-12 years of age diagnosed with ADHD	7 weeks	course effects of MTS vs PTS via SKAMP-A, SKAMP-D, PERMP, ADHD-RS-IV, CPRS-R, CGI-I, and PGA rating scales Secondary: Acute efficacy and tolerability of MTS	score 3.2 vs 8.0) and at all time points assessed including 12 hours post-application (P<0.01). 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),	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
12.5 cm^2 (0.9 mg/hour), and 25 cm^2 (1.8 mg/hour), 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).				patch had been removed (i.e., throughout the 12-hour assessment). Incidence of skin rash was reported as 40%-50%.
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)	RCT, DB, MC, PC	N=268	Primary: Children's Sleep	Primary: No significant difference in the severity of sleep problems was

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Methylphenidate transdermal system (MTS) 10-30 mg daily worn for 9 hours per day or MPH-ER (Concerta®) 18-54 mg daily vs placebo	Children 6-12 years of age diagnosed with ADHD (predominantly hyperactive-impulsive, predominantly inattentive, or combined type)	5 weeks	Habits Questionnaire (CSHQ)	observed among the treatment and placebo groups (P≥0.233). No significant differences in the numbers of sleep problems were 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.
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).
Spencer et al.[60] (2002) Atomoxetine up to 90 mg daily vs placebo	DB, MC, PC, RCT (pooled data from 2 trials) 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).
Cheng et al.[61] (2007) Atomoxetine vs placebo	MA Patients diagnosed with ADHD	N=1,828 (9 RCT) 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).
Prasad et al.[62] (2007) Atomoxetine 0.5-1.8 mg/kg/day vs standard current therapy (SCT)	MC, OL, PRO, 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There was not a statistically significant difference between groups in reduction in FBIM scores (P>0.05).
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, PG, 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 were similar in both groups. Most adverse events reported 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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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 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.	RCT, DB, PC, and 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 subjects 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, 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	OL, R African-American children 6-12 years of age diagnosed	N=183 3 weeks	Primary: Investigator-related ADHD-RS and CGI-I, performed at weeks 1, 2, and	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
daily vs MPH-ER (Concerta®) 18 mg once daily	with ADHD		3; parental satisfaction questionnaire (PSQ)	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). 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	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs MPH-IR titrated up to 60 mg daily				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.
Adler et al.[46] (2008) Atomoxetine 60-120 mg/day	OL, MC Adults diagnosed with ADHD	N=384 4 years	Primary: CAARS-Inv:SV Total ADHD Symptom score Secondary: CAARS-Self:SV, CGI-ADHD-S, $HAMD_{17}$, HAMA, WRAADDS, and Sheehan Disability Scale	Primary: The mean CAARS-Inv:SV Total ADHD Symptom scores decreased 30.2% from baseline to endpoint (-8.8, P<0.001). Secondary: Significant decreases were found on the CAARS-Inv:SV subscales, and the CAARS-Self:SV total and subscales (P<0.001). CGI-ADHD-S and WRAADDS scores improved significantly from baseline (-1.1 and -5.0, respectively; 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).
Faraone et al.[63] (2006) AMP-IR, AMP-XR, atomoxetine, bupropion, DEX-IR,	MA Patients diagnosed with ADHD	N=2,988 (29 RCT) Variable duration	Primary: Effect sizes	Primary: All of the drugs groups produced a significant measure of effect compared to placebo (P<0.0001). 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
DEX-ER, DEXM-IR, modafinil, MPH-ER, MPH-IR, MPH-XR, MTS, pemoline				The 2 classes of stimulant medications (short acting and long acting) did not differ significantly from one another (P=0.14).
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 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There was 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 Group[83] (1998) Modafinil 200-400 mg daily	DB, MC, PC, PG, RCT Adults 18-68 years of age diagnosed with narcolepsy	N=283 9 weeks	Primary: ESS Secondary: MSLT, MWT, CGI-C	Primary: Both modafinil treatment groups reduced mean ESS scores and subjective sleepiness at each time point (weeks 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				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 vs placebo	MC, PC, RCT, XO Patients 27-59 years of age diagnosed with narcolepsy	N=75 6 weeks	Primary: MWT results, patient assessed sleepiness Secondary: ESS	Primary: MWT (sleep latency) increased by 40% with modafinil 200 mg (P<0.002) and by 54% with modafinil 400 mg (P<0.001) compared with placebo. There was not a significant difference between modafinil treatment groups. 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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) Modafinil 200 mg daily, then 400 mg daily without a washout period between treatments, with a	OL, RCT Adults 17-65 years of age diagnosed with narcolepsy who had been receiving MPH for EDS for a month	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 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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
2-day washout period between treatments, or by using a taper-down/titrate-up protocol				
Obstructive Sleep Apnea (OSA)				
Hirshkowitz et al.[41] (2007) Armodafinil 150 mg daily 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 sleepiness (ES) during continuous positive airway pressure therapy	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 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 h at weeks 4 and 12 and at the final visit compared with placebo (all P<0.05).
Roth et al.[44] (2006)	RCT, DB, MC, PC Patients 18-65 years	N=395 12 weeks	Primary: MWT, CGI-C	Primary: The mean changes in MWT sleep latency across the first 4 tests were significantly greater in the armodafinil 150mg/d, 250mg/d, and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Armodafinil 150-250 mg daily vs placebo	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		Secondary: ESS, CDR, BFI	combined groups compared with placebo at the final visit (all, P<0.001). The 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/d, 250 mg/d, and combined groups compared with placebo (all, P<0.001). The 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). 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/d compared with placebo at week 4 (both, P<0.05) and with armodafinil 250 mg/d 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/d, 250 mg/d, 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				was generally mild or moderate in patients receiving armodafinil (58.4%) or placebo (46.9%).
Black et al.[33] (2005) Modafinil 200-400 mg daily vs placebo	DB, MC, PC, PG, 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.
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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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 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.[36] (2005) Modafinil 200 mg daily administered 30-60 minutes before the start of work shift	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,	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	with ≥6 hours or worked between 10 PM and 8 AM and at least three shifts occurring consecutively			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).

Drug regimen abbreviations: AMP=mixed amphetamine salts, BID=twice a day, DEX=dextroamphetamine, DXM=dexmethylphenidate, ER=extended release, FD=forced dose, FXD=fixed dose, IR=immediate release, LDX=lisdexamfetamine, MPH=methylphenidate, MTS=methylphenidate transdermal system, PTS=placebo transdermal system, QD=daily, SR=sustained release, TID=three times a day, XR=extended release

Study abbreviations: DB=double blind, HTH=head-to-head trial, MA=meta-analysis, MC=multi-center, OL=open-label, OS=observational study, PC=placebo-controlled, PG=parallel-group, PRO=prospective trial, RCT=randomized controlled trial, XO=crossover design

Other abbreviations: ADHD-RS=ADHD rating scale, BFI=Brief Fatigue Inventory, CAARS=Conner's adult ADHD rating scale, CAARS-Inv:SV= Conners'Adult ADHD Rating Scale–Investigator Rated: ScreeningVersion, 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, CDR=Cognitive Drug Research, 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:form, CSHQ= Children's Sleep Habits Questionnaire, CTRS-R=Conners teacher rating scale–revised, DBP=diastolic blood pressure, EDS=excessive daytime sleepiness, ESS=Epworth sleep scale, FCRTT=four-choice reaction time test, FIBM=Family Burden of Illness Module, HAMA=Hamilton Anxiety Rating Scale, $HAMD_{17}$=Hamilton 17-item Depression Rating scale, HR=heart rate, HSPP=Harter Self-Perception Profile, I/O=inattention/overactivity, KSS=Karolinska Sleepiness Scale, MSLT=multiple sleep latency test, MWT=maintenance of wakefulness test, nCAP=Nasal continuous positive airway pressure, O/D=oppositional/defiance, PERMP=permanent product measure of performance, PLM=periodic leg movements, 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, SF-36=36-item Short Form Health Survey, SERS=side effect ratings scale, SKAMP=Swanson, Kotkin, Agler, M-Flynn, and Pelham, SKAMP-A=SKAMP-Attention, SKAMP-D=SKAMP-Deportment, SNAP=Swanson, Nolan and Pelham, SNAP-P=Swanson, Nolan and Pelham-parent rating scale, SNAP-T=Swanson, Nolan and Pelham-teacher rating scale TEAEs=treatment-emergent adverse events, WRAADDS=Wender-Reimherr Adult Attention-Deficit Disorder Scale

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 branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage 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 15. Relative Cost of the Cerebral Stimulants/Agents Used for ADHD

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
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®	$$$$	N/A
Methamphetamine	tablet	Desoxyn®	$$$$$	N/A
Anorexigenic Agents and Respiratory and Cerebral Stimulants, Miscellaneous				
Armodafinil	tablet	Nuvigil®	$$$$$	N/A

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Dexmethylphenidate	extended-release capsule, tablet	Focalin®*, Focalin XR®	$$-$$$$	$-$$
Methylphenidate	chewable tablet, extended-release capsule, extended-release tablet (osmotic release), sustained-release tablet, solution, tablet, transdermal patch	Concerta®, Daytrana®, Metadate CD®, Metadate ER®*, Methylin®*, Ritalin®*, Ritalin LA®, Ritalin-SR®*	$$-$$$$	$-$$
Modafinil	tablet	Provigil®	$$$$$	N/A
Central Nervous System Agents, Miscellaneous				
Atomoxetine	capsule	Strattera®	$$$$	N/A

*Generic is available in at least one dosage form or strength.
†Sustained-release formulation
N/A=Not available

X. Conclusions

The central nervous system agents included in this review are used to treat ADHD and to improve wakefulness in patients with excessive sleepiness associated with narcolepsy, OSA and shift work sleep disorder.[1-20] The cerebral stimulants are classified as Schedule II (amphetamines and methylphenidate derivatives) or Schedule IV (armodafinil and modafinil) controlled substances. Atomoxetine is not considered a cerebral stimulant; therefore, it is not classified as a controlled substance. The stimulants are available in a variety of dosage forms, which primarily differ in their release mechanism and duration of action.

The American Academy of Child and Adolescent Psychiatry recommends 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] The specific agent used should be the choice of the family and the clinician, and each patient's treatment should be individualized.[24] Other organizations recommend the initial use of a stimulant for the treatment of ADHD; atomoxetine is recommended for patients with comorbid anxiety disorders, tics, sleep disorders, substance abuse, stimulant failure, or adverse events with stimulants.[25,27] Stimulants and atomoxetine have been shown to be effective for the treatment of ADHD in a variety of clinical trials.[24,47-57,64-68,70,73,75-79] 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]

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 is not a controlled substance, 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 and modafinil are all effective for the treatment of daytime sleepiness due to narcolepsy.[29] However, the European Federation of Neurological Sciences recommends modafinil as the initial treatment option for narcolepsy; methylphenidate is considered a second-line agent.[30] Modafinil is 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. Although modafinil and armodafinil have been shown to be more effective than placebo, there were no studies found in the medical literature directly comparing these agents to each other, or to other cerebral stimulants.[33,36,40-41,44-45,83-88]

There is insufficient evidence to support that one brand cerebral stimulant/agent used for ADHD is more efficacious than another within its given indication. There is at least one short-acting, intermediate-acting and long-acting agent available in a generic formulation. 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 cerebral stimulant/agent used for ADHD is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

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

The barbiturates were discovered in the early 1900s and were among the first synthetic agents developed for their anesthetic, hypnotic and sedative properties. The barbiturates affect the gamma-aminobutyric acid (GABA) system and cause reversible depression of all excitable tissues, especially the central nervous system.[1-3,10-11] These agents depress the sensory cortex, decrease motor activity and alter cerebellar function.[1-9] Depression of the central nervous system may range from sedation to general anesthesia.[1-3,10-11]

The barbiturates are approved for the treatment of insomnia and for the induction of sedation.[1-3] Some agents are also approved for use as an adjunct to anesthesia, as well as for the treatment of seizure disorders.[1-3] The use of barbiturates is associated with abuse and psychological/physical dependence.[1-9] Individuals who have psychological dependence may increase the dosage or decrease the dosing interval.[1-9] 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.[1-11] 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. Mephobarbital and phenobarbital are available in a generic formulation. This class was last reviewed in November 2007.

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
Mephobarbital	tablet	Mebaral®*	mephobarbital
Pentobarbital	injection	Nembutal Sodium®	none
Phenobarbital	elixir, injection, tablet	Luminal Sodium®	phenobarbital
Secobarbital	capsule	Seconal Sodium®	none

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

II. Evidence-Based Medicine and Current Treatment Guidelines

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

Table 2. Treatment Guidelines Using the Barbiturates

Clinical Guideline	Recommendation(s)
American Academy of Sleep Medicine (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 within a class, should be directed by: o Symptom pattern o Treatment goals o Past treatment responses o Patient preference

Clinical Guideline	Recommendation(s)
	o Availability of other treatments o Comorbid conditions o Contraindications o Concurrent medication interactions o 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. Examples include zolpidem, eszopiclone, zaleplon, and temazepam. o Alternate short-intermediate acting BzRAs or ramelteon if the initial agent has been unsuccessful. o Sedating antidepressants, especially when used in conjunction with treating comorbid depression/anxiety. Examples of these include trazodone, amitriptyline, doxepin, and mirtazapine. o Combined 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), State-of-the-Science Conference Statement: **Manifestations and Management of Chronic**	<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

Clinical Guideline	Recommendation(s)
Insomnia in Adults[13] (2005)	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 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. 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 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. 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. • 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)**	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

Clinical Guideline	Recommendation(s)
	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. • Refractory status epilepticus, or GCSE that does not respond to initial anticonvulsant agents, needs to be treated on an intensive care unit. <u>Pharmacological Treatment Recommendations for Refractory GCSE and Subtle Status Epilepticus</u> • 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). <u>Pharmacological Treatment Recommendations for Refractory NCSE</u> • 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[21] (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[1-9]

Indication	Amo-barbital	Buta-barbital	Mepho-barbital	Pento-barbital	Pheno-barbital	Seco-barbital
Anesthesia						
Preanesthetic	✔			✔		✔
Anticonvulsant						
Anticonvulsant in the emergency control of certain acute convulsive episodes (status epilepticus, cholera, eclampsia, meningitis, tetanus, and toxic reactions to strychnine or local anesthetics)				✔	✔	
Treatment of generalized and partial seizures					✔	
Treatment of grand mal and petit mal epilepsy			✔			
Sedative-Hypnotic						
Short-term treatment of insomnia	✔	✔		✔	✔	✔
Sedation	✔	✔	✔	✔	✔	✔

IV. Pharmacokinetics

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

Table 4. Pharmacokinetic Parameters of the Barbiturates[1-9]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism	Excretion (%)	Half-Life (hours)
Amobarbital	Not reported	Not reported	Hepatic	Fecal (4-5) Renal (79-92)	8-42
Butabarbital	Not reported	Not reported	Hepatic	Renal	34-100
Mephobarbital	50	Not reported	Hepatic	Renal	11-67
Pentobarbital	95	5	Hepatic	Renal	15-48
Phenobarbital	80-100	20-60	Hepatic	Renal (21)	36-117
Secobarbital	90	52-57	Hepatic	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	1	Anticoagulants	Barbiturates reduce the effects of anticoagulants through increased metabolic clearance of anticoagulants, probably caused by induction of hepatic microsomal enzymes.
Barbiturates	1	Contraceptives, oral	Barbiturate induction of contraceptive-steroid hepatic metabolism and sex

Generic Name(s)	Significance Level	Interaction	Mechanism
			hormone-binding globulin synthesis combine to reduce effective concentrations of oral contraceptives and loss of oral contraceptive efficacy, possibly leading to unintended pregnancy.
Barbiturates	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.
Phenobarbital	1	Acitretin	Phenobarbital may enhance the formation of etretinate from acitretin. Anti-conceptive measures should be employed for 2 years following cessation of acitretin.
Barbiturates	2	Clozapine	Clozapine plasma concentrations may be reduced, possibly through induction of hepatic metabolism of clozapine, decreasing the pharmacologic effects.
Barbiturates	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	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 (mephobarbital, phenobarbital)	2	Maraviroc	Induction of CYP3A4 isoenzymes by long-acting barbiturates may increase the metabolic elimination of maraviroc and decrease its pharmacologic effects.
Barbiturates	2	Methoxyflurane	Barbiturates appear to stimulate degradation of methoxyflurane, perhaps to nephrotoxic metabolites. Enhanced renal toxicity may occur.
Barbiturates	2	Metronidazole	Barbiturate induction of metronidazole metabolism resulting in more rapid elimination and lower serum concentrations may cause therapeutic failure of metronidazole.
Barbiturates	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	2	Sodium oxybate	Concurrent use of sodium oxybate may result in an increase in sleep duration and CNS depression, possibly due to additive effects.
Barbiturates (amobarbital,	2	Tacrolimus	Plasma concentrations and pharmacologic effects of tacrolimus may be decreased,

Generic Name(s)	Significance Level	Interaction	Mechanism
butabarbital, pentobarbital, phenobarbital, secobarbital)			due to increased hepatic metabolism of tacrolimus via CYP3A4.
Barbiturates	2	Theophylline	Decreased theophylline levels may possibly result in reduced therapeutic effects. Barbiturates may induce cytochrome P450, stimulating theophylline metabolism and increasing clearance.
Barbiturates (mephobarbital, phenobarbital)	2	Voriconazole	Certain long-acting barbiturates may increase the metabolism (CYP3A4) of voriconazole. Voriconazole plasma concentrations may be reduced, decreasing the therapeutic effect.
Phenobarbital	2	Acetaminophen	The risk of acetaminophen-induced hepatotoxicity may be increased by chronic intake of phenobarbital; the mechanism of this interaction is unknown.
Phenobarbital	2	Aromatase inhibitors	Induction of CYP3A4 isoenzymes by phenobarbital l may increase the metabolic elimination of aromatase inhibitors and thereby decrease their plasma concentrations and pharmacological effects.
Phenobarbital	2	Benzodiazepines	CNS depressant effects of benzodiazepines and phenobarbital may be increased. Excessive sedation and impaired psychomotor function may occur due to additive effects.
Phenobarbital	2	Erlotinib/imatinib	Induction of CYP3A4 isoenzymes by phenobarbital may increase the metabolic elimination and decrease plasma concentrations of erlotinib or imatinib. Alternate treatments lacking CYP3A4 inducing activity should be considered.
Phenobarbital	2	MTOR inhibitors	Induction of CYP34A isoenzymes by phenobarbital may increase the metabolic elimination and decrease pharmacological of MTOR inhibitors. Concomitant use is not recommended.
Phenobarbital	2	NNRT inhibitors	Induction of CYP34A isoenzymes by phenobarbital may increase the metabolic elimination and decrease pharmacological of NNRT inhibitors. Concomitant use is not recommended.
Phenobarbital	2	Protease inhibitors	Induction of hepatic microsomal enzymes by phenobarbital may increase the metabolic elimination and bring about decreased plasma concentrations and pharmacologic effects of protease inhibitors. Therapeutic failures of protease inhibitors may result.
Phenobarbital	2	Ranolazine	Induction of CYP34A isoenzymes by phenobarbital may increase the metabolic elimination of ranolazine. Concomitant use is not recommended.

Generic Name(s)	Significance Level	Interaction	Mechanism
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.
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.

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. Barbiturates may be habit forming; tolerance and psychological/physical dependence may occur with continued use.[1-11] Abrupt cessation after prolonged use may result in withdrawal symptoms, including delirium, convulsions and possibly death.[1-11] Barbiturates have a narrow therapeutic index and the risk of overdose is increased in the presence of other central nervous system depressants.

Table 6. Adverse Drug Events (%) Reported with the Barbiturates[1-9]

Adverse Events	Amo-barbital	Buta-barbital	Mepho-barbital	Pento-barbital	Pheno-barbital	Seco-barbital
Cardiovascular						
Bradycardia	✔	✔	-	✔	✔	-
Hypotension	✔	✔	<1	✔	✔	✔
Syncope	✔	✔	-	✔	✔	-
Central Nervous System						
Abnormal thinking	✔	✔	-	-	-	-
Agitation	✔	✔	-	✔	✔	-
Anxiety	✔	✔	-	✔	✔	-
Ataxia	✔	✔	-	✔	✔	-
Confusion	✔	✔	1-10	✔	✔	✔
Central nervous system depression	✔	-	-	✔	✔	✔
Central nervous system excitation	-	-	-	✔	✔	-
Complex sleep-related activities	-	<1	-	-	-	-
Dizziness	✔	✔	>10	✔	✔	✔
Drowsiness	-	-	-	✔	✔	✔
Faint feeling	-	-	1-10	-	-	✔
Fever	✔	✔	-	-	-	✔
Hallucinations	✔	✔	<1	✔	✔	✔
Hangover effect	-	-	>10	✔	✔	✔
Headache	✔	✔	1-10	✔	✔	✔
Hyperkinesia	✔	✔	-	✔	✔	-
Impaired judgment	-	-	-	✔	✔	-
Insomnia	✔	✔	1-10	✔	✔	✔
Lethargy	-	-	-	✔	✔	-
Lightheadedness	-	-	>10	-	-	✔
Mental depression	-	✔	1-10	-	-	✔
Nervousness	✔	✔	1-10	✔	✔	✔
Nightmares	✔	✔	1-10	✔	✔	✔
Psychiatric disturbances	✔	✔	-	-	-	-
Somnolence	✔	1-3	-	✔	✔	-

Adverse Events	Amo-barbital	Buta-barbital	Mepho-barbital	Pento-barbital	Pheno-barbital	Seco-barbital
Unusual excitement	-	-	1-10	-	-	✔
Dermatological						
Exfoliative dermatitis	-	✔	<1	✔	✔	✔
Injection site reaction	✔	-	-	-	-	-
Rash	-	✔	<1	✔	✔	✔
Stevens-Johnson syndrome	-	✔	<1	✔	✔	✔
Urticaria	-	-	-	-	-	✔
Gastrointestinal						
Constipation	✔	✔	1-10	✔	✔	✔
Nausea	✔	✔	1-10	✔	✔	✔
Vomiting	✔	✔	1-10	✔	✔	✔
Hematologic						
Agranulocytosis	-	✔	<1	✔	✔	✔
Megaloblastic anemia	-	✔	<1	✔	✔	✔
Thrombocytopenia	-	✔	<1	✔	✔	✔
Thrombophlebitis	-	✔	<1	✔	✔	✔
Respiratory						
Apnea	✔	✔	-	✔	✔	✔
Atelectasis	✔	-	-	-	-	-
Hypoventilation	✔	✔	-	✔	✔	-
Laryngospasm	-	-	-	✔	✔	✔
Respiratory depression	-	✔	<1	✔	✔	✔
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[1-9]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Amobarbital	Hypnotic: 65-200 mg IM/IV at bedtime Sedation: 30-50 mg IM/IV 2 to 3 times daily	Sedation: 6-12 years: 65-500 mg IM/IV	Injection: 500 mg
Butabarbital	Hypnotic: 50-100 mg orally at bedtime Preoperative Sedation: 50-100 mg orally 60-90 minutes before surgery	Preoperative Sedation: 2-6 mg/kg orally 60-90 minutes before surgery	Elixir: 30 mg/5 ml Tablet: 30 mg 50 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Sedation: 15-30 mg orally 3 to 4 times daily		
Mephobarbital	Epilepsy: 400-600 mg/day orally in 2 to 4 divided doses Sedation: 32-100 mg orally 3 to 4 times a day	Epilepsy: <5 years of age: 16-32 mg orally 3 to 4 times per day ≥5 years of age: 32-64 mg orally 3 to 4 times per day Sedation: 16-32 mg orally 3 to 4 times per day	Tablet: 32 mg 50 mg 100 mg
Pentobarbital	Hypnotic: 150-200 mg IM or 100 mg IV at bedtime; may repeat every 1-3 minutes up to 200-500 mg total dose Preoperative Sedation: 150-200 mg IM Status Epilepticus: Initial: 10-20 mg/kg IV slowly over 1-2 hours Maintenance: 0.5-3 mg/kg/hour	Hypnotic: 2-6 mg/kg IM Preoperative Sedation: ≥ 6 months: 2-6 mg/kg IM or 1-3 mg/kg IV Sedation: 5-12 years: 2 mg/kg IV 5-10 minutes prior to procedure; may repeat one time >12 years: 100 mg prior to procedure Status Epilepticus: Initial: 5-15 mg/kg IV slowly over 1-2 hours Maintenance: 0.5-5 mg/kg/hour	Injection: 50 mg/ml
Phenobarbital	Hypnotic: 100-320 mg IM/IV/PO at bedtime Preoperative Sedation: 100-200 mg IM 60-90 minutes prior to procedure Sedation: 30-120 mg/day IM/PO in 2-3 divided doses Seizure/Status Epilepticus: Initial: 10-20 mg/kg IV followed by repeated dose at 20 minute intervals until seizures controlled Maintenance: 1-3 mg/kg/day IV/PO in divided doses or 50-100 mg two to three times daily	Hypnotic: 3-5 mg/kg IM/IV at bedtime Preoperative Sedation: 1-3 mg/kg IM/IV/PO 60-90 minutes prior to procedure Sedation: 2 mg/kg orally 3 times daily Status Epilepticus: Infants and children: 15-20 mg/kg IV; may administer additional doses every 15 minutes until seizures are controlled Seizures: Infants: 5-8 mg/kg/day IV/PO in 1-2 divided doses 1-5 years: 6-8 mg/kg/day IV/PO in 1-2 divided doses 5-12 years: 4-6 mg/kg/day IV/PO in 1-2 divided doses >12 years: 1-3 mg/kg/day	Injection: 60 mg/ml 65 mg/ml 130 mg/ml Elixir: 20 mg/5 ml Tablet: 15 mg 16.2 mg 30 mg 32.4 mg 60 mg 64.8 mg 97.2 mg 100 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
		IV/PO in divided doses or 50- 100 mg 2 to 3 times daily	
Secobarbital	Hypnotic: 100-200 mg orally at bedtime	Preoperative Sedation: 2-6 mg/kg orally 1-2 hours prior to procedure Sedation: 6 mg/kg/day orally divided every 8 hours	Capsule: 100 mg

VIII. Effectiveness

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

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 between the ages of 18 and 60 years, 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 Adult patients with insomnia and at least 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 less than 7 hours, at least 2 awakenings per night, total time awake exceeding 30 minutes, awakening at least 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 18-60 years of age with a known 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 compared to 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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Seizures				
Painter et al.[18] (1999) Phenobarbital 25 mcg/ml vs phenytoin 3 mcg/ml	RCT, SB Neonates with seizures	N=59 5 years	Primary: Complete seizure control determined by electro-encephalography	Primary: Phenobarbital controlled seizures completely in 43% of patients, while phenytoin controlled seizures in 45% of patients (*P*=1.00).
Smith et al.[19] (2003) Phenobarbital vs carbamazepine	MA Children or adults with partial-onset seizures or generalized-onset tonic-clonic seizures	N=684 (4 RCT) 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.[20] (1998) Phenobarbital 15 mg/kg vs diazepam 0.15 mg/kg followed by phenytoin 18 mg/kg vs	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	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
lorazepam 0.1 mg/kg vs phenytoin 18 mg/kg			posttreatment	

*Agent not available in the United States (US)
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, 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 branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage 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®	$$$$$	N/A
Butabarbital	elixir, tablet	Butisol Sodium®	$$$$	N/A
Mephobarbital	tablet	Mebaral®*	$$$	$$-$$$
Pentobarbital	injection	Nembutal Sodium®	$$$	N/A
Phenobarbital	elixir, injection, tablet	Luminal Sodium®	$$$	$
Secobarbital	capsule	Seconal Sodium®	$-$$$	N/A

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

X. Conclusions

The barbiturates are approved for the treatment of insomnia and for the induction of sedation.[1-3] Some agents are also approved for use as an adjunct to anesthesia, as well as for the treatment of seizure disorders.[1-3] Mephobarbital and phenobarbital are 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.[12-14,21] 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.[1-9] Individuals who have psychological dependence may increase the dosage or decrease the dosing interval.[1-9] 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.[1-11] The use of barbiturates has been largely replaced by benzodiazepines.

There is insufficient evidence to support that one brand barbiturate agent is safer or more efficacious than another. 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.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Anxiolytics, Sedatives, and Hypnotics – Benzodiazepines
AHFS Class 282408
February 10, 2010

I. Overview

Benzodiazepines have been primarily used for the treatment of anxiety disorders and insomnia since they were first introduced in the 1960s.[1-19] Anxiety disorders include generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder and social phobia.[20] 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.[20] 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 or 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.[1-19] 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.[21-23] 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.[21-23]

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 quazepam. This class was last reviewed in November 2007.

Table 1. Benzodiazepines Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Alprazolam	orally disintegrating tablet, extended-release tablet, tablet	Niravam®*‡, Xanax®*‡, Xanax XR®*‡	alprazolam, alprazolam ER
Chlordiazepoxide	capsule	Librium®*	chlordiazepoxide
Clonazepam	orally disintegrating tablet, tablet	Klonopin®*	clonazepam
Clorazepate	tablet	Tranxene T-Tab®*	clorazepate
Diazepam	injection, oral concentrate, rectal gel, solution, tablet	Diastat®, Diastat AcuDial®	Diastat®, Diastat AcuDial®, diazepam
Estazolam‡	tablet	N/A	none
Flurazepam	capsule	N/A	flurazepam

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Lorazepam	injection, oral concentrate, tablet	Ativan®*, Lorazepam Intensol®*	lorazepam
Midazolam‡	injection, syrup	N/A	none
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)
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.
National Institute for Health and Clinical Excellence (NICE): **Management of Anxiety (Panic Disorder, With or Without**	Panic Disorder General Considerations • Benzodiazepines are associated with a less effective outcome in the long term and should not be prescribed for panic disorder.

Clinical Guideline	Recommendation(s)

Agoraphobia, and Generalized Anxiety Disorder) in Adults in Primary, Secondary and Community Care[28] (2007)	• 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)
	<u>Panic Disorder - Additional Considerations for Pharmacologic Therapy</u>
	• 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 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.
	<u>Generalized Anxiety Disorder General Considerations</u>
	• If immediate management of generalized anxiety disorder is necessary, any or all of the following should be considered:
	  o Support and information
	  o Problem solving
	  o Benzodiazepines
	  o Sedating antihistamines
	  o Self-help
	• Benzodiazepines may be used for acute treatment, but they should not usually be used beyond 2 to 4 weeks.
	• In the longer-term care of individuals with generalized anxiety disorder, any of the following types of intervention should be offered and the preference of the person with generalized anxiety disorder should be taken into account. The interventions which have evidence for the longest duration of effect, in descending order, are:
	  o Psychological therapy
	  o Pharmacological therapy (antidepressant medication)
	  o Self-help
	<u>Generalized Anxiety Disorder – Additional Considerations for Pharmacologic Therapy</u>
	• Antidepressants should be the only pharmacological intervention used in the longer-term management of generalized anxiety disorder.
	• There is an evidence base for the effectiveness of the SSRIs. Paroxetine and venlafaxine ER have marketing authorization for the treatment of generalized anxiety disorder. Unless otherwise indicated, an SSRI should be offered; if one SSRI is not suitable, another SSRI should be offered.
	• 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

Clinical Guideline	Recommendation(s)
	to minimize the risk of discontinuation/withdrawal symptoms. • If there is no improvement after a 12 week course with an SSRI and if a further medication is appropriate, another SSRI may be considered, or another form of therapy may be offered.

American Academy of Child and Adolescent Psychiatry (AACAP): **Practice Parameter for the Assessment and Treatment of Children and Adolescents with Anxiety Disorders**[29] **(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.

Clinical Guideline	Recommendation(s)
	• 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. • 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: **Practice Guideline for the Treatment of Patients with Obsessive-Compulsive Disorder**[56] **(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

Clinical Guideline	Recommendation(s)
	treatment strategies may be considered. These include augmenting SRIs with clomipramine, buspirone, pindolol, riluzole, or once- weekly oral morphine sulfate. • Evidence for beneficial effects of benzodiazepines as monotherapy for OCD is limited to case reports with clonazepam and alprazolam. Modest doses of benzodiazepines may relieve anxiety and distress in OCD without directly diminishing the frequency or duration of obsessions or compulsions. Given their limited evidence for efficacy, benzodiazepines cannot be recommended as monotherapy for OCD, except in those rare individuals who are unable or unwilling to take standard anti-OCD medications.
American Psychiatric Association (APA): **Practice Guideline for the Treatment of Patients with Acute Stress Disorder and Posttraumatic Stress Disorder (PTSD)[57] (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

Clinical Guideline	Recommendation(s)
	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 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

Clinical Guideline	Recommendation(s)
	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 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), State-of-the-Science Conference Statement: **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.

Clinical Guideline	Recommendation(s)
	Antidepressants • 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. 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. • 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 of Addiction Medicine (ASAM), Committee on Practice Guidelines: **Pharmacological Management of Alcohol Withdrawal[30] (1997)**	• Benzodiazepines are recommended over nonbenzodiazepine sedative-hypnotics for alcohol withdrawal. • Phenobarbital is an alternative to benzodiazepines but may have a less optimal safety profile at high doses. • All benzodiazepines are equally effective in reducing the signs and symptoms of withdrawal. • Long-acting benzodiazepines may be more effective in preventing withdrawal seizures by contributing to a “smoother” withdrawal with less rebound symptoms. • Short-acting benzodiazepines may cause less over-sedation. • The benzodiazepines with a rapid onset of action such as alprazolam, diazepam, and lorazepam have a higher abuse potential as compared to the slower onset agents (chlordiazepoxide, halazepam or oxazepam). • Alcohol withdrawal cannot be treated with a standard fixed dose so treatment is based on individual need. • The use of a structured assessment scale (e.g., Clinical Institute Withdrawal Assessment-Alcohol, revised [CIWA-Ar]) is recommended in substance abuse treatment programs to allow for dose titration and the reduction of unnecessary medication. Use with caution in patients with acute medical or psychiatric co-morbidities or patients with concurrent substance withdrawal. • For mild withdrawal symptoms (CIWA-Ar scores <8), supportive nonpharmacological therapy and continual monitoring every 4-8 hours is recommended. • The addition of medications to control symptoms is recommended for moderate (CIWA-Ar scores 8-15) to severe alcohol withdrawal symptoms (CIWA-Ar scores ≥15). Give 1 of the following agents every hour: chlordiazepoxide 50-100 mg, diazepam 10-20 mg or lorazepam 2-4 mg. • It is recommended that patients with severe withdrawal symptoms be given benzodiazepines at a dose necessary to control these symptoms. • In patients with acute medical or psychiatric conditions or with concurrent substance withdrawal, a fixed-schedule regimen is recommended over a symptom-regimen. • Examples of this fixed-schedule regimen include: chlordiazepoxide 50 mg every 6 hours for 4 doses, then 25 mg every 6 hours for 8 doses; or diazepam 10 mg every 6 hours for 4 doses, then 5 mg every 6 hours for

Clinical Guideline	Recommendation(s)
	8 doses; or lorazepam 2 mg every 6 hours for 4 doses, then 1 mg every 6 hours for 8 doses. Alternative benzodiazepines may be substituted at equivalent doses. • Additional medication should be provided on an as needed basis when symptoms are not controlled. • For patients with a history of withdrawal seizures or notable comorbid medical illnesses, initiate a recommended medication regardless of symptom severity. • Patients using sedative-hypnotic medications may be at increased risk for major complications or may exhibit tolerance to benzodiazepines. • Alternative agents such as β-blockers, clonidine and carbamazepine are not recommended as monotherapy as they have not been shown to decrease delirium or seizures. • β-Blockers may be considered as adjunct treatment with benzodiazepines in patients with coronary artery disease, whereas patients with opiate withdrawal may benefit from the addition of clonidine. • Combination therapy with carbamazepine may be considered in patients with benzodiazepine withdrawal. • Neuroleptics (e.g., haloperidol, phenothiazines) may be effective in patients with notable agitation or hallucinations. • Thiamine administration is recommended at initiation of treatment to prevent Wernicke's disease and Wernicke-Korsakoff syndrome. • Recommendations for adolescents are the same as for adults.
European Federation of Neurological Societies (EFNS): **Guideline on the Management of Status Epilepticus[31] (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. • Refractory status epilepticus, or GCSE that does not respond to initial anticonvulsant agents, needs to be treated on an intensive care unit. <u>Pharmacological Treatment Recommendations for Refractory GCSE and Subtle Status Epilepticus</u> • 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). <u>Pharmacological Treatment Recommendations for Refractory NCSE</u> • Phenobarbital 20 mg/kg intravenously. • Valproic acid 25-45 mg/kg as intravenous bolus followed by maximum rates up to 6 mg/kg/min.

Clinical Guideline	Recommendation(s)
Journal of Child Neurology: **Treatment of Pediatric Epilepsy: Expert Opinion**[25] **(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 benzodiazepines 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 Benzodiazepines[1-19]

Indication	Alpra-zolam	Chlordia-zepoxide	Clona-zepam	Clora-zepate	Dia-zepam	Esta-zolam	Flura-zepam	Lora-zepam	Mida-zolam	Oxa-zepam	Qua-zepam	Tema-zepam	Tria-zolam
Anesthesia													
Induction of anesthesia, before administration of other anesthetic agents									✔				
Preoperative sedation/anxiolysis/amnesia									✔				
Sedation/anxiolysis/amnesia prior to or during diagnostic, therapeutic, or endoscopic procedures (bronchoscopy, gastroscopy, cystoscopy, coronary angiography, cardiac catheterization), oncology procedures, radiologic procedures, suture of lacerations and other procedures either alone or in combination with other CNS depressants									✔				
Anticonvulsant													
Adjunctive therapy in the management of partial seizures				✔									
Seizure disorders (Lennon-Gastaut syndrome, akinetic and myoclonic seizures)			✔										
Seizure disorders, adjunctive therapy					✔ †								
Status epilepticus								✔ §					
Anxiety Disorders													
Management of anxiety disorders	✔ *‡	✔		✔	✔			✔ ‡		✔ ‡			
Short-term relief of symptoms of anxiety	✔ *	✔		✔	✔			✔		✔			
Treatment of panic disorder, with or without agoraphobia	✔		✔										
Preoperative apprehension/anxiety		✔						✔ ^					
Sedative-Hypnotic													
Sedation of intubated and mechanically ventilated patients as a component of									✔				

Indication	Alpra-zolam	Chlordia-zepoxide	Clona-zepam	Clora-zepate	Dia-zepam	Esta-zolam	Flura-zepam	Lora-zepam	Mida-zolam	Oxa-zepam	Qua-zepam	Tema-zepam	Tria-zolam
anesthesia or during treatment in a critical care setting													
Short-term treatment of insomnia												✔	✔
Short-term treatment of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings						✔	✔				✔		
Miscellaneous													
Acute alcohol withdrawal		✔		✔	✔					✔			
Adjunct for the relief of skeletal muscle spasm due to reflex spasm to local pathology (inflammation of muscles/joints or trauma), spasticity caused by upper motor neuron disorders (cerebral palsy and paraplegia), athetosis, stiff-man syndrome					✔								

*Immediate-release formulation only.
§Injectable formulation only.
^Tablet formulation only.
†The rectal gel formulation is intended for the 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.
‡Includes anxiety associated with depression.

IV. Pharmacokinetics

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

Table 4. Pharmacokinetic Parameters of the Benzodiazepines[1-19]

Generic Name(s)	Onset of Action (hours)	Bioavailability (%)	Protein Binding (%)	Metabolism	Excretion (%)	Half-Life (hours)
Alprazolam	1-1.5 (IR)	90	80	Hepatic	Renal	6.3-26.9 (IR) 10.7-15.9 (ER)
Chlordiazepoxide	2	Not reported	90-98	Hepatic	Renal (1-2)	24-48
Clonazepam	1-2	90	85	Hepatic	Renal (<2)	30-40
Clorazepate	1-2.5	91	97-98	Hepatic	Renal (62-67) Feces (15-19)	46-48
Diazepam	0.5-2	98	94-99	Hepatic	Renal (75)	0.83-2.25 days
Estazolam	2	Not reported	93	Hepatic	Renal Feces (4)	10-24
Flurazepam	0.5-2	Not reported	97	Hepatic	Renal (78)	47-100
Lorazepam	0.5-2	90	85-91	Hepatic	Renal (88) Feces (7)	12
Midazolam	<1	36-74.5	95	Hepatic	Renal (45-57)	1.8-6.4
Oxazepam	3	93	86-99	Hepatic	Renal (50) Bile (<0.1)	5.7-10.9
Quazepam	2.5	Not reported	95	Hepatic	Renal (31) Feces (23)	25-41
Temazepam	0.5-2	Not reported	96	Hepatic	Renal (80-90)	3.5-18.4
Triazolam	0.5-2	Not reported	89-94	Hepatic	Renal (80) Feces (9)	2.3

ER=extended-release, IR=immediate-release

V. Drug Interactions

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

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

Generic Name(s)	Significance Level	Interaction	Mechanism
Benzodiazepines	1	Clozapine	Pharmacologic/toxic effects of certain benzodiazepines may be increased. Mechanism is unknown.
Benzodiazepines	1	Opioid analgesics (buprenorphine, methadone)	Concurrent use may increase risk of sedation and life-threatening respiratory depression due to synergistic effects of opioids and benzodiazepines.
Benzodiazepines (alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, estazolam, flurazepam, midazolam, oxazepam, quazepam, temazepam, triazolam)	1	Protease inhibitors (amprenavir, atazanavir, darunavir, indinavir, lopinavir, ritonavir, nelfinavir, ritonavir, saquinavir)	Concurrent use may lead to severe sedation and respiratory depression due to inhibition of hepatic metabolism. Coadministration of protease inhibitors with benzodiazepines metabolized by CYP3A4 is contraindicated.
Benzodiazepines (alprazolam, chlordiazepoxide,	2	Azole antifungals	Increased and prolonged serum levels, CNS depression, and psychomotor impairment have been

Generic Name(s)	Significance Level	Interaction	Mechanism
clonazepam, clorazepate, diazepam, flurazepam, midazolam, quazepam, triazolam)			reported with benzodiazepines undergoing oxidative metabolism. Consider giving a lower benzodiazepine dose or using a benzodiazepine that undergoes glucuronidation when giving fluconazole. Use of alprazolam or triazolam with itraconazole or ketoconazole is contraindicated.
Benzodiazepines (alprazolam, clonazepam, estazolam, midazolam)	2	Carbamazepine	The pharmacologic effects of certain benzodiazepines may be decreased due to CYP3A4 induction by carbamazepine.
Benzodiazepines (alprazolam, midazolam, triazolam)	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. Concomitant use is contraindicated.
Benzodiazepines (diazepam, midazolam, triazolam)	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 (chlordiazepoxide, clonazepam, clorazepate, diazepam, estazolam, flurazepam, midazolam, quazepam, temazepam)	2	Disulfiram	Pharmacologic effects of certain benzodiazepines may be increased by disulfiram due to inhibition of benzodiazepine hepatic metabolism.
Benzodiazepines (midazolam, triazolam)	2	Efavirenz	Pharmacologic and toxic effects of midazolam and triazolam may be increased by efavirenz due to inhibition of CYP2C9, 2C19 and 3A4 by efavirenz. Use of midazolam or triazolam with efavirenz is contraindicated.
Benzodiazepines	2	Hydantoins	Serum hydantoin concentrations may be increased and phenytoin may increase the clearance of certain benzodiazepines.
Benzodiazepines (alprazolam, diazepam, estazolam, midazolam, triazolam)	2	Macrolides (clarithromycin, erythromycin, telithromycin)	CNS depression and prolonged sedation have been reported with the concurrent use of benzodiazepines and macrolides.
Benzodiazepines (midazolam, triazolam)	2	Modafinil	Triazolam and midazolam plasma levels may be reduced due to CYP3A4/5 induction by modafinil.

Generic Name(s)	Significance Level	Interaction	Mechanism
Benzodiazepines (alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, estazolam, flurazepam, midazolam, quazepam, triazolam)	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 (alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, estazolam, flurazepam, midazolam, quazepam, triazolam)	2	Omeprazole	Pharmacologic effects of certain benzodiazepines may be increased by omeprazole due to decreased hepatic oxidative metabolism. Toxicity may occur.
Benzodiazepines (alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, estazolam, flurazepam, midazolam, quazepam, triazolam)	2	Rifamycins	Pharmacologic effects of certain benzodiazepines may be decreased by rifamycins due to CYP3A4 induction and increased metabolic elimination.
Benzodiazepines	2	Sodium oxybate	Concurrent use may result in an increase in sleep duration and central nervous system depression. Pharmacologic effects of sodium oxybate and benzodiazepines may be additive.
Benzodiazepines (alprazolam, clonazepam, diazepam, midazolam, triazolam)	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). Mechanism is unknown.

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

VI. Adverse Drug Events

The most common adverse drug events reported with the benzodiazepines are listed in Table 6. The boxed warning for midazolam is listed in Table 7. 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.[1-19] 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 6. Adverse Drug Events (%) Reported with the Benzodiazepines[1-19]

Adverse Events	Alpra-zolam	Chlordia-zepoxide	Clona-zepam	Clora-zepate	Dia-zepam	Esta-zolam	Flura-zepam	Lora-zepam	Mida-zolam	Oxa-zepam	Qua-zepam	Tema-zepam	Tria-zolam
Cardiovascular													
Bigeminy	-	-	-	-	-	-	-	-	<1	-	-	-	-
Chest pain	10.6	-	✔	-	-	-	✔	-	-	-	-	-	✔
Decreased systolic blood pressure	-	-	-	✔	-	-	-	-	-	-	-	-	-
Dyspnea	-	-	-	-	-	-	-	-	-	-	-	✔	-
EEG changes	-	✔	-	-	-	-	-	-	-	-	-	-	-
Flushing	-	-	✔	-	-	1-10	✔	-	3	-	-	-	-
Hypotension	4.7	-	✔	-	✔	-	✔	✔	-	-	-	-	-
Palpitations	-	-	✔	-	-	1-10	✔	-	-	-	-	✔	-
Shortness of breath	-	-	✔	-	-	-	✔	-	-	-	-	-	-
Syncope	3	✔	-	-	-	-	-	-	-	✔	-	-	✔
Tachycardia	7-15	-	-	-	-	-	-	-	-	-	-	-	<1
Central Nervous System													
Abnormal coordination	-	-	6	-	-	1-10	-	-	-	-	-	-	-
Abnormal involuntary movement	14.8	-	-	-	-	-	-	-	-	-	-	-	-
Abnormal thinking	-	-	-	-	-	-	-	-	-	-	✔	-	-
Aggression	-	-	✔	-	-	-	-	✔	-	-	-	-	✔
Agitation	2.9	-	✔	-	-	1-10	-	✔	<1	-	✔	✔	-
Akathisia	1.6	-	-	-	-	-	-	-	-	-	-	-	-
Amnesia	-	-	✔	-	-	-	-	✔	<1	-	✔	✔	✔
Anxiety	16.6	-	✔	-	-	1-10	-	✔	-	-	✔	2.0	-

Adverse Events	Alpra-zolam	Chlordia-zepoxide	Clona-zepam	Clora-zepate	Dia-zepam	Esta-zolam	Flura-zepam	Lora-zepam	Mida-zolam	Oxa-zepam	Qua-zepam	Tema-zepam	Tria-zolam
Apathy	-	-	✔	-	✔	1-10	-	-	-	-	✔	-	-
Aphonia	-	-	✔	-	-	-	-	-	-	-	-	-	-
Apprehension	-	-	-	-	-	-	✔	-	-	-	-	-	-
Ataxia	-	✔	5-30	✔	✔	-	✔	✔	-	✔	✔	✔	4.6
Blurred vision	6-21	-	1	✔	✔	-	✔	✔	-	-	-	1.3	-
Change in libido, unspecified	7.1	-	-	-	✔	-	-	✔	-	✔	-	-	✔
Cognitive disorder	28.8	-	-	-	-	-	-	-	-	-	-	-	-
Complex sleep-related behavior	-	-	-	-	-	<1	-	-	-	-	-	-	-
Confusion	9-10	✔	1	✔	✔	1-10	✔	✔	-	-	✔	1.3	<1
Coma	-	-	✔	-	-	-	✔	✔	-	-	-	-	-
Convulsions/seizure	-	-	-	-	-	1-10	-	✔	1	-	-	-	-
Decreased libido	14.4	✔	1	-	-	-	-	✔	-	-	✔	-	-
Delusions	-	-	-	-	-	-	-	-	-	-	-	-	✔
Depersonalization	-	-	✔	-	-	-	-	-	-	-	-	-	✔
Depression	13.9	-	7	✔	✔	-	✔	✔	-	-	✔	1.7	<1
Derealization	1.9	-	-	-	-	-	-	-	-	-	-	-	✔
Difficulty focusing	-	-	-	-	-	-	✔	-	-	-	-	-	-
Diplopia	-	-	✔	✔	✔	-	-	✔	-	-	-	-	-
Disinhibition	2.7	-	✔	-	-	-	-	✔	-	-	-	-	-
Disorientation	-	-	-	-	-	-	✔	✔	-	-	-	-	✔
Dizziness	1-29	-	8	✔	-	1-10	✔	6.9	-	✔	1.5	4.5	7.8
Dream abnormalities	1.8	-	-	-	-	-	-	-	-	-	-	✔	0.5
Dreaming, excessive	-	-	✔	-	-	-	-	-	-	-	-	-	-
Drowsiness	41-76	✔	50	✔	✔	1	✔	✔	-	✔	8.7	9.1	14.0
Drunkenness	-	-	✔	-	-	-	-	-	-	-	-	-	-
Dry mouth	14.7	-	✔	✔	-	-	✔	-	-	-	-	1.7	0.5
Dysesthesia	-	-	-	-	-	-	-	-	-	-	-	-	0.5
Dystonia	-	-	-	-	-	-	-	-	-	-	✔	-	-
Dysarthria	23.3	-	2	-	✔	-	-	✔	-	-	-	-	✔
Emergence delirium	-	-	-	-	-	-	-	-	<1	-	-	-	-
Emotional lability	-	-	-	-	-	1-10	-	-	-	-	-	-	-
Equilibrium loss	-	-	-	-	-	-	-	-	<1	-	-	✔	-
Euphoria	-	-	-	-	-	1-10	✔	✔	-	-	✔	1.5	<1
Excitement	-	-	✔	-	✔	-	✔	✔	-	✔	-	-	✔
Fatigue	48.6	-	7	✔	✔	-	-	✔	-	-	2	-	✔
Fear	1.4	-	-	-	-	-	-	-	-	-	-	-	-
Feeling warm	1.3	-	-	-	-	-	-	-	-	-	-	-	-

Adverse Events	Alpra-zolam	Chlordia-zepoxide	Clona-zepam	Clora-zepate	Dia-zepam	Esta-zolam	Flura-zepam	Lora-zepam	Mida-zolam	Oxa-zepam	Qua-zepam	Tema-zepam	Tria-zolam
Glassy-eyed appearance	-	-	✔	-	-	-	-	-	-	-	-	-	-
Hallucinations	-	-	✔	-	✔	-	✔	✔	<1	-	✔	✔	✔
Head fullness	-	-	✔	-	-	-	-	-	-	-	-	-	-
Headache	12-29	-	✔	✔	✔	1	✔	✔	-	✔	2.3	8.5	9.7
Hemiparesis	-	-	✔	-	-	-	-	-	-	-	-	-	-
Hoarseness	-	-	✔	-	-	-	-	-	-	-	-	-	-
Hostility	-	-	✔	-	-	1-10	-	✔	-	-	-	-	-
Hyperkinesia	-	-	-	-	-	-	-	-	-	-	✔	-	-
Hypoesthesia	-	-	✔	-	-	-	-	-	-	-	-	-	-
Hypokinesia	-	-	-	-	-	1-10	-	-	-	-	-	-	-
Hypotonia	-	-	✔	-	-	-	-	-	-	-	-	-	-
Hysteria	-	-	✔	-	-	-	-	-	-	-	-	-	-
Illusion	-	-	✔	-	-	-	-	-	-	-	-	-	-
Impaired coordination	40.1	-	-	-	-	-	-	-	-	-	✔	-	-
Impotence	-	-	1	-	-	-	-	✔	-	-	-	-	-
Inattention	-	-	✔	-	-	-	-	-	-	-	-	-	-
Increased libido	7.7	✔	✔	-	-	-	-	-	-	-	-	-	-
Insomnia	8-29	-	✔	✔	✔	-	-	✔	-	-	-	-	0.5
Intellectual ability reduced	-	-	2	-	-	-	-	-	-	-	-	-	-
Irritability	33.1	-	✔	✔	-	-	✔	-	-	-	✔	-	✔
Lethargy	-	-	-	-	-	-	✔	-	-	✔	-	4.5	-
Lightheadedness	20.8	-	-	-	-	-	✔	-	-	-	-	-	4.9
Malaise	-	-	✔	-	-	-	-	-	-	-	✔	-	-
Memory impairment	33.1	-	4	-	-	-	-	✔	-	-	✔	-	<1
Migraine	-	-	✔	-	-	-	-	-	-	-	-	-	-
Muscle tone disorders	6.3	-	-	-	-	-	-	-	-	-	-	-	-
Muscular twitching	7.9	-	-	-	-	-	-	-	-	-	-	-	-
Nervousness	4.1	-	3	✔	-	-	✔	-	-	-	✔	4.6	5.2
Nightmares	-	-	✔	-	-	-	-	-	-	-	✔	1.2	0.5
Nystagmus	-	-	✔	-	-	-	-	-	1	-	-	✔	-
Paresis	-	-	✔	-	-	-	-	-	-	-	-	-	-
Paranoid reaction	-	-	-	-	-	-	-	-	-	-	✔	-	-
Paresthesia	2.4	-	✔	-	-	1-10	-	-	-	-	-	-	0.5
Psychosis	-	-	✔	-	-	-	-	-	-	-	-	-	-
Rage	-	-	-	-	✔	-	-	✔	-	-	-	-	-
Restlessness	-	-	-	-	-	-	✔	-	-	-	-	✔	✔
Sedation	-	-	-	-	-	1	✔	15.9	-	-	-	-	✔

Adverse Events	Alpra-zolam	Chlordia-zepoxide	Clona-zepam	Clora-zepate	Dia-zepam	Esta-zolam	Flura-zepam	Lora-zepam	Mida-zolam	Oxa-zepam	Qua-zepam	Tema-zepam	Tria-zolam
Sexual dysfunction	7.4	-	-	-	-	-	-	-	-	-	-	-	-
Sleep disturbances	-	-	✔	-	✔	1-10	-	✔	-	-	✔	-	✔
Slurred speech	-	-	✔	✔	✔	-	✔	✔	-	✔	✔	-	✔
Somnolence	-	-	37	-	-	>10	-	-	-	-	-	-	✔
Staggering	-	-	-	-	-	-	✔	-	-	-	-	-	-
Stupor	-	-	-	-	-	1-10	-	-	-	-	-	-	-
Talkativeness	2.2	-	-	-	-	-	✔	-	-	-	-	-	-
Tiredness	-	-	-	-	-	-	-	-	-	-	-	-	<1
Tremor	4	-	✔	✔	✔	1-10	-	✔	-	✔	✔	✔	-
Unsteadiness	-	-	-	-	-	-	-	3.4	-	-	-	-	-
Vasomotor disturbances	2	-	-	-	-	-	-	-	-	-	-	-	-
Vertigo	-	-	✔	-	✔	-	-	✔	-	✔	-	1.2	-
Visual disturbances	-	-	✔	-	-	-	-	✔	-	-	✔	-	<1
Vivid dreams	-	-	✔	-	-	-	-	-	-	-	-	-	-
Weakness	7.1	-	-	-	-	>10	✔	4.2	-	-	✔	1.4	0.5
Dermatological													
Acne flare	-	-	✔	-	-	-	-	-	-	-	-	-	-
Allergic skin reactions	3.8	-	-	-	-	-	-	✔	-	-	-	-	0.5
Angioedema	-	-	-	-	-	1-10	-	-	-	-	-	-	-
Burning skin	-	-	✔	-	-	-	-	-	-	-	-	-	-
Contact dermatitis	-	-	✔	-	-	-	-	-	-	-	-	-	-
Dermatological symptoms	-	-	-	-	-	1-10	-	✔	-	-	✔	-	0.5
Pruritus	-	-	✔	-	-	1-10	✔	-	-	-	✔	-	✔
Pustular reaction	-	-	✔	-	-	-	-	-	-	-	-	-	-
Rash	10.8	-	✔	✔	✔	1-10	✔	-	<1	✔	✔	-	-
Skin disorder	-	-	✔	-	-	-	-	-	-	-	-	-	-
Skin eruptions	-	✔	-	-	-	-	-	-	-	-	-	-	-
Xeroderma	-	-	✔	-	-	-	-	-	-	-	-	-	-
Endocrine and Metabolic													
Edema	4.9	✔	✔	-	-	-	-	-	-	✔	-	-	-
Hyponatremia	-	-	-	-	-	-	-	✔	-	-	-	-	-
Hypothermia	-	-	-	-	-	-	-	✔	-	-	-	-	-
SIADH	-	-	-	-	-	-	-	✔	-	-	-	-	-
Gastrointestinal													
Abdominal distress	18.3	-	1	-	-	-	-	-	-	-	✔	1.5	-
Anorexia	-	-	✔	-	-	-	✔	-	-	-	✔	✔	✔
Bowel movements, frequent	-	-	✔	-	-	-	-	-	-	-	-	-	-

Adverse Events	Alpra-zolam	Chlordia-zepoxide	Clona-zepam	Clora-zepate	Dia-zepam	Esta-zolam	Flura-zepam	Lora-zepam	Mida-zolam	Oxa-zepam	Qua-zepam	Tema-zepam	Tria-zolam
Change in appetite	-	-	✔	-	-	1-10	-	✔	-	-	✔	-	-
Constipation	10-26	✔	2	-	✔	1-10	✔	✔	-	-	✔	-	0.5
Decreased appetite	27.8	-	1	-	-	-	-	-	-	-	-	-	-
Diarrhea	10-20	-	✔	-	-	-	✔	-	-	-	✔	1.7	0.5
Dyspepsia	-	-	✔	-	-	-	-	-	-	-	1	-	-
Flatulence	-	-	✔	-	-	1-10	-	-	-	-	-	-	-
Gastritis	-	-	✔	-	-	1-10	-	-	-	-	-	-	-
Gastrointestinal complaints	-	-	-	✔	-	-	-	-	-	-	-	-	-
Gastrointestinal inflammation	-	-	✔	-	-	-	-	-	-	-	-	-	-
Gastrointestinal pain	-	-	-	-	-	-	✔	-	-	-	✔	-	-
Heartburn	-	-	-	-	-	-	✔	-	-	-	-	-	-
Hemorrhoids	-	-	✔	-	-	-	-	-	-	-	-	-	-
Hepatic dysfunction	-	✔	-	-	-	-	-	-	-	✔	-	-	0.5
Hepatomegaly	-	-	✔	-	-	-	-	-	-	-	-	-	-
Increased appetite	32.7	-	✔	-	-	-	-	-	-	-	-	-	-
Jaundice	-	✔	-	-	✔	-	-	✔	-	✔	✔	-	✔
Kidney function test abnormalities	-	-	-	✔	-	-	-	-	-	-	-	-	-
Liver function test abnormalities	-	-	-	✔	-	-	-	-	-	-	✔	-	-
Nausea	9-22	✔	✔	-	✔	-	✔	✔	3	✔	-	3.1	4.6
Pyrosis	-	-	✔	-	-	-	-	-	-	-	-	-	-
Upset stomach	-	-	✔	-	-	-	✔	-	-	-	-	-	-
Vomiting	9-22	-	-	-	-	-	✔	-	3	-	-	✔	4.6
Xerostomia	-	-	-	-	-	1-10	-	-	-	-	1.5	-	-
Genitourinary													
Bladder dysfunction	-	-	✔	-	-	-	-	-	-	-	-	-	-
Cystitis	-	-	✔	-	-	-	-	-	-	-	-	-	-
Dysmenorrhea	-	-	3	-	-	-	-	-	-	-	-	-	-
Dysuria	-	-	✔	-	-	-	-	-	-	-	-	-	-
Enuresis	-	-	✔	-	-	-	-	-	-	-	-	-	-
Genitourinary complaints	-	-	-	✔	-	-	✔	-	-	-	-	-	-
Impotence	-	-	-	-	-	-	-	-	-	-	✔	-	-
Incontinence	1.5	-	✔	-	✔	-	-	-	-	-	✔	-	✔
Menstrual disorders/ irregularities	10.4	✔	✔	-	-	1-10	-	-	-	-	✔	-	✔
Micturition difficulties	12.2	-	-	-	-	1-10	-	-	-	-	-	-	-
Micturition frequency	-	-	1	-	-	1-10	-	-	-	-	-	-	-
Nocturia	-	-	✔	-	-	-	-	-	-	-	-	-	-
Pelvic pain	-	-	✔	-	-	-	-	-	-	-	-	-	-

Adverse Events	Alpra-zolam	Chlordia-zepoxide	Clona-zepam	Clora-zepate	Dia-zepam	Esta-zolam	Flura-zepam	Lora-zepam	Mida-zolam	Oxa-zepam	Qua-zepam	Tema-zepam	Tria-zolam
Polyuria	-	-	✔	-	-	-	-	-	-	-	-	-	-
Urine discoloration	-	-	✔	-	-	-	-	-	-	-	-	-	-
Urinary retention	-	-	✔	-	✔	-	-	-	-	-	✔	-	✔
Urinary tract bleeding	-	-	✔	-	-	-	-	-	-	-	-	-	-
Urinary tract infection	-	-	1	-	-	-	-	-	-	-	-	-	-
Vaginal discharge/itching	-	-	-	-	-	1-10	-	-	-	-	-	-	-
Hematologic													
Agranulocytosis	-	✔	-	-	-	-	-	✔	-	-	-	-	-
Anemia	-	-	✔	-	-	-	-	-	-	-	-	-	-
Blood dyscrasias	-	✔	-	-	-	-	-	-	-	-	✔	-	-
Decreased hematocrit	-	-	-	✔	-	-	-	-	-	-	-	-	-
Dermal bleeding	-	-	✔	-	-	-	-	-	-	-	-	-	-
Eosinophilia	-	-	✔	-	-	-	-	-	-	-	-	-	-
Granulocytopenia	-	-	-	-	-	-	✔	-	-	-	-	-	-
Leukopenia	-	-	✔	-	-	-	✔	-	-	✔	-	-	-
Neutropenia	-	-	-	-	✔	-	-	-	-	-	-	-	-
Pancytopenia	-	-	-	-	-	-	-	✔	-	-	-	-	-
Thrombocytopenia	-	-	✔	-	-	-	-	✔	-	-	-	-	-
Laboratory Test Abnormalities													
Elevated alkaline phosphatase	-	-	✔	-	-	-	✔	✔	-	-	-	-	-
Elevated bilirubin, direct	-	-	-	-	-	-	✔	-	-	-	-	-	-
Elevated bilirubin, total	-	-	-	-	-	-	✔	✔	-	-	-	-	-
Elevated liver transaminases	-	-	✔	-	-	-	-	✔	-	-	-	-	-
Elevated SGOT	-	-	-	-	-	-	✔	-	-	-	✔	-	-
Elevated SGPT	-	-	-	-	-	-	✔	-	-	-	-	-	-
Musculoskeletal													
Ankle pain	-	-	✔	-	-	-	-	-	-	-	-	-	-
Asthenia	-	-	-	-	-	-	-	✔	-	-	-	-	-
Arthralgia	-	-	✔	-	-	-	-	-	-	-	-	-	-
Back ache	-	-	-	-	-	-	-	-	-	-	-	✔	-
Back pain	-	-	✔	-	-	-	-	-	-	-	-	-	-
Dysarthria	-	-	-	-	-	-	-	-	-	-	✔	-	-
Feet pain	-	-	✔	-	-	-	-	-	-	-	-	-	-
Fracture, traumatic	-	-	✔	-	-	-	-	-	-	-	-	-	-
Hypertonia	-	-	✔	-	-	-	-	-	-	-	-	-	-
Increased muscle spasticity	-	-	-	-	✔	-	-	-	-	-	-	-	✔
Jaw pain	-	-	✔	-	-	-	-	-	-	-	-	-	-

Adverse Events	Alpra-zolam	Chlordia-zepoxide	Clona-zepam	Clora-zepate	Dia-zepam	Esta-zolam	Flura-zepam	Lora-zepam	Mida-zolam	Oxa-zepam	Qua-zepam	Tema-zepam	Tria-zolam
Joint pain	-	-	-	-	-	-	✔	-	-	-	-	-	-
Knee pain	-	-	✔	-	-	-	-	-	-	-	-	-	-
Knee swelling	-	-	✔	-	-	-	-	-	-	-	-	-	-
Leg cramps	-	-	✔	-	-	-	-	-	-	-	-	-	-
Leg pain	-	-	✔	-	-	-	-	-	-	-	-	-	-
Lumbago	-	-	✔	-	-	-	-	-	-	-	-	-	-
Muscle cramps	2.4	-	✔	-	-	<1	-	-	-	-	✔	-	-
Muscle pain	-	-	✔	-	-	-	-	-	-	-	-	-	-
Muscle stiffness	2.2	-	-	-	-	-	-	-	-	-	-	-	-
Muscle weakness	-	-	✔	-	-	-	-	-	-	-	-	-	-
Myalgia	-	-	1	-	-	<1	-	-	-	-	-	-	-
Neck pain	-	-	-	-	-	<1	-	-	-	-	-	-	-
Rigidity	4.2	-	-	-	-	-	-	-	-	-	✔	-	-
Shoulder pain	-	-	✔	-	-	-	-	-	-	-	-	-	-
Tendinitis	-	-	✔	-	-	-	-	-	-	-	-	-	-
Respiratory													
Apnea	-	-	-	-	-	3-10	-	✔	-	-	-	-	-
Asthmatic attack	-	-	✔	-	-	1-10	-	-	-	-	-	-	-
Bronchitis	-	-	1	-	-	-	-	-	-	-	-	-	-
Chest congestion	-	-	✔	-	-	-	-	-	-	-	-	-	-
COPD exacerbation	-	-	-	-	-	-	-	✔	-	-	-	-	-
Cough	-	-	2	-	-	1-10	-	-	1	-	-	-	-
Dyspnea	-	-	✔	-	-	1-10	-	-	-	-	-	-	-
Hyperventilation	9.7	-	-	-	-	-	-	-	-	-	-	-	-
Laryngospasm	-	-	-	-	-	-	-	-	<1	-	-	-	-
Pharyngitis	-	-	2	-	-	-	-	-	-	-	-	-	-
Pleurisy	-	-	✔	-	-	-	-	-	-	-	-	-	-
Pneumonia	-	-	✔	-	-	-	-	-	-	-	-	-	-
Rhinitis	-	-	2	-	-	1-10	-	-	-	-	-	-	-
Sinusitis	-	-	4	-	-	1-10	-	-	-	-	-	-	-
Sneezing, excessive	-	-	✔	-	-	-	-	-	-	-	-	-	-
Tidal volume/respiratory rate decrease	-	-	-	-	-	10	-	-	-	-	-	-	-
Upper respiratory infection	4.3	-	8	-	-	-	-	-	-	-	-	-	-
Worsening of sleep apnea	-	-	-	-	-	-	-	✔	-	-	-	-	-
Other													
Abnormal/blurred vision	-	-	-	-	-	-	-	-	-	-	✔	-	-
Abrasions	-	-	✔	-	-	-	-	-	-	-	-	-	-

Adverse Events	Alpra-zolam	Chlordia-zepoxide	Clona-zepam	Clora-zepate	Dia-zepam	Esta-zolam	Flura-zepam	Lora-zepam	Mida-zolam	Oxa-zepam	Qua-zepam	Tema-zepam	Tria-zolam
Allergic reaction	-	-	2	-	-	<1	-	-	-	-	-	-	-
Alopecia	-	-	✔	-	-	-	-	✔	-	-	-	-	-
Anaphylactic reactions	-	-	-	-	-	<1	-	✔	-	-	-	-	-
Bitter taste	-	-	-	-	-	-	✔	-	-	-	-	-	-
Breast pain	-	-	✔	-	-	-	-	-	-	-	-	-	-
Chills	-	-	-	-	-	<1	-	-	-	-	-	-	-
Colpitis	-	-	1	-	-	-	-	-	-	-	-	-	-
Congestion	-	-	-	-	-	-	-	-	-	-	-	-	0.5
Cramps	-	-	-	-	-	-	-	-	-	-	-	-	<1
Dehydration	-	-	✔	-	-	-	-	-	-	-	-	-	-
Deterioration, general	-	-	✔	-	-	-	-	-	-	-	-	-	-
Drug dependence /withdrawal	-	-	-	-	-	<1	-	-	-	-	✔	-	-
Earache	-	-	✔	-	-	-	-	-	-	-	-	-	-
Extrapyramidal symptoms	-	✔	-	-	-	-	-	✔	-	-	-	-	-
Eye irritation	-	-	✔	-	-	-	-	-	-	-	-	-	-
Eye pain/swelling	-	-	-	-	-	1-10	-	-	-	-	-	-	-
Eye twitching	-	-	✔	-	-	-	-	-	-	-	-	-	-
Faintness	-	-	-	-	-	-	✔	-	-	-	-	-	-
Falling	-	-	✔	-	-	-	-	-	-	-	-	-	✔
Glossitis	-	-	-	-	-	-	-	-	-	-	-	-	✔
Hangover	-	-	-	-	-	1-10	-	-	1-4	-	-	2.5	-
Hiccups	-	-	-	-	-	-	-	-	-	-	-	-	-
Hypersensitivity reactions	-	-	-	-	-	-	-	✔	-	-	-	-	-
Inappropriate behavior	-	-	25.0	-	-	-	-	-	-	-	-	-	✔
Infection	1.3	-	✔	-	-	-	-	-	-	-	-	-	-
Injection site reaction	-	-	-	-	-	-	-	-	4-5	-	-	-	-
Influenza	-	-	4	-	-	-	-	-	-	-	-	-	-
Lymphadenopathy	-	-	✔	-	-	-	-	-	-	-	-	-	-
Motion sickness	-	-	✔	-	-	-	-	-	-	-	-	-	-
Nasal congestion	7-17	-	-	-	-	-	-	-	-	-	-	-	-
Nosebleed	-	-	✔	-	-	-	-	-	-	-	-	-	-
Pain	-	-	✔	-	-	-	✔	-	-	-	-	-	<1
Paradoxical reaction	-	-	-	-	-	-	-	-	2	-	-	-	-
Photophobia	-	-	-	-	-	1-10	-	-	-	-	-	-	-
Physical/psychological dependence	-	-	-	-	-	-	-	-	<1	-	-	-	-
Salivation changes, unspecified	-	-	-	-	✔	-	-	-	-	-	-	-	-
Salivation, decreased	32.8	-	-	-	-	-	-	-	-	-	-	-	-

Adverse Events	Alpra-zolam	Chlordia-zepoxide	Clona-zepam	Clora-zepate	Dia-zepam	Esta-zolam	Flura-zepam	Lora-zepam	Mida-zolam	Oxa-zepam	Qua-zepam	Tema-zepam	Tria-zolam
Salivation, increased	4-5	-	✔	-	-	-	✔	-	-	-	-	-	-
Shivering	-	-	✔	-	-	-	-	-	-	-	-	-	-
Sore gums	-	-	✔	-	-	-	-	-	-	-	-	-	-
Stimulation/ overstimulation	-	-	-	-	✔	-	✔	-	-	-	-	✔	✔
Stomatitis	-	-	-	-	-	-	-	-	-	-	-	-	✔
Suicidal ideation	-	-	✔	-	-	-	-	✔	-	-	-	-	-
Sweating	15.1	-	-	-	-	1-10	✔	-	-	-	-	-	-
Thirst	-	-	✔	-	-	-	-	-	-	-	-	-	-
Tinnitus	6.6	-	-	-	-	-	-	-	-	-	-	-	0.5
Taste alteration	-	-	✔	-	-	1-10	-	-	-	-	✔	-	0.5
Thrombophlebitis	-	-	✔	-	-	-	-	-	-	-	-	-	-
Toothache	-	-	✔	-	-	-	-	-	-	-	-	-	-
Visual field defect	-	-	✔	-	-	-	-	-	-	-	-	-	-
Weight gain	2-27	-	✔	-	-	-	-	-	-	-	-	-	-
Weight loss	2-22	-	✔	-	-	-	-	-	-	-	-	-	-
Yawning	-	-	✔	-	-	-	-	-	-	-	-	-	-

✔ Percent not specified
- Event not reported

Table 7. Boxed Warning for Midazolam[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.

VII. Dosing and Administration

The usual dosing regimens for the benzodiazepines are listed in Table 8.

Table 8. Usual Dosing Regimens for the Benzodiazepines[1-19]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Alprazolam	Anxiety: Initial (IR): 0.25 to 0.5 mg orally three times daily; usual dosage range is 0.5 to 4 mg/day (in two to four divided doses); maximum: 4 mg/day Panic Disorder (With or Without Agoraphobia): 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	Safety and efficacy in children less than 18 years old have not been established.	Orally disintegrating tablet: 0.25 mg 0.5 mg 1 mg 2 mg Tablet (ER): 0.5 mg 1 mg 2 mg 3 mg Tablet (IR):

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Initial (ER): 0.5 to 1 mg orally in the morning; may increase dosage by up to 1 mg/day every three to four days; usual dosage range is 3 to 6 mg/day; maximum: 10 mg/day		0.25 mg 0.5 mg 1 mg 2 mg
Chlordiazepoxide	Alcohol Withdrawal Syndrome: IM/IV: 50-100 mg every two to four hours as needed; maximum: 300 mg in 24 hours Oral: 50-100 mg initially, followed by repeated doses as needed until agitation is controlled; maximum: 300 mg/day Anxiety (mild-to-moderate): 5 or 10 mg orally three to four times daily Anxiety (Severe): 20 or 25 mg orally three to four times daily Anxiety (Geriatric Patients or in the Presence of Debilitating Disease): 5 mg orally two to four times daily Anxiety (Preoperative): IM: 50 to 100 mg 1 hour prior to surgery Oral: 5 to 10 mg three to four times per day on days preceding surgery	Anxiety (Preoperative): ≥6 years of age: 5 mg orally two to four times daily; may be increased to 10 mg orally two to three times daily, initiate therapy with the lowest dose and increase as required	Capsule: 5 mg 10 mg 25 mg
Clonazepam	Panic Disorder: Initial: 0.25 mg orally twice daily for three days, then 0.5 mg twice daily Maintenance: increase dosage by 0.125 to 0.25 mg orally twice daily every three days; maximum: total daily dose of 1-4 mg Seizure: Initial: 0.5 mg orally three times daily	Seizure: ≤10 years of age (≤30 kg): 0.01 to 0.03 mg/kg/day orally divided into two to three daily doses; may increase daily dose by 0.25 to 0.5 mg orally every three days; maximum: total daily dose of 0.1 to 0.2 mg/kg/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

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Maintenance: increase daily dose by 0.5 to 1 mg orally every three days; maximum: total daily dose of 20 mg		
Clorazepate	Alcohol Withdrawal Syndrome: Day 1: 30 mg orally, then 30 to 60 mg orally in divided doses for the remainder of the day Day 2: 45 to 90 mg/day orally in divided doses Day 3: 22.5 to 45 mg/day orally in divided doses Day 4: 15-30 mg/day orally in divided doses Day 5 and thereafter: 7.5 to 15 mg/day orally in divided doses until the patient's condition is stable Anxiety: 15 to 60 mg/day orally in divided doses; usual dose is 30 mg/day Epilepsy (Adjunct): 7.5 mg orally three times daily; may increase dose by 7.5 mg/week; maximum: 90 mg/day orally	Epilepsy (Adjunct): 9 to 12 years of age: 7.5 mg orally twice daily; may increase dose by 7.5 mg/week; maximum: 60 mg/day orally	Tablet 3.75 mg 7.5 mg 15 mg
Diazepam	Alcohol Withdrawal Syndrome: Initial (oral): 10 mg orally three to four times a day for 1 day Initial (IM/IV): 10 mg, then 5 to 10 mg in three to four hours if needed Maintenance: 5 mg orally three to four times a day as needed Anxiety: IM/IV: 2 to 10 mg every three to four hours if needed Oral: 2 to 10 mg orally two to four times a day Anxiety (Cardioversion): 5 to 15 mg IV five to ten minutes prior to procedure	Safety and efficacy have not been established in children less than 6 months of age. Anxiety: 1 to 2.5 mg orally three to four times daily; increase gradually as needed Seizure (Adjunct): IV (≥6 months): 1 to 2.5 mg orally three to four times daily; if severe, 0.2 to 0.5 mg IV slowly (preferred) or IM every two to five minutes up to a maximum of 5 mg Rectal (2 to 5 years): 0.5 mg/kg; may repeat in four to twelve hours Rectal (6 to 11 years): 0.3 mg/kg; may repeat in four to twelve hours	Injection : 5 mg/ml Oral concentrate: 5 mg/ml Rectal gel: 2.5 mg 5-7.5-10 mg 12.5-15-20 mg Solution: 5 mg/5 ml Tablet: 2 mg 5 mg 10 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Anxiety (Endoscopic Procedure): IM: 5 to 10 mg 30 minutes prior to procedure IV: ≤10 mg immediately prior to procedure Seizure (Adjunct): IV: 5 to 10 mg every ten to fifteen minutes as needed; maximum: 30 mg; may repeat in two to four hours if needed Oral: 2 to 10 mg two to four times a day Rectal: 0.2 mg/kg; may repeat in four to twelve hours Skeletal Muscle Spasm: IM/IV: 5 to 10 mg, repeat in three to four hours if needed Oral: 2 to 10 mg three to four times daily Status Epilepticus: 5 to 10 mg IV every ten to fifteen minutes to a total dose of 30 mg; may repeat in two to four hours if needed	Rectal (≥12 years of age): 0.2 mg/kg; may repeat in four to twelve hours Skeletal Muscle Spasm, Adjunct: ≥6 months of age: 1 to 2.5 mg orally three to four times daily Skeletal Muscle Spasm, Tetanus: 30 days to 5 years of age: 1 to 2 mg IM or IV slowly every three to four hours as needed ≥5 years of age: 5 to 10 mg IM or IV slowly every three to four hours as needed Status Epilepticus: 30 days to 5 years of age: 0.2 to 0.5 mg IV slowly (preferred) or IM every two to five minutes up to a maximum of 5 mg ≥5 years of age: 1 mg IV slowly (preferred) or IM every two to five minutes up to a maximum of 10 mg; repeat in two to four hours if necessary	
Estazolam	Insomnia: 1 to 2 mg orally at bedtime	Safety and efficacy in patients less than 18 years old have not been established.	Tablet: 1 mg 2 mg
Flurazepam	Insomnia: 15 to 30 mg orally at bedtime	Safety and efficacy in patients less than 15 years old have not been established.	Capsule: 15 mg 30 mg
Lorazepam	Anxiety: Initial: 2 to 3 mg/day orally divided into two to three daily doses Maintenance: 2 to 6 mg/day orally divided into two to three daily doses; maximum: 10 mg/day Insomnia: 2 to 4 mg orally at bedtime Premedication for Anesthetic Procedure: IM: 0.05 mg/kg two to three hours before procedure;	Safety and efficacy of lorazepam tablets in children less than 12 years old have not been established. Safety and efficacy of lorazepam injection in children less than 18 years old have not been established. Insomnia: ≥12 years of age: 2 to 4 mg orally at bedtime Status Epilepticus: 0.05 to 0.1 mg/kg IV; maximum: 4 mg/dose	Injection: 2 mg/mL 4 mg/mL Oral solution: 2 mg/ml Tablet: 0.5 mg 1 mg 2 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	maximum: 4 mg/dose IV: 0.044 mg/kg or 2 mg (whichever is less); maximum: 0.05 mg/kg or 4 mg (whichever is less) Sublingual: 0.05 mg/kg one to two hours before procedure; maximum: 4 mg/dose Status Epilepticus: IV: 0.05 mg/kg up to a maximum of 4 mg; may repeat dose in ten to fifteen minutes if needed		
Midazolam	Anesthesia (Induction): Unpremedicated patients: 0.3-0.35 mg/kg Premedicated patients: 0.15-0.35 mg/kg 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): IM: 0.07 to 0.08 mg/kg 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): Loading dose: 0.01-0.05 mg/kg IV over several minutes; may be repeated at 10-15 minute intervals until adequate sedation is achieved. Maintenance: 0.02-0.10 mg/kg/hr	Sedation/Anxiolysis/Amnesia (Preoperative): Non-neonatal (IM): 0.1-0.15 mg/kg 6 months to 5 years of age (IV): 0.05-0.1 mg/kg 6 to 12 years of age (IV): 0.025- 0.05 mg/kg 12 to 16 years of age: refer to adult dosing Sedation/Anxiolysis/Amnesia (Critical Care Settings): 6 months to 6 years of age: ≤1 mg/kg orally 6 to 16 years of age: 0.25- 0.5 mg/kg orally	Injection: 1 mg/ml 2 mg/ml 2 mg/2 ml 5 mg/ml Syrup: 2 mg/ml

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Oxazepam	Alcohol Withdrawal Syndrome: 15 to 30 mg orally three to four times daily Anxiety (Mild-to-Moderate): 10 to 15 mg orally three to four times daily Anxiety (Severe): 15 to 30 mg orally three to four times daily	Safety and efficacy in children under age 6 years have not been established and the absolute dose for children ages 6 to 12 years has not been determined. Alcohol Withdrawal Syndrome: ≥12 years of age: 15 to 30 mg orally three to four times daily Anxiety (Mild-to-Moderate): ≥12 years of age: 10 to 15 mg orally three to four times daily Anxiety (Severe): ≥12 years of age: 15 to 30 mg orally three to four times daily	Capsule: 10 mg 15 mg 30 mg
Quazepam	Insomnia: 7.5 to 15 mg orally at bedtime	Safety and efficacy in children less than 18 years old have not been established.	Tablet: 15 mg
Temazepam	Insomnia: 7.5 to 30 mg orally at bedtime	Safety and efficacy in children less than 18 years old have not been established.	Capsule: 7.5 mg 15 mg 22.5 mg 30 mg
Triazolam	Insomnia: 0.25 mg orally 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 9.

Table 9. 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 RCT) Variable duration (1 to 180 days)	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	MA Patients with alcohol dependence	N=4,051 Variable duration	Primary: Severity of overall alcohol withdrawal syndrome, alcohol	Primary: Compared to placebo, there was a benefit with the benzodiazepines against alcohol withdrawal seizures (P=0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
alone or in combination with other agents vs alternate benzodiazepines vs other agents (e.g., anticonvulsants) vs placebo	who experienced alcohol withdrawal		withdrawal seizures, alcohol withdrawal delirium Secondary: Adverse events, discontinuation due to adverse events, withdrawal rate, mortality	Benzodiazepines had similar success rates as other drugs and offered a 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
chlordiazepoxide 80 mg/day (20 mg in the morning, 20 mg in the afternoon, 40 mg at night) for 2 days. The dose was reduced by 20 mg per day every 2 days Dosing was down-titrated to zero across 8 treatment days				the last 4 days of the study, nor were there impairing adverse events 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 RCT) 2-24 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.
Mitte et al.[34] (2005) Benzodiazepines vs azaspirones vs	MA Patients with generalized anxiety disorder	N=12,053 (48 RCT) 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				
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 RCT) 6-20 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 vs antidepressants vs psychological panic management vs exposure in vivo vs placebo	MA Patients with panic disorder (with or without agoraphobia)	N=5,011 (106 RCT) Variable duration	Primary: Panic, agoraphobia, depression, and general anxiety	Primary: Antidepressants, psychological panic management and antidepressants/exposure in vivo demonstrated significant improvement in the reduction of panic, agoraphobia, depression, and anxiety compared to a control conditions. High-potency benzodiazepines showed significant improvement in panic, agoraphobia, and anxiety compared to control conditions. There were no significant differences between the treatments for panic disorder. Antidepressant test groups had significant improvements compared to other treatments except exposure in vivo in agoraphobia. A significantly greater improvement was noted in antidepressant/exposure in vivo compared to exposure in vivo alone and psychological panic management/exposure in vivo in treatment of depression and anxiety.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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 benzodiazepines are reported in this review.	MA Patients with generalized anxiety disorder	N=5,908 (36 RCT) 4-14 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 40% of patients on lorazepam (P<0.001).
Insomnia				
Piccione et al.[51] (1980) Chloral hydrate 250 mg vs chloral hydrate 500 mg vs	DB, XO Elderly patients (>60 years) 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
triazolam 0.25 mg vs triazolam 0.50 mg vs placebo				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.
Holbrook et al.[38] (2000) Benzodiazepines vs zopiclone*, diphenhydramine, glutethimide, promethazine, cognitive behavioral therapy, placebo	MA Patients with insomnia	N=2,672 (45 RCT) 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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Smith et al.[39] (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) 1 to 10 weeks	Primary: Sleep latency, total sleep time, number of awakenings, wake time after sleep onset, 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 total sleep time by 12% compared to 6% with 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,	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
antidepressants vs placebo				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. 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	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:	Study Subjects 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
diphenhydramine 50 mg for 2 weeks vs placebo for 2 weeks			Morning-after psychomotor impairment (using the digit symbol substitution task [DSST] and the manual tracking task [MTT]); morning-after memory impairment (using free-recall)	There was a significant difference in the number of awakenings with diphenhydramine and temazepam compared to placebo (both P<0.05). Secondary: There were no changes in the DSST or the MTT scores with any treatment. No treatment effects could be detected on the memory assessment performed.
Okawa et al.[43] (1978) Triazolam 0.5 mg vs secobarbital 100 mg vs placebo	2 DB, R, XO Patients 18-60 years of age with a known 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) vs failure, adverse effects	Primary: One trial compared triazolam to placebo and involved 19 patients. Sixteen patients preferred triazolam compared to 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				effects. Nineteen patients reported drowsiness, dizziness, nausea and lightheadedness.
Seizures				
Pavlidou et al.[44] (2006) Diazepam 0.33 mg/kg administered every 8 hours rectally for 1 day, followed by every 12 hours on day 2 vs no treatment	PRO, R Children aged 6 months to 3 years 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).
Appleton et al.[45] (2002) lorazepam intravenously or rectally (dose not specified) vs diazepam intravenously 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Treiman et al.[46] (1998) Diazepam 0.15 mg/kg, followed by phenytoin 18 mg/kg vs lorazepam 0.1 mg/kg vs phenobarbital 15 mg/kg vs phenytoin 18 mg/kg	DB, MC, R 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.
Other				
Johnson et al.[52] (2006) Triazolam 0.25 mg, 0.5 mg or 0.75 mg vs ramelteon 16mg, 80 mg or 160 mg vs	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 subjects 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 and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				
Leufkens et al.[47] (2007) alprazolam XR 1 mg vs alprazolam IR 1 mg vs placebo	DB, PC, XO Healthy individuals aged 20-45 years	N=18 Up to 5.5 hours after administration	Primary: Comparison of effects on actual driving ability (as assessed in a standard on-the-road driving test) measured by 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	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 and either formulation of alprazolam in terms of mean speed and speed variability. Ten driving tests were terminated prematurely due to subjects 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	DB, DD, RCT, XO Healthy volunteers ≥65 years of age	N=24 Single dose, treatment	Primary: Psychometric tests performed 8 hours after study	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs zolpidem, modified release (MR) 6.25 mg vs zolpidem MR 12.5 mg vs placebo			medication (CFF, CRT, word recall, CTT, DSST), subjective evaluation of sleep (LSEQ), safety, pharmacokinetics (zolpidem MR only)	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. 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.

*Agent not available in the US
Study abbreviations**:** CI=confidence interval, DB=double-blind, MA=meta-analysis, MC=multi-center, PC=placebo controlled, PRO=prospective trial, OR=odds ratio, R=randomized, 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 branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

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

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

Rx=prescription

Table 10. Relative Cost of the Benzodiazepines

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Alprazolam	orally disintegrating tablet, extended-release tablet, tablet	Niravam®*‡, Xanax®*‡, Xanax XR®*‡	$$$-$$$$$	$-$$$
Chlordiazepoxide	capsule	Librium®*	$$$	$
Clonazepam	orally disintegrating tablet, tablet	Klonopin®*	$$-$$$	$-$$$$
Clorazepate	tablet	Tranxene T-Tab®*	$$$$$	$
Diazepam	injection, oral concentrate, rectal gel, solution, tablet	Diastat®, Diastat AcuDial®	$$$$$	$
Estazolam‡	tablet	N/A	N/A	$
Flurazepam	capsule	N/A	N/A	$
Lorazepam	injection, oral concentrate, tablet	Ativan®*, Lorazepam Intensol®*	$$$-$$$$$	$
Midazolam‡	injection, syrup	N/A	N/A	$
Oxazepam	capsule	N/A	N/A	$-$$$
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 used for the treatment of anxiety disorders and for the short-term treatment of insomnia.[1-19] 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).[21-23] All of the benzodiazepines are available in a generic formulation, with the exception of 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 may be used for acute treatment, but they should not generally not be used beyond 2 to 4 weeks.[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.[56-57]

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]

The American Society of Addiction Medicine recommends the use of benzodiazepines over nonbenzodiazepine sedative/hypnotic agents for the management of alcohol withdrawal.[30] They do not give preference to one particular benzodiazepine over another. Clinical studies have demonstrated similar efficacy in reducing the signs and symptoms of withdrawal.[30,32-33,53] Long-acting agents may be more effective in preventing withdrawal seizures and short-acting agents may cause less over-sedation.[30]

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 (AEDs) are not currently included in the Preferred Drug Program. Diazepam is available in a rectal gel formulation, which is specifically indicated for the management of selected, refractory, patients with epilepsy (on stable regimens of AEDs) who require intermittent use of diazepam to control bouts of increased seizure activity.[6] This product provides a beneficial route of administration compared to other agents in this class.

Currently, Alabama Medicaid does not cover several brand and generic benzodiazepines (refer to Table 1 and Table 10 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, are comparable to each other and offer no significant clinical advantage over other alternatives in general use. Diazepam rectal gel offers significant clinical advantages in general use over the other brands and generics in the class.

XI. Recommendations

No brand benzodiazepine, with the exception of diazepam rectal gel, is recommended for preferred status. Alabama Medicaid should consider not covering brand benzodiazepines.

Alabama Medicaid should consider covering all generic benzodiazepines.

Diazepam rectal gel (Diastat® and Diastat AcuDial®) is recommended for preferred status.

XII. References

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Anxiolytics, Sedatives, and Hypnotics – Miscellaneous
AHFS Class 282492
February 10, 2010

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.[1-3,4,7] The exact mechanism of action of buspirone is unknown. It lacks anticonvulsant, muscle relaxant or sedative properties, which are seen with other agents.[4] 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.[7] Meprobamate has been shown to have effects at multiple sites in the central nervous system, including the thalamus and limbic system.[1-3]

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.[6,9-12] 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.[6,9-12] 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.[8] 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.[8] Ramelteon is not a controlled substance. Discontinuation after chronic administration did not produce withdrawal signs and it does not appear to produce physical dependence.[8]

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.[5] 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.[1-3]

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. Buspirone, chloral hydrate, droperidol, hydroxyzine, meprobamate, zaleplon and zolpidem are available in a generic formulation. This class was last reviewed in November 2007.

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	BuSpar®*	buspirone
Chloral hydrate	capsule, rectal suppository, syrup	N/A	chloral hydrate
Dexmedetomidine	injection	Precedex®	none
Droperidol	injection	Inapsine®*	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, sublingual tablet, tablet	Ambien®*, Ambien CR®, Edluar®	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)
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

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

National Institute for Health and Clinical Excellence (NICE): **Management of Anxiety (Panic Disorder, With or Without Agoraphobia, and Generalized Anxiety Disorder) in Adults in Primary, Secondary and Community Care[15] (2007)**	<u>Panic Disorder General Considerations</u>
	• Benzodiazepines are associated with a less effective outcome in the long term and should not be prescribed for panic disorder.
	• Sedating antihistamines or antipsychotics should not be prescribed for panic disorder.
	• Interventions with evidence for the longest duration of effect are listed in descending order, where preference of the patient should be taken into account:
	  o Psychological therapy Pharmacological therapy (antidepressant therapy)
	  o Self-help interventions
	<u>Panic Disorder - Additional Considerations for Pharmacologic Therapy</u>
	• 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 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.
	<u>Generalized Anxiety Disorder General Considerations</u>
	• If immediate management of generalized anxiety disorder is necessary, any or all of the following should be considered:
	  o Support and information
	  o Problem solving
	  o Benzodiazepines
	  o Sedating antihistamines
	  o Self-help
	• Benzodiazepines may be used for acute treatment, but they should not usually be used beyond 2 to 4 weeks.
	• In the longer-term care of individuals with generalized anxiety disorder, any of the following types of intervention should be offered and the preference of the person with generalized anxiety disorder should be taken into account. The interventions which have evidence for the longest duration of effect, in descending order, are:
	  o Psychological therapy
	  o Pharmacological therapy (antidepressant medication)
	  o Self-help
	<u>Generalized Anxiety Disorder – Additional Considerations for Pharmacologic Therapy</u>
	• Antidepressants should be the only pharmacological intervention used in the longer-term management of generalized anxiety disorder.
	• There is an evidence base for the effectiveness of the SSRIs.

Clinical Guideline	Recommendation(s)
	Paroxetine and venlafaxine ER have marketing authorization for the treatment of generalized anxiety disorder. Unless otherwise indicated, an SSRI should be offered; if one SSRI is not suitable, another SSRI should be offered. • 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. • If there is no improvement after a 12 week course with an SSRI and if a further medication is appropriate, another SSRI may be considered, or another form of therapy may be offered.

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

Clinical Guideline	Recommendation(s)
	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. • 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: **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

Clinical Guideline	Recommendation(s)
	dose of the same medication. <u>Changing Treatments and Pursuing Sequential Treatment Trials</u> • Augmentation strategies may be preferred to switching strategies in patients who have a partial response to the initial treatment. • Augmentation of SRIs with trials of different antipsychotic medications or with 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. • 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

Clinical Guideline	Recommendation(s)
	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 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:

Clinical Guideline	Recommendation(s)
	○ 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. • 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), State-of-the-Science Conference Statement: **Manifestations and Management of Chronic Insomnia in Adults[18] (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.

Clinical Guideline	Recommendation(s)
	<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.

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

Clinical Guideline	Recommendation(s)
	with regard to patient satisfaction and safety. Therefore, the routine use of propofol in average- risk patients cannot be endorsed.
The International Anesthesia Research Society: **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-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.
American Society of Addiction Medicine (ASAM), Committee on Practice Guidelines: **Pharmacological Management of Alcohol Withdrawal**[51] **(1997)**	• Benzodiazepines are recommended over nonbenzodiazepine sedative-hypnotics for alcohol withdrawal. • Phenobarbital is an alternative to benzodiazepines but may have a less optimal safety profile at high doses. • All benzodiazepines are equally effective in reducing the signs and symptoms of withdrawal. • Long-acting benzodiazepines may be more effective in preventing withdrawal seizures by contributing to a “smoother” withdrawal with

Clinical Guideline	Recommendation(s)
	less rebound symptoms. • Short-acting benzodiazepines may cause less over-sedation. • The benzodiazepines with a rapid onset of action such as alprazolam, diazepam, and lorazepam have a higher abuse potential as compared to the slower onset agents (chlordiazepoxide, halazepam or oxazepam). • Alcohol withdrawal cannot be treated with a standard fixed dose so treatment is based on individual need. • The use of a structured assessment scale (e.g., Clinical Institute Withdrawal Assessment-Alcohol, revised [CIWA-Ar]) is recommended in substance abuse treatment programs to allow for dose titration and the reduction of unnecessary medication. Use with caution in patients with acute medical or psychiatric co-morbidities or patients with concurrent substance withdrawal. • For mild withdrawal symptoms (CIWA-Ar scores <8), supportive nonpharmacological therapy and continual monitoring every 4-8 hours is recommended. • The addition of medications to control symptoms is recommended for moderate (CIWA-Ar scores 8-15) to severe alcohol withdrawal symptoms (CIWA-Ar scores ≥15). Give 1 of the following agents every hour: chlordiazepoxide 50-100 mg, diazepam 10-20 mg or lorazepam 2-4 mg. • It is recommended that patients with severe withdrawal symptoms be given benzodiazepines at a dose necessary to control these symptoms. • In patients with acute medical or psychiatric conditions or with concurrent substance withdrawal, a fixed-schedule regimen is recommended over a symptom-regimen. • Examples of this fixed-schedule regimen include: chlordiazepoxide 50 mg every 6 hours for 4 doses, then 25 mg every 6 hours for 8 doses; or diazepam 10 mg every 6 hours for 4 doses, then 5 mg every 6 hours for 8 doses; or lorazepam 2 mg every 6 hours for 4 doses, then 1 mg every 6 hours for 8 doses. Alternative benzodiazepines may be substituted at equivalent doses. • Additional medication should be provided on an as needed basis when symptoms are not controlled. • For patients with a history of withdrawal seizures or notable comorbid medical illnesses, initiate a recommended medication regardless of symptom severity. • Patients using sedative-hypnotic medications may be at increased risk for major complications or may exhibit tolerance to benzodiazepines. • Alternative agents such as β-blockers, clonidine and carbamazepine are not recommended as monotherapy as they have not been shown to decrease delirium or seizures. • β-Blockers may be considered as adjunct treatment with benzodiazepines in patients with coronary artery disease, whereas patients with opiate withdrawal may benefit from the addition of clonidine. • Combination therapy with carbamazepine may be considered in patients with benzodiazepine withdrawal. • Neuroleptics (e.g., haloperidol, phenothiazines) may be effective in patients with notable agitation or hallucinations. • Thiamine administration is recommended at initiation of treatment to prevent Wernicke's disease and Wernicke-Korsakoff syndrome. • Recommendations for adolescents are the same as for adults.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the miscellaneous anxiolytics, sedatives, and hypnotics 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 Miscellaneous Anxiolytics, Sedatives, and Hypnotics[1-12]

Indication	Buspirone	Chloral Hydrate	Dexmede-tomidine	Droperidol	Eszopiclone	Hydroxyzine	Meprobamate	Ramelteon	Zaleplon	Zolpidem
Anxiety Disorders										
Management of anxiety disorders	✔					✔	✔			
Hypnotic										
Short-term treatment of insomnia		✔								
Short-term treatment of insomnia characterized by 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					✔					✔ ‡
Sedative										
Preoperative sedation to lessen anxiety and induce sleep without depressing respiration or cough reflex		✔								
Sedation of intubated and mechanically ventilated patients			✔							
Sedation of non-intubated patients prior to and/or during surgical and other procedures			✔							
Sedation when used as premedication and following general anesthesia						✔				
Miscellaneous										
Prevention or suppression of alcohol withdrawal symptoms		✔								
Prevention and/or treatment of nausea and vomiting from surgical and diagnostic procedures				✔						

Indication	Buspirone	Chloral Hydrate	Dexmede-tomidine	Droperidol	Eszopiclone	Hydroxyzine	Meprobamate	Ramelteon	Zaleplon	Zolpidem
Pruritus caused by allergic conditions such as chronic urticaria and atopic or contact dermatoses and in histamine-mediated pruritus						✔				

†Immediate-release formulation
‡Extended-release formulation

IV. Pharmacokinetics

The pharmacokinetic parameters of the miscellaneous anxiolytics, sedatives, and hypnotics are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Miscellaneous Anxiolytics, Sedatives, and Hypnotics[1-12]

Generic Name(s)	Onset of Action	Bioavailability (%)	Protein Binding (%)	Metabolism	Excretion (%)	Half-Life (hours)
Buspirone	1 week	90	86	Hepatic	Fecal (18-38) Renal (29-63)	2-3
Chloral hydrate	Not reported	Well absorbed	70-80	Hepatic	Not reported	8-11
Dexmedetomidine	30 min	73	94	Hepatic	Fecal (4) Renal (95)	2-5
Droperidol	3-10 min	Not reported	Extensive	Hepatic	Fecal (22) Renal (75)	2
Eszopiclone	10 min	75	Not reported	Hepatic	Not reported	5-6
Hydroxyzine	Not reported	Not reported	Not reported	Hepatic	Not reported	3-20
Meprobamate	Not reported	Not reported	0-30	Hepatic	Renal (10-20)	9-11
Ramelteon	Not reported	1.8	82	Hepatic	Fecal (4) Renal (84)	1-2.6
Zaleplon	30 min	30	60	Hepatic	Fecal (17) Renal (71)	1
Zolpidem	7-27 min	70	93	Hepatic	Biliary Fecal Renal	2.5-2.8

V. Drug Interactions

Significant drug interactions with the miscellaneous anxiolytics, sedatives, and hypnotics are listed in Table 5.

Table 5. Significant Drug Interactions with the Miscellaneous Anxiolytics, Sedatives, and Hypnotics[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
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. Coadministration of dofetilide, dronedarone and ibutilide is contraindicated with droperidol.
Droperidol	1	Macrolides	Pharmacologic effects of macrolides/ketolides and droperidol on ventricular myocardium may be additive. Prolonged QT interval and cardiac arrhythmias are possible when macrolides/ ketolides and droperidol are used concurrently.
Droperidol	1	Methadone	Coadministration of methadone and droperidol may cause significant prolongation of the cardiac QT interval and possibly lead to torsades de pointes arrhythmias.
Droperidol	1	Nilotinib	Additive QT prolongation may occur during coadministration of nilotinib and droperidol.

Generic Name(s)	Significance Level	Interaction	Mechanism
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.
Droperidol	1	Quinolones	Droperidol and quinolones may cause additive QT interval prolongation and possible arrhythmias.
Droperidol	1	Tricyclic and tetracyclic antidepressants	Droperidol and tricyclic/ tetracyclic antidepressants may cause additive QT interval prolongation and possible arrhythmias.
Droperidol	1	Ziprasidone	The combination of ziprasidone and droperidol may have cause additive prolongation of the QT interval. Ziprasidone is contraindicated in patients receiving droperidol due to the increased risk of life-threatening cardiac arrhythmias, including torsades de pointes.
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. The mechanism of this interaction is unknown.
Buspirone, eszopiclone	2	Macrolide and related antibiotics	Inhibition of CYP3A4 by macrolides and ketolides may decrease the metabolic elimination and increase plasma concentrations of buspirone or eszopiclone.
Buspirone	2	MAO inhibitors	Concurrent administration of buspirone with monoamine oxidase inhibitors (MAOIs) is not recommended. Cases of hypertensive crisis have occurred when MAOIs have been administered simultaneously with buspirone. This interaction may be mediated by the affinity of buspirone for serotonin receptors.
Buspirone, eszopiclone, ramelteon, zaleplon, zolpidem	2	Rifampin	Induction of CYP3A4 isoenzymes by rifampin may increase the metabolic elimination of eszopiclone, ramelteon, zaleplon or zolpidem.
Buspirone	2	Serotonin modulators (nefazodone, trazodone)	Inhibition of CYP3A4 isoenzymes by serotonin modulators may decrease the metabolic elimination and increase plasma concentrations of buspirone.

Generic Name(s)	Significance Level	Interaction	Mechanism
Buspirone, chloral hydrate, droperidol, hydroxyzine, meprobamate, zaleplon, zolpidem	2	Sodium oxybate	Concurrent use of sodium oxybate may result in an increase in sleep duration and CNS depression. Pharmacologic effects of sodium oxybate and sedative-hypnotics may be additive. Coadministration is contraindicated.
Chloral hydrate	2	Anticoagulants, oral	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. The mechanism of this interaction is unknown.
Eszopiclone,	2	Nefazodone	Inhibition of CYP3A4 by nefazodone may decrease the metabolic elimination and increase plasma concentrations of eszopiclone.
Eszopiclone, zolpidem	2	Protease inhibitors	Inhibition of CYP3A4 by protease inhibitors may decrease the metabolic elimination and increase plasma concentrations of eszopiclone and zolpidem.
Ramelteon	2	Fluvoxamine	Inhibition of CYP1A2 by fluvoxamine may decrease the metabolic elimination and increase plasma concentrations of ramelteon.
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 6. The boxed warning for droperidol is listed in Table 7. 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. There was no evidence of tolerance to eszopiclone with up to 12 months of nightly use, and no significant withdrawal symptoms were observed after discontinuation.[14] The longest placebo-controlled studies with zaleplon were 4 weeks in duration.[14] In these studies, zaleplon use did not appear to result in rebound insomnia, withdrawal symptoms or tolerance. After 4 weeks of nightly use, withdrawal symptoms and rebound insomnia have been reported upon discontinuation of zolpidem; however, the potential for dependence, tolerance or rebound insomnia appears minimal when zolpidem is used at the recommended dosages.[14] Buspirone has shown no potential for abuse or diversion, and there is no evidence that it causes tolerance or physical/psychological dependence.[4] Tolerance, rebound insomnia or withdrawal effects have not been observed with ramelteon.[8]

Table 6. 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	-	-	-	-	-	-	-
AV block	-	-	<1	-	-	-	-	-	-	-
Bigeminy	-	-	-	-	-	-	-	-	<1	-
Blood pressure increased	-	-	-	-	-	-	-	-	-	✔
Bradycardia	-	-	5-14	-	-	-	-	-	<1	-
Bundle branch block	-	-	-	-	-	-	-	-	<1	-
Cardiac arrest	-	-	✔	✔	-	-	-	-	-	-
Cerebrovascular disorder	-	-	-	-	-	-	-	-	<1	<1
Chest pain	>1	-	-	-	✔	-	-	-	>1	✔
ECG changes, transient	-	-	-	-	-	-	✔	-	-	-
Extrasystoles	-	-	✔	-	-	-	-	-	-	✔
Hemorrhage	-	-	3	-	-	-	-	-	-	-
Hypertension	<1	-	✔	✔	✔	-	-	-	<1	<1
Hypotension	<1	-	24-54	✔	-	-	✔	-	<1	<1
Hypovolemia	-	-	3	-	-	-	-	-	-	-
Migraine	-	-	-	-	>1	-	-	-	>1	<1
Myocardial infarction	-	-	✔	-	-	-	-	-	-	-
Palpitation	1	-	-	✔	-	-	✔	-	<1	✔
Pericardial effusion	-	-	-	-	-	-	-	-	<1	-
Peripheral edema	-	-	-	-	✔	-	✔	-	<1	-

Adverse Events	Buspirone	Chloral Hydrate	Dexmede-tomidine	Droperidol	Eszopiclone	Hydroxyzine	Meprobamate	Ramelteon	Zaleplon	Zolpidem
QT interval prolongation	-	-	-	✔	-	-	-	-	-	-
Syncope	<1	-	-	✔	-	-	✔	-	-	≤1
T-waves abnormal	-	-	-	✔	-	-	-	-	-	-
Tachycardia	1	-	✔	✔	-	-	✔	-	<1	≤1
Torsades de pointes	-	-	-	✔	-	-	-	-	-	-
Vasodilation	-	-	-	-	-	-	-	-	<1	-
Ventricular tachycardia	-	-	✔	✔	-	-	-	-	<1	-
Central Nervous System										
Abnormal gait	-	-	-	-	✔	-	-	-	-	-
Agitation	-	-	2	-	✔	-	-	-	-	≤1
Akathisia	<1	-	-	✔	-	-	-	-	-	-
Amnesia/memory disorder	-	-	-	-	-	-	-	-	2-4	✔
Anger/hostility	2	-	-	-	✔	-	-	-	-	-
Anxiety	-	-	-	✔	1-3	-	-	-	>1	✔
Ataxia	-	✔	-	-	-	-	✔	-	<1	✔
Complex sleep-related activities	-	-	-	-	✔	-	-	✔	<1	≤1
Confusion	2	✔	✔	-	≤3	-	-	-	<1	✔
Convulsions/seizure	<1	-	-	✔	-	✔	-	-	-	-
Decreased concentration	2	-	-	-	-	-	-	-	>1	✔
Delirium	-	-	✔	-	-	-	-	-	-	-
Delusions	-	-	-	-	-	-	-	-	<1	-
Depersonalization	-	-	-	-	-	-	-	-	1-2	✔
Depression	2	-	-	✔	1-4	-	-	2	>1	✔
Disorientation	-	✔	-	-	-	-	-	-	-	✔
Dizziness	12	✔	✔	✔	5-7	✔	✔	4-5	7-9	✔
Dream disturbances	>1	-	-	-	1-3	-	-	-	-	✔
Drowsiness	10	-	-	✔	-	✔	✔	-	-	✔
Dysarthria	-	-	-	-	-	-	-	≤1	≤1	≤1
Dysphoria	-	-	-	✔	-	-	-	-	-	-
Dystonia	-	-	-	✔	-	-	-	-	<1	-
Emotional lability	-	-	-	-	✔	-	-	-	-	≤1
Euphoria	-	-	-	-	✔	-	✔	-	-	✔
Excitement	2	✔	-	-	-	-	✔	-	-	-
Extrapyramidal symptoms	-	-	-	✔	-	-	-	-	-	-
Falling	-	-	-	-	-	-	-	-	-	≤1
Fatigue	4	-	-	-	-	✔	-	4	-	✔

Adverse Events	Buspirone	Chloral Hydrate	Dexmede-tomidine	Droperidol	Eszopiclone	Hydroxyzine	Meprobamate	Ramelteon	Zaleplon	Zolpidem
Hallucinations	<1	✔	✔	✔	1-3	✔	-	-	<1	✔
Hangover effect	-	✔	-	-	-	-	-	-	-	-
Headache	6	✔	✔	-	15-21	✔	✔	7	30-42	✔
Heat stroke	-	-	-	✔	✔	✔	-	-	-	-
Hyperactivity	-	-	-	✔	-	-	-	-	-	-
Hypesthesia	-	-	-	-	-	-	-	-	<2	-
Hypertonia	-	-	-	-	-	-	-	-	1	-
Hypoesthesia	-	-	-	-	-	-	-	-	1-2	✔
Illusion	-	-	✔	-	-	-	-	-	-	<1
Incoordination	1	✔	-	-	-	-	-	-	-	-
Insomnia	3	-	-	-	-	-	-	3	-	✔
Involuntary movements	-	-	-	-	-	✔	-	-	-	-
Lethargy	-	-	-	-	-	-	-	-	-	✔
Lightheadedness	3	✔	-	-	-	-	-	-	-	✔
Malaise	<1	-	-	-	✔	-	-	-	<2	<1
Migraine	-	-	-	-	✔	-	-	-	>1	-
Myasthenia	-	-	-	-	✔	-	-	-	<1	-
Nervousness	5	-	-	-	≤5	✔	-	-	>1	<1
Neuralgia	-	-	✔	-	≤3	-	-	-	-	-
Neuritis	-	-	✔	-	✔	-	-	-	-	-
Neuroleptic malignant syndrome	-	-	-	✔	-	-	-	-	-	-
Neuropathy	-	-	-	-	✔	-	-	-	-	-
Nightmares	-	✔	-	-	-	-	-	-	-	-
Numbness/paresthesia	1-2	-	-	-	-	-	✔	-	3	<1
Nystagmus	-	-	-	-	✔	-	-	-	-	-
Oculogyric crisis	-	-	-	✔	-	-	-	-	-	-
Overstimulation	-	-	-	-	-	-	✔	-	-	-
Paresthesia	-	-	-	-	✔	✔	✔	-	3	✔
Pseudoparkinsonism	-	-	-	✔	-	-	-	-	-	-
Psychosis	<1	-	-	-	✔	-	-	-	-	-
Restlessness	-	-	-	✔	-	-	-	-	-	-
Sedation, residual	-	✔	-	✔	-	-	-	-	-	3
Sleep disorder	-	-	-	-	-	-	-	-	-	✔
Somnolence	10	✔	-	✔	8-10	✔	✔	3-5	5-6	✔
Speech disorder	-	-	✔	-	-	-	✔	-	-	<1
Stupor	-	-	-	-	-	-	-	-	-	<1

Adverse Events	Buspirone	Chloral Hydrate	Dexmede-tomidine	Droperidol	Eszopiclone	Hydroxyzine	Meprobamate	Ramelteon	Zaleplon	Zolpidem
Suicidal ideation	<1	-	-	-	-	-	-	-	-	-
Tardive dyskinesia	-	-	-	✔	-	-	-	-	-	-
Temperature regulation altered	-	-	-	✔	-	-	-	-	-	✔
Tremor	1	-	-	-	✔	✔	-	-	2	✔
Vertigo	-	-	-	-	✔	-	✔	-	<1	✔
Dermatological										
Alopecia	-	-	-	✔	✔	-	-	-	<1	-
Angioedema	-	✔	-	-	✔	-	-	✔	<1	✔
Bullous lesions	-	✔	-	-	✔	-	-	-	-	-
Ecchymosis	-	-	-	-	-	-	✔	-	<1	-
Eczema	-	✔	-	-	✔	-	-	-	-	-
Edema	<1	-	-	-	-	-	-	<1	<1	<1
Erythema multiforme	-	✔	-	-	✔	-	-	-	-	-
Hyperpigmentation	-	-	-	✔	-	-	-	-	-	-
Pallor	-	-	-	-	-	-	-	-	-	<1
Petechiae	-	-	-	-	-	-	✔	-	-	-
Photosensitivity reaction	-	-	-	✔	✔	-	-	-	<1	-
Pruritus	-	-	-	-	1-4	✔	✔	-	>1	<1
Purpura	-	-	-	-	-	-	✔	-	<1	-
Rash	1	✔	-	✔	3-4	✔	✔	-	>1	✔
Urticaria	-	✔	-	-	✔	✔	✔	-	-	✔
Endocrine and Metabolic										
Acidosis	-	-	✔	-	-	-	-	-	-	-
Acidosis, respiratory	-	-	✔	-	-	-	-	-	-	-
Bilirubinemia	-	-	-	-	-	-	-	-	<1	-
Blood cortisol decreased	-	-	-	-	-	-	-	1	-	-
Breast neoplasm	-	-	-	-	✔	-	-	-	-	-
Cholelithiasis	-	-	-	-	✔	-	-	-	<1	-
Diabetes mellitus	-	-	-	-	-	-	-	-	<1	-
Goiter	-	-	-	-	-	-	-	-	<1	-
Gout	-	-	-	-	✔	-	-	-	-	-
Gynecomastia	-	-	-	✔	≤3	-	-	-	-	-
Hepatitis	-	-	-	-	✔	-	-	-	-	-
Hepatomegaly	-	-	-	-	✔	-	-	-	-	-
Hypercholesterolemia	-	-	-	-	✔	-	-	-	-	-
Hyperglycemia	-	-	-	-	-	-	-	-	<1	-

Adverse Events	Buspirone	Chloral Hydrate	Dexmede-tomidine	Droperidol	Eszopiclone	Hydroxyzine	Meprobamate	Ramelteon	Zaleplon	Zolpidem
Hyperglycemia	-	-	✔	-	-	-	-	-	-	<1
Hyperkalemia	-	-	✔	-	-	-	-	-	-	-
Hyperuricemia	-	-	-	-	-	-	-	-	<1	-
Hypocalcemia	-	-	1	-	-	-	-	-	-	-
Hypoglycemia	-	-	-	-	-	-	-	-	<1	-
Hypokalemia	-	-	-	-	✔	-	-	-	-	-
Hypothyroidism	-	-	-	-	-	-	-	-	<1	-
Jaundice	-	-	-	✔	-	-	-	-	-	-
Ketosis	-	-	-	-	-	-	-	-	<1	-
Lactose intolerance	-	-	-	-	-	-	-	-	<1	-
Liver damage	-	-	-	-	✔	-	-	-	-	-
Mastitis	-	-	-	-	✔	-	-	-	-	-
Prolactin levels increased	-	-	-	-	-	-	-	✔	-	-
Testosterone levels decreased	-	-	-	-	-	-	-	✔	-	-
Gastrointestinal										
Abdominal pain	2	✔	✔	-	✔	-	-	-	6	✔
Anorexia/weight loss	<1	-	-	-	✔	-	-	-	1-2	✔
Appetite increased/weight gain	-	-	-	✔	-	-	-	-	-	-
Colitis	-	-	-	-	✔	-	-	-	<1	-
Constipation	1	-	-	✔	-	-	-	-	>1	✔
Diarrhea	2	✔	✔	-	2-4	-	✔	2	-	✔
Dry mouth	3	-	3-4	-	3-7	✔	-	-	>1	✔
Dyspepsia	-	-	-	-	2-6	-	-	-	>1	✔
Dysphagia	-	-	-	-	✔	-	-	-	-	✔
Flatulence	-	✔	-	-	-	-	-	-	-	✔
Gastric irritation	-	✔	-	-	-	-	-	-	-	-
Gastroenteritis	-	-	-	-	-	-	-	-	<1	✔
Hiccup	-	-	-	-	-	-	-	-	-	✔
Ileus, adynamic	-	-	-	✔	-	-	-	-	-	-
Intestinal obstruction	-	-	-	-	-	-	-	-	<1	-
Melena	-	-	-	-	✔	-	-	-	-	-
Nausea	8	✔	3-9	-	4-5	-	✔	3	6-8	✔
Rectal bleeding	<1	-	-	-	✔	-	-	-	<1	-
Stomach/duodenal ulcer	-	-	-	-	✔	-	-	-	<1	-
Thirst	-	-	✔	-	-	-	-	-	-	<1
Tongue edema	-	-	-	-	✔	-	-	-	<1	-

Adverse Events	Buspirone	Chloral Hydrate	Dexmede-tomidine	Droperidol	Eszopiclone	Hydroxyzine	Meprobamate	Ramelteon	Zaleplon	Zolpidem
Ulcerative stomatitis	-	-	-	-	✔	-	-	-	<1	-
Vomiting	1	✔	✔	-	≤3	-	✔	-	-	✔
Genitourinary										
Cystitis	-	-	-	-	✔	-	-	-	-	≤1
Dysuria	-	-	-	✔	✔	-	-	-	-<1	✔
Hematuria	-	-	-	-	✔	-	-	-	<1	-
Kidney calculus	-	-	-	-	✔	-	-	-	-	-
Kidney failure	-	-	-	-	-	-	✔	-	-	-
Kidney pain	-	-	-	-	✔	-	-	-	-	-
Libido decreased	-	-	-	-	≤3	-	-	-	<1	-
Menstrual irregularities	<1	-	-	-	≤3	-	-	-	3-4	✔
Oliguria	-	-	2	-	✔	-	-	-	-	-
Priapism	-	-	-	✔	-	-	-	-	-	-
Pyelonephritis	-	-	-	-	✔	-	-	-	-	-
Urethritis	-	-	-	-	✔	-	-	-	-	-
Urinary frequency/ incontinence	-	-	-	-	✔	-	-	-	<1	≤1
Urinary retention	-	-	1	✔	-	-	-	-	<1	-
Urinary tract infection	-	-	-	-	≤3	-	-	-	-	✔
Vaginal hemorrhage	-	-	-	-	✔	-	-	-	-	-
Vaginitis	-	-	-	-	✔	-	-	-	-	≤1
Hematologic										
Acute intermittent porphyria	-	✔	-	-	-	-	-	-	-	-
Agranulocytosis	-	-	-	-	-	-	✔	-	-	-
Anemia	-	-	3	-	-	-	-	-	<1	-
Aplastic anemia	-	-	-	-	-	-	✔	-	-	-
Eosinophilia	-	✔	-	-	-	-	✔	-	<1	-
Leukocytosis	-	-	-	-	-	-	-	-	<1	-
Leukopenia	-	✔	-	✔	-	-	✔	-	-	-
Lymphadenopathy	-	-	-	-	-	-	-	-	<1	-
Lymphocytosis	-	-	-	-	-	-	-	-	<1	-
Thrombophlebitis	-	-	-	-	✔	-	-	-	<1	-
Laboratory Test Abnormalities										
Abnormal hepatic function	-	-	-	-	-	-	-	-	<1	≤1
Alkaline phosphatase increased	-	-	✔	-	-	-	-	-	<1	-
GGT elevation	-	-	✔	-	-	-	-	-	-	-
Musculoskeletal										

Adverse Events	Buspirone	Chloral Hydrate	Dexmede-tomidine	Droperidol	Eszopiclone	Hydroxyzine	Meprobamate	Ramelteon	Zaleplon	Zolpidem
Arthralgia	-	-	-	-	-	-	-	2	>1	✔
Arthritis	-	-	-	-	-	-	-	-	>1	<1
Back pain	-	-	-	-	✔	-	-	-	>1	✔
Leg/muscle cramps	<1	-	-	-	-	-	-	-	-	<1
Myalgia	1	-	-	✔	✔	-	-	2	>1	✔
Osteoporosis	-	-	-	-	-	-	-	-	<1	-
Weakness	2	-	-	-	✔	-	✔	-	5-7	✔
Respiratory										
Apnea	-	-	✔	-	-	-	-	-	-	-
Asthma	-	-	-	-	✔	-	-	-	-	-
Bronchial secretions thickened	-	-	-	-	-	✔	-	-	-	-
Bronchitis	-	-	-	-	✔	-	-	-	>1	<1
Bronchospasm	-	-	✔	✔	-	-	✔	-	-	-
Coughing	-	-	-	-	-	-	-	-	-	<1
Dyspnea	-	-	✔	-	✔	-	-	-	-	<1
Epistaxis	-	-	-	-	✔	-	✔	-	<1	-
Hypercapnia	-	-	✔	-	-	-	-	-	-	-
Hypoventilation	-	-	✔	-	-	-	-	-	-	-
Hypoxia	-	-	✔	-	-	-	-	-	-	-
Laryngospasm	-	-	-	✔	-	-	-	-	-	-
Nasal congestion	>1	-	-	-	-	-	-	-	-	-
Pharyngitis	-	-	-	-	✔	-	-	-	-	✔
Pleural effusion	-	-	32	-	-	-	-	-	-	-
Pulmonary congestion	-	-	✔	-	-	-	-	-	-	-
Respiratory depression	-	-	3	✔	-	-	-	-	-	-
Rhinitis	-	-	-	-	✔	-	-	-	-	<1
Shortness of breath	<1	-	-	-	-	-	-	-	-	-
Sinusitis	-	-	-	-	-	-	-	-	-	✔
Throat sore/irritation	>1	-	-	-	-	-	-	-	-	✔
Respiratory tract infection	-	-	-	-	5-10	-	-	3	-	✔
Wheezing	-	-	1	-	-	-	✔	-	-	-
Special Senses										
Accommodation impaired	-	-	-	-	-	-	✔	-	-	-
Blurred vision	-	-	-	-	-	✔	✔	-	-	✔
Conjunctivitis	<1	-	-	-	✔	-	-	-	>1	-
Dry eyes	-	-	-	-	✔	-	-	-	-	-

Adverse Events	Buspirone	Chloral Hydrate	Dexmede-tomidine	Droperidol	Eszopiclone	Hydroxyzine	Meprobamate	Ramelteon	Zaleplon	Zolpidem
Dysgeusia/taste perversion	-	-	-	-	8-34	-	-	2	>1	<1
Ear pain	-	-	-	-	-	-	-	-	<1	-
Eye pain	-	-	-	-	-	-	-	-	3-4	<1
Eye redness/itching	-	-	-	-	-	-	-	-	-	✔
Hyperacusis	-	-	-	-	-	-	-	-	1-2	-
Mydriasis	-	-	-	-	✔	-	-	-	-	-
Parosmia	<1	-	-	-	-	-	-	-	1-2	-
Photophobia	-	-	-	-	✔	-	-	-	<1	-
Photopsia	-	-	✔	-	-	-	-	-	-	-
Retinal pigmentation	-	-	-	✔	-	-	-	-	-	-
Scleritis	-	-	-	-	-	-	-	-	-	<1
Tinnitus	>1	-	-	-	✔	-	-	-	-	✔
Vestibular disorder	-	-	-	-	✔	-	-	-	-	✔
Visual disturbance	2	-	✔	✔	-	-	✔	-	<2	>1
Other										
Accidental injury/trauma	-	-	-	-	≤3	-	-	-	-	<1
Adenopathy	-	-	-	-	-	-	✔	-	-	-
Allergic reactions	-	-	-	-	✔	✔	✔	-	-	✔
Anaphylaxis	-	-	-	✔	✔	-	-	✔	✔	✔
Binge eating	-	-	-	-	-	-	-	-	-	✔
Chills/rigors	-	-	✔	✔	-	-	-	✔	✔	-
Fever/hyperpyrexia	-	✔	✔	-	✔	-	✔	-	>1	✔
Flu syndrome	-	-	-	-	✔	-	-	1	-	✔
Infection	-	-	-	-	5-10	-	-	-	-	1
Pain	-	-	2	-	4-5	-	-	-	-	-
Physical/psychological dependence	-	✔	-	-	-	-	-	-	-	-
Sore throat	>1	-	-	-	-	-	-	-	-	-
Sweating/clamminess	1	-	-	-	✔	-	-	-	-	<1
Viral infection	-	-	-	-	3	-	-	-	-	-

✔ Percent not specified
- Event not reported

Table 7. 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 8.

Table 8. Usual Dosing Regimens for the Miscellaneous Anxiolytics, Sedatives, and Hypnotics[1-12]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Buspirone	Anxiety: 15 mg daily (7.5 mg twice daily); dosage may be increased 5 mg per day every two to three days as needed	Safety and efficacy in children <18 years 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 orally or rectally every six hours as needed Hypnotic: 500 mg to 1 g orally or rectally at bedtime or 30 minutes before surgery Sedative: 250 mg orally or rectally three times daily	Hypnotic: 50 mg/kg/day in divided doses Sedative: 25 mg/kg/day in divided doses Premedication for Electroencephalographic Evaluation: 20-25 mg/kg orally or rectally prior to procedure	Capsule: 500 mg Rectal suppository: 500 mg Syrup: 500 mg/5 ml

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Dexmedetomidine	Sedation: 1 mcg/kg IV over 10 minutes, followed by a maintenance infusion of 0.2-0.7 mcg/kg/hour; duration of infusion should not exceed 24 hours	Safety and efficacy in children <18 years have not been established.	Injection: 200 mcg/2 ml
Droperidol	Nausea and Vomiting: 2.5 mg IM/IV; additional 1.25 mg doses may be given to achieve desired effect	Nausea and Vomiting: 2-12 years of age: 0.1 mg/kg IM/IV; additional doses should be administered with caution, and only if potential benefit outweighs the potential risks >12 years of age: 2.5 mg IM/IV; additional 1.25 mg doses may be given to achieve desired effect	Injection: 2.5 mg/ml
Eszopiclone	Insomnia: Nonelderly adults: 2 mg immediately before bed; dose may be increased to 3 mg Elderly adults: 1 mg immediately before bed if difficulty falling asleep; 2 mg immediately before bed if difficulty staying asleep	Safety and efficacy in children <18 years have not been established.	Tablet: 1 mg 2 mg 3 mg
Hydroxyzine	Anxiety: 50-100 mg four times daily Pruritus: 25 mg three to four times per day Sedation (Premedication or Following Anesthesia): 25-100 mg IM or 50-100 mg orally	Anxiety, pruritus: ≥6 years of age: 50-100 mg daily in divided doses <6 years of age: 50 mg daily in divided doses Preoperative Sedation: 0.5-1 mg/kg IM or 0.6 mg/kg orally	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: 400 mg three or four times per day	Anxiety: 6-12 years: 100-200 mg two or three times per day Safety and efficacy in children <6 years of age have not been established.	Tablet: 200 mg 400 mg
Ramelteon	Insomnia: 8 mg taken within 30 minutes before going to bed	Safety and efficacy in children have not been established.	Tablet: 8 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Zaleplon	Insomnia: Nonelderly adults: 10 mg at bedtime Elderly or debilitated patients: 5 mg at bedtime	Safety and efficacy in children have not been established.	Capsule: 5 mg 10 mg
Zolpidem	Insomnia: Nonelderly adults: 10 mg (IR) or 12.5 mg (ER) immediately before bedtime Elderly or debilitated patients: 5 mg (IR) or 6.25 mg (ER) immediately before bedtime	Safety and efficacy in children <18 years old have not been established.	Sublingual tablet (IR): 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 9.

Table 9. Comparative Clinical Trials with the Miscellaneous Anxiolytics, Sedatives, and Hypnotics

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Anxiety				
Gammans et al.[27] (1992) Buspirone 10-60 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 ($P \leq 0.001$) 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%) ($P \leq 0.001$). Patients with GAD and concurrent depressive symptoms exhibited significantly greater improvement with buspirone compared to placebo ($P \leq 0.01$ to $P \leq 0.03$ 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).
Chessick et al.[28] (2006) Azaspirones (buspirone, gepirone*, ipsapirone*, lesopitron*) vs benzodiazepines, hydroxyzine, kava	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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
kava, placebo, venlafaxine XR or psychotherapy				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 participants dropped out who were on buspirone compared to placebo (RR: 0.68; 95% CI: 0.49 to 0.94, P=0.02). Significantly fewer participants 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 (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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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) Benzodiazepines, SSRIs, MAOIs, RIMAs*, β-blockers, gabapentin, buspirone vs placebo	MA Patients with social anxiety disorder	N=2,954 (23 trials) 6-20 weeks	Primary: Outcome data on the Liebowitz Social Anxiety Scale (LSAS) or a categorical measure of status Secondary: Proportion of responders with CGI score change of 1 or 2	Primary: In terms of LSAS, effect sizes of each medication group were: clonazepam (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.
Lader et al.[31] (1998) Buspirone 20 mg/day vs	DB, MC, PC, PG, RCT Adult outpatients with generalized anxiety disorder	N=244 6 weeks	Primary: HAM-A scores Secondary: CGI, Montgomery-Asberg Depression Rating Scale (MADRS),	Primary: Hydroxyzine (P<0.02), but not buspirone (P=NS), significantly improved HAM-A scores over placebo after 28 days of treatment. HAM-A scores were not significantly different between hydroxyzine and buspirone. Secondary: Significantly (P<0.02) more patients on hydroxyzine improved CGI scores than placebo. There was no significant difference between buspirone and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
hydroxyzine 50 mg/day vs placebo			Hospital Anxiety and Depression (HAD) Scale, Ferreri Anxiety Rating Diagram (FARD), Tyrer Withdrawal Symptom Scale	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 very 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) <1 week 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 and 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 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 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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Zammit et al.[34] (2004) Eszopiclone 2-3 mg vs placebo	DB, MC, PC, RCT Adults 21-64 years of age with chronic primary insomnia	N=308 6 weeks	Primary: Efficacy (polysomnography [PSG] and patient reports), next day residual effects (Digit-Symbol Substitution Test [DSST]), tolerance, rebound insomnia, safety	Primary: Eszopiclone 2 mg and 3 mg had significantly less time to sleep onset ($P \leq 0.001$ and $P \leq 0.0001$, respectively), more TST ($P \leq 0.01$ and $P \leq 0.0001$), better sleep efficiency ($P \leq 0.001$ and $P \leq 0.0001$), and enhanced quality and depth of sleep (both $P<0.05$) across the double-blind period compared with placebo. Eszopiclone 3 mg ($P \leq 0.01$) 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.
Scharf et al.[35] (2005) Eszopiclone 1-2 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 sleep, depth of sleep, ratings of daytime alertness, sense of physical well-being, morning sleepiness, ability to function, quality	Primary: Patients treated with eszopiclone 1mg 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 ($P>0.1$). 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 ($P=0.058$).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			of life (Quality of Life Enjoyment and Satisfaction Questionnaire [Q-LES-Q]), safety	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.
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 21-64 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, physical well-	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 placebo for each month and the Month 1-6 average (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			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)	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 21-64 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.
Johnson et al.[39] (2006) Ramelteon 16-160 mg vs triazolam 0.25-0.75 mg vs	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	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 subjects 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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo			(balance task, DSST, word recall)	
Roth et al.[41] (2006) Ramelteon 4 mg vs ramelteon 8 mg vs placebo	DB, PC, RCT Patients 64-93 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; sleep diaries; rebound insomnia and withdrawal effects during the 7-day placebo run out	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. 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 4-32 mg vs placebo	DB, MC, 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-	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			day performance and alertness, safety	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) Ramelteon 8 mg at bedtime vs placebo	RCT, DB, PC Patients ≥18 years of age with chronic primary insomnia	N=451 6 months	Primary: Latency to 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	Primary: Greater reductions in LPS occurred with ramelteon compared to placebo (P<0.05 for each time point). A greater change from baseline occurred with ramelteon (54%-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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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.
Dunbar et al.[45] (2004) Zaleplon 5-20 mg vs zolpidem 5-10 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 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).
Elie et al.[46] (1999)	DB, MC, PC, RCT	N=615	Primary: Patient's	Primary: Median sleep latency was significantly lower with zaleplon 10 mg and 20

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Zaleplon 5-20 mg or zolpidem 10 mg vs placebo	Adults with primary insomnia or insomnia associated with mild nonpsychotic psychiatric disorders	4 weeks	assessment of sleep latency Secondary: Patient's assessment of sleep duration, sleep quality, number of awakenings, rebound insomnia, withdrawal effects, safety	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 ($P \leq 0.05$) increased sleep duration compared with placebo in all but week 3 of the study, while zolpidem 10 mg significantly ($P \leq 0.05$) increased sleep duration at all time points. Mean scores for sleep quality were significantly ($P \leq 0.05$) 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 discontinuation of 4 weeks of treatment. Significant differences in sleep latency ($P \leq 0.05$) and number of awakenings ($P \leq 0.01$) were noted in patients treated with zolpidem 10 mg. On the second night after discontinuation of treatment, there were significantly more patients ($P \leq 0.05$) 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 ($P \leq 0.05$) 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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Scharf et al.[48] (1994) Zolpidem 10 or 15 mg vs placebo	DB, MC, PC, PG, 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). 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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.
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] (2008) Zolpidem ER 12.5 mg vs placebo Treatments were taken 3-7 nights per week.	RCT, MC, DB, PC Patients 18-64 years of age with chronic primary insomnia	N=1,025 26 weeks	Primary: 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	Primary: 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			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	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 SL tablets vs zolpidem 10 mg SL tablets vs zolpidem 10 mg tablets	RCT, OL, XO Healthy volunteers in a post-nap model of insomnia	N=21 single dose	Primary: Latency to persistent sleep (LPS), sleep onset latency (SOL), latency to stage 1 (LTS1), total sleep time, sleep efficiency, awakening after sleep onset, REM sleep latency (RSL), stage 4 duration (ST4)	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). 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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 (getting to sleep, quality of sleep, awakening from sleep, behavior following wakefulness). Next-day residual effects were comparable between treatments. Vigilance, psychomotor performances, attention and concentration were comparable between treatments. None of the subjects withdrew due to safety reasons. Both routes of administration were well tolerated. The most frequent adverse events were somnolence, headache and fatigue. All were of moderate or mild intensity and resolved spontaneously.
Zammit et al.[26] (2006) Zaleplon 10 mg for 2 nights vs zolpidem 10 mg for 2 nights vs placebo for	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
2 nights Each treatment period was separated by a 5- or 12-day washout period.				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).

*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 branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

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

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

Rx=prescription

Table 10. Relative Cost of the Miscellaneous Anxiolytics, Sedatives, and Hypnotics

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Buspirone	tablet	BuSpar®*	$$$$	$
Chloral hydrate	capsule, rectal suppository, syrup	N/A	N/A	$
Dexmedetomidine	injection	Precedex®	$$$-$$$$	N/A
Droperidol	injection	Inapsine®*	$	$
Eszopiclone	tablet	Lunesta®	$$$$	N/A
Hydroxyzine	capsule, injection, syrup, tablet	Vistaril®*	$$$	$
Meprobamate	tablet	N/A	N/A	$$$
Ramelteon	tablet	Rozerem®	$$$$	N/A
Zaleplon	capsule	Sonata®*	$$$$$	$
Zolpidem	extended-release tablet, sublingual tablet, tablet	Ambien®*, Ambien CR®, Edluar®	$$$-$$$$	$

*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. The majority of the products in this review are available in a generic formulation.

The agents that are approved for the treatment of anxiety disorders include buspirone, hydroxyzine and meprobamate.[1-3,4,7]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.[1-3,6,9-12] 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] The clinical trials performed in support of efficacy for eszopiclone, ramelteon and zolpidem ER were up to 6 months in duration.[6,8,11,36-37,44,47] There were very few studies found in the medical literature which directly compared the efficacy and safety of these agents.

The American Society of Addiction Medicine recommends the use of benzodiazepines over nonbenzodiazepine sedative/hypnotic agents for the management of alcohol withdrawal.[51] Droperidol is effective for the prevention/treatment of nausea and vomiting from surgical/diagnostic procedures.[20-21] However, cases of QT prolongation and/or torsade de pointes have been reported in patients receiving droperidol.[1-3] Some cases have occurred in patients with no known risk factors for QT prolongation, and some cases have been fatal.[1-3] Due to its potential for serious proarrhythmic effects and death, droperidol should be reserved for patients who fail to respond to other adequate treatments.[1-3,20]

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.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
New Drug Pharmacotherapy Review – Samsca® (tolvaptan)
Diuretics, Miscellaneous, AHFS Class 402892
February 10, 2010

I. Overview

Tolvaptan is an oral vasopressin V_2 receptor antagonist, which was approved by the FDA in May 2009. It is indicated for the treatment of clinically significant euvolemic and hypervolemic hyponatremia (serum sodium <125 mEq/L or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction), including patients with heart failure, cirrhosis, and Syndrome of Inappropriate Antidiuretic Hormone (SIADH).[1] The major disorders associated with euvolemic hyponatremia include SIADH, nephrogenic syndrome of inappropriate antidiuresis (NSIAD), glucocorticoid deficiency, hypothyroidism, exercise-associated hyponatremia (EAH), low solute intake and primary polydipsia.[5] Hypervolemic hyponatremia is most often caused by heart failure, cirrhosis, nephrotic syndrome, as well as acute and chronic renal failure.[5]

Hyponatremia is frequently associated with elevated plasma levels of arginine vasopressin (AVP). AVP is normally secreted in response to increased plasma osmolality, decreased blood volume, or decreased blood pressure.[5] Suppression of AVP secretion occurs when osmolality falls below a certain threshold, which results in renal excretion of free water. Failure to suppress AVP secretion may result in water retention and hyponatremia.[5] The use of traditional diuretics leads to both water and electrolyte excretion (diuresis); whereas, the use of tolvaptan leads to an increase in water excretion only (aquaresis), a decrease in urine osmolality, and an increase in serum sodium concentration.[1] Urinary excretion of sodium and potassium, as well as plasma potassium concentrations, are not significantly affected by tolvaptan.[1]

The management of hyponatremia depends on the clinical presentation and duration of the disease (acute versus chronic hyponatremia). Treatment options include fluid restriction, sodium chloride administration and diuresis.[6] Patients with chronic mild hyponatremia are often asymptomatic and treatment consists of fluid restriction or isotonic saline administration.[6] Acute severe hyponatremia requires more aggressive initial therapy as it may increase morbidity and mortality.[5-6] Treatment of hyponatremia must be approached carefully as overly rapid correction may cause osmotic demyelination. Symptoms of osmotic demyelination are often irreversible and include quadriparesis, paraparesis, dysphagia, dysarthria, diplopia, seizures, coma and death.[5-6]

The tolvaptan products that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths.

Table 1. Tolvaptan Products Included in this Review

Generic Name	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Tolvaptan	tablet	Samsca®	none

PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

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

Table 2. Treatment Guidelines Using the Diuretics, Miscellaneous

Clinical Guideline	Recommendation(s)
American Journal of Medicine: **Hyponatremia Treatment Guidelines 2007: Expert Panel Recommendations[5] (2007)**	General Information • There are no data to suggest that the etiology of the hyponatremia, nor the methodology used to correct hyponatremia, alters the susceptibility for producing osmotic demyelination with overly rapid correction. • The rate of correction of hyponatremia must be taken into account before deciding on the most appropriate therapy for any patient with hyponatremia.

Clinical Guideline	Recommendation(s)

	• Patients with acute (<48 hours) hyponatremia may present with alarming neurologic findings, and they sometimes die of brain herniation. When hyponatremia develops over several days, brain swelling is minimized so that patients with chronic (<48 hours) hyponatremia have more modest symptoms and almost never die of brain herniation.
	Rate of Correction of Hyponatremia
	• In patients with chronic hyponatremia, neurologic sequelae are associated with more rapid rates of correction. The osmotic demyelination syndrome can usually be avoided by limiting correction of chronic hyponatremia to <10 to 12 mmol/L in 24 hours and to <18 mmol/L in 48 hours. These estimates should be regarded as approximate limits and not goals of therapy.
	• Patients with severe symptoms from chronic hyponatremia, particularly those with seizures, may benefit from a brief infusion of hypertonic saline, increasing the serum sodium by 2 to 4 mmol/L within 2 to 4 hours. There is no evidence that a quick but limited increase in the serum sodium is harmful; such therapy should not be considered "rapid" if the total increase in serum sodium over 24 hours is maintained at <10 mmol/L in 24 hours or <18 mmol/L in 48 hours.
	Conventional Therapy of Euvolemic Hyponatremia
	• Treatment of patients with euvolemic hyponatremia will vary greatly depending on their presentation. The single most important factor guiding initial therapy is the presence of neurologic symptoms.
	• Cases of acute hyponatremia (<48 hours in duration) are usually symptomatic if the hyponatremia is severe (<120 mmol/L). These patients are at greatest risk from neurologic complications from the hyponatremia itself and should be corrected to higher serum sodium levels promptly.
	• Patients with more chronic hyponatremia (>48 hours in duration) who have minimal neurologic symptomatology are at little risk from complications of hyponatremia itself, but can develop osmotic demyelination following rapid correction. There is no indication to correct these patients rapidly, and they should be treated using slower-acting therapies.
	• Syndrome of inappropriate antidiuretic hormone secretion (SIADH):
	  o Correction of acute symptomatic hyponatremia is best accomplished with hypertonic (3%) saline given via continuous infusion. Intravenous furosemide 20 to 40 mg should be used to treat volume overload. Acute treatment should be discontinued when the patient's symptoms are abolished, a safe serum sodium level (≥120 mmol/L) is achieved, or a total correction of 18 mmol/L is achieved.
	  o For the treatment of mild-to-moderate chronic hyponatremia, fluid restriction represents the least toxic therapy, and has generally been the treatment of choice. Several days of restriction are usually necessary before a significant increase in plasma osmolality occurs.
	  o Pharmacologic interventions are reserved for refractory cases where the degree of fluid restriction required to avoid hypo-osmolality is so severe that the patient is unable, or unwilling, to maintain it. The preferred drug is demeclocycline, which causes a nephrogenic form of diabetes insipidus. Treatment must be continued for several days to achieve maximal diuretic effects. Other agents, such as lithium, have similar renal effects but are less desirable because of inconsistent

Clinical Guideline	Recommendation(s)

	results and significant side effects and toxicities. Urea is as an alternative treatment for SIADH.
	• Glucocorticoid deficiency:
	  o Glucocorticoid replacement should be started immediately after completion of a rapid ACTH stimulation test. Several days of glucocorticoids are sometimes required for normalization of the plasma osmolality. Primary treatment of hyponatremia may be indicated if significant neurologic symptoms are present.
	• Hypothyroidism:
	  o The primary therapy of hypothyroidism is thyroid hormone replacement.
	  o Hyponatremia with hypothyroidism is infrequent and generally of mild severity; therefore, modest fluid restriction is generally the only treatment necessary.
	  o Symptomatic hyponatremia may be seen in patients with more severe hypothyroidism and altered mental status, primary treatment of hyponatremia may be indicated to ascertain whether the hyponatremia is contributing to the patient's neurologic symptoms.
	• Exercise-associated hyponatremia (EAH):
	  o EAH can be severe and life threatening as a result of cerebral edema and noncardiogenic pulmonary edema.
	  o Hyponatremia occurring in the setting of endurance exercise is acute, and treatment of symptomatic hyponatremia should be rapid.
	  o With significant CNS impairment, hypertonic saline should begin immediately and continued until the serum sodium reaches 125 mmol/L or symptoms resolve.
	• Low solute intake:
	  o Hyponatremia from low solute intake is corrected by instituting proper nutrition, with increased content of solute both as electrolytes and protein.
	• Primary polydipsia:
	  o Therapy should be directed at reducing fluid intake into the normal range.
	  o Fluid ingestion in patients with psychogenic causes of polydipsia responds variably to behavior modification and pharmacologic therapy (e.g., clozapine).
	<u>Conventional Therapy of Hypervolemic Hyponatremia</u>
	• For all diseases associated with edema formation, dietary sodium restriction and diuretic therapy are the mainstays of therapy.
	• Congestive heart failure (CHF):
	  o Currently, there are no guidelines specifically regarding treatment of hyponatremia in CHF.
	  o Severely symptomatic hyponatremia is uncommon in CHF, but it can be treated with hypertonic saline provided adequate diuresis is established. However, the volume expansion associated with the use of hypertonic saline makes this an unattractive option for all but emergent situations.
	  o Treatment of mild-to-moderate hyponatremia in CHF is largely empiric. Options include demeclocycline, urea, and fluid restriction. Difficulty in use and toxicity make demeclocycline and urea less attractive treatment options. Fluid restriction is not very effective or well tolerated. There are no outcomes studies available to guide the use of fluid

Clinical Guideline	Recommendation(s)

	restriction in acute or chronic CHF.
	• Cirrhosis:
	  o There are no guidelines specifically regarding treatment of hyponatremia in cirrhosis.
	  o Demeclocycline is relatively contraindicated because of a high incidence of nephrotoxicity, and urea has not been used often. Fluid restriction is the usual approach, but without outcome studies to assess its effectiveness.
	• Nephrotic syndrome, acute and chronic renal failure:
	  o In patients with hyponatremia with advanced acute and chronic renal failure and GFR <20 mL/min, fluid restriction to amounts less than insensible losses plus urine output is generally necessary to cause a negative solute-free water balance and correction of hyponatremia.
	<u>Use of Vasopressin Receptor Antagonists in Hyponatremia</u>
	• The optimum use of vasopressin receptor in any setting has not yet been determined.
	• For the treatment of acute severe hyponatremia, there is insufficient data from clinical trials to know if sufficiently rapid correction can be achieved with vasopressin receptor antagonists without the use of hypertonic saline.
	• Most studies to date in patients with hyponatremia have only been of relatively short duration. The most appropriate way to use these agents, their long-term response rates, how important the role of water restriction will remain during chronic use, and whether correction of chronic hyponatremia will result in improved cognitive function as suggested by 30-day studies of tolvaptan, and quality of life, or functional status, as suggested by initial studies of gait stability and falls, are unknown at the present time and will require additional study.
	• Safety issues must be considered carefully with any new class of drugs. The possibility of overcorrection has been of significant concern in all of the vasopressin receptor antagonist clinical trials, but to date osmotic demyelination has not been reported with any agent. The potential for serious drug interactions via interference with CYP3A4-mediated metabolism of other drugs must also be recognized. Whether there will be any adverse effect of V_2 receptor inhibition in vascular endothelium is unknown.
	• Further studies will be needed to assess the appropriate use of vasopressin receptor antagonists, such as for correction of symptomatic hyponatremia either alone or in conjunction with hypertonic saline infusions; to assess the benefits of correction of hyponatremia in hospitalized patients in terms of disease outcomes and decreased lengths of intensive care unit and hospital stay; and for long-term treatment of minimally symptomatic hyponatremia in order to decrease the risks of neurocognitive dysfunction and gait instability.

III. Indications

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

Indication	Tolvaptan*†
Treatment of clinically significant hypervolemic and euvolemic hyponatremia (serum sodium <125 mEq/L or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction), including patients with heart failure, cirrhosis, and Syndrome of Inappropriate Antidiuretic Hormone (SIADH)	✔

*Patients requiring intervention to raise serum sodium urgently to prevent or to treat serious neurological symptoms should not be treated with tolvaptan.
†It has not been established that tolvaptan provides a symptomatic benefit to patients.

IV. Pharmacokinetics

The pharmacokinetic parameters of tolvaptan are listed in Table 4.

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

Generic Name	Bioavailability (%)	Protein Binding (%)	Metabolism	Elimination (%)	Half-Life (hours)
Tolvaptan	≥40	99	Liver, extensive	Eliminated by non-renal routes	12

V. Drug Interactions

Significant drug interactions with tolvaptan are listed in Table 5. Tolvaptan is metabolized by CYP3A, and use with strong CYP3A inhibitors causes a marked (5-fold) increase in exposure.[1] Tolvaptan is contraindicated in combination with strong cytochrome CYP3A inhibitors, such as clarithromycin, ketoconazole, itraconazole, ritonavir, indinavir, nelfinavir, saquinavir, nefazodone and telithromycin.[1] The use of tolvaptan in combination with CYP3A inducers and moderate CYP3A inhibitors should also be avoided.[1]

Table 5. Significant Drug Interactions with Tolvaptan[1-4]

Generic Name	Significance Level	Interaction	Mechanism
Tolvaptan	1	HIV protease inhibitors	Inhibition of CYP3A4 by HIV protease inhibitors may decrease the metabolic elimination of tolvaptan. Plasma concentrations and pharmacologic effects of tolvaptan may be increased by HIV protease inhibitors.
Tolvaptan	1	Imidazoles	Inhibition of CYP3A4 by imidazoles may decrease the metabolic elimination of tolvaptan. Plasma concentrations and pharmacologic effects of tolvaptan may be increased by imidazoles.

Generic Name	Significance Level	Interaction	Mechanism
Tolvaptan	1	Macrolides and ketolides	Inhibition of CYP3A4 and P-glycoprotein by macrolides and ketolides may decrease the metabolic elimination of tolvaptan. Plasma concentrations and pharmacologic effects of tolvaptan may be increased by macrolides and ketolides.
Tolvaptan	1	Nefazodone	Inhibition of CYP3A4 by nefazodone may decrease the metabolic elimination of tolvaptan. Plasma concentrations and pharmacologic effects of tolvaptan may be increased by nefazodone.
Tolvaptan	2	Barbiturates	Induction of CYP3A isoenzymes by barbiturates may increase the metabolic elimination of tolvaptan. Plasma concentrations and pharmacologic effects of tolvaptan may be decreased by barbiturates compromising therapeutic effectiveness.
Tolvaptan	2	Carbamazepine	Induction of CYP3A isoenzymes by carbamazepine may increase the metabolic elimination of tolvaptan. Plasma concentrations and pharmacologic effects of tolvaptan may be decreased by carbamazepine compromising therapeutic effectiveness.
Tolvaptan	2	Hydantoins	Induction of CYP3A isoenzymes by hydantoins may increase the metabolic elimination of tolvaptan. Plasma concentrations and pharmacologic effects of tolvaptan may be decreased by hydantoins compromising therapeutic effectiveness.
Tolvaptan	2	Rifamycins	Induction of CYP3A isoenzymes by rifamycins may increase the metabolic elimination of tolvaptan. Plasma concentrations and pharmacologic effects of tolvaptan may be decreased by rifamycins compromising therapeutic effectiveness.
Tolvaptan	2	St. John’s wort	Induction of CYP3A isoenzymes by St. John's wort may increase the metabolic elimination of tolvaptan. Plasma concentrations and pharmacologic effects of tolvaptan may be decreased by St. John's wort compromising therapeutic effectiveness.

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

VI. Adverse Drug Events

The most common adverse drug events reported with tolvaptan are listed in Table 6. The boxed warning for tolvaptan is listed in Table 7.

Table 6. Adverse Drug Events (%) Reported with Tolvaptan[1-4]

Adverse Events	Tolvaptan
Cardiovascular	
Intracardiac thrombus	<2
Ventricular fibrillation	<2
Central Nervous System	
Cerebrovascular accident	<2
Pyrexia	4
Endocrine and Metabolic	
Diabetic ketoacidosis	<2
Hyperglycemia	6
Gastrointestinal	
Anorexia	4
Constipation	7
Ischemic colitis	<2
Nausea	21
Xerostomia	7-13
Genitourinary	
Pollakiuria	4-11
Polyuria	4-11
Urethral hemorrhage	<2
Vaginal hemorrhage	<2
Laboratory Abnormalities	
Prothrombin time prolonged	<2
Musculoskeletal	
Rhabdomyolysis	<2
Weakness	9
Respiratory	
Pulmonary embolism	<2
Respiratory failure	<2
Other	
Deep vein thrombosis	<2
Disseminated intravascular coagulation	<2
Thirst	12-16

Table 7. Boxed Warning for Tolvaptan[1-4]

WARNING
Initiation of therapy: Initiate and reinitiate tolvaptan in patients only in a hospital where serum sodium can be closely monitored. **Monitor serum sodium:** Too rapid correction of hyponatremia (e.g., more than 12 mEq/L per 24 hours) can cause osmotic demyelination, resulting in dysarthria, mutism, dysphagia, lethargy, affective changes, spastic quadriparesis, seizures, coma, and death. In susceptible patients, including those with severe malnutrition, alcoholism, or advanced liver disease, slower rates of correction may be advisable.

VII. Dosing and Administration

The usual dosing regimen for tolvaptan is listed in Table 8.

Table 8. Usual Dosing Regimen for Tolvaptan[1-4]

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Tolvaptan	Hypervolemic and euvolemic hyponatremia: Initial: 15 mg once daily; increase to 30 mg once daily after ≥24 hours, to a maximum of 60 mg once daily, as needed to achieve the desired level of serum sodium.	Safety and effectiveness have not been established in pediatric patients.	Tablet: 15 mg 30 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of tolvaptan are summarized in Table 9.

Table 9. Comparative Clinical Trials with Tolvaptan

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Gheorghiade et al.[11] (2006) Tolvaptan 10 mg daily, with titration to larger doses (15, 30, 45, and 60 mg/day) as needed to achieve serum sodium concentrations within normal limits vs fluid restriction (initially 1,200 ml/24 hours) plus placebo	RCT, MC, OL, AC Inpatients ≥18 years, serum sodium <135 mmol/L for ≥2 consecutive days, and normovolemia or signs of fluid overload	N=28 Inpatient treatment: 14 days Outpatient treatment: 14 days Follow-up: 65 days	Primary: Normalization of serum sodium concentration (defined as ≥135 mmol/L or an increase of >10% from baseline to the last inpatient assessment) Secondary: Changes in serum sodium from baseline to the last outpatient visit (day 65), urine osmolality, urine volume, urine sodium concentration, body weight, total fluid intake, and thirst score from baseline to the last inpatient assessment	Primary: A higher proportion of subjects in the tolvaptan group had achieved the normalization of serum sodium compared with those in the fluid restriction group by the last inpatient visit (P=0.049). The normalization of serum sodium was achieved more rapidly in the tolvaptan group than in the fluid restriction group, occurring in 50% of tolvaptan-treated subjects by day 4, compared with day 8 in the fluid restriction group (P<0.03). Patients in the tolvaptan group had a significantly greater increase in serum sodium concentration 4 hours after the first dose (1.6 mmol/L; P=0.016), at day 5 (5.2 mmol/L; P=0.019) and at the last inpatient visit (5.7 mmol/L; P=0.0065) compared to patients receiving fluid restriction (-0.8 mmol/L, 0.7 mmol/L and 1.0 mmol/L, respectively). Secondary: At day 65, the mean change in serum sodium was 4.7 mmol/L in the tolvaptan group compared to -0.3 mmol/L in the placebo group (P=0.039). Urine sodium was significantly lower (P=0.021) and urine output was significantly greater (P=0.014) in the tolvaptan group compared to the placebo group. No significant differences in urine osmolality (P=0.058), serum potassium (P=0.45), blood pressure (no P value reported), heart rate (no P value reported), body weight (P=NS), thirst score (P=0.8) or adverse events requiring drug discontinuation were observed between the treatment groups.
Schrier et al.[12] (2006) Tolvaptan 15 mg daily for 30 days	RCT, MC, DB, PC (Results of 2 trials; SALT-1 and SALT-2)	N=102 (SALT-1) N=123 (SALT-2)	Primary: Change in the average daily AUC for the serum sodium from	Primary: By day 4, the increase in the average daily AUC for the serum sodium concentration was 3.62 and 4.33 for tolvaptan (SALT-1 and SALT-2, respectively) compared to 0.25 and 0.42 for placebo (P<0.001 for all comparisons).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(dose could be titrated to 60 mg daily) vs placebo	Patients ≥18 years of age with euvolemic or hypervolemic hyponatremia (serum sodium <135 mmol/L). Patients also had chronic heart failure, cirrhosis, or the syndrome of inappropriate antidiuretic hormone secretion (SIADH) in association with the hyponatremia.	37 days	baseline to day 4 and from baseline to day 30 Secondary: Change in the AUC for the serum sodium in patients with marked hyponatremia, serum sodium concentration at each visit, time to normalization of the serum sodium, percent of patients with serum sodium concentrations that normalized at day 4 and day 30, serum sodium concentration on day 4 and day 30 for patients with mild or marked hyponatremia at baseline, change from baseline in scores on the Physical Component Summary and Mental Component Summary of the Medical Outcomes Study 12-item Short-Form (SF-	By day 30, the increase in the average daily AUC for the serum sodium concentration was 6.22 and 6.20 for tolvaptan (SALT-1 and SALT-2, respectively) compared to 1.66 and 1.84 for placebo (P<0.001 for all comparisons). Secondary: By day 30, the increase in the average daily AUC for the serum sodium concentration in patients with marked hyponatremia was 8.24 and 7.60 for tolvaptan (SALT-1 and SALT-2, respectively) compared to 2.54 and 2.72 for placebo (P<0.001 for all comparisons). By day 4, serum sodium concentrations were 133.9 mmol/L and 135.3 mmol/L for tolvaptan (SALT-1 and SALT-2, respectively) compared to 129.7 mmol/L and 129.6 mmol/L for placebo (P<0.001 for all comparisons). By day 30, serum sodium concentrations were 135.7 mmol/L and 135.9 mmol/L for tolvaptan (SALT-1 and SALT-2, respectively) compared to 131.0 mmol/L and 131.5 mmol/L for placebo (P<0.001 for all comparisons). By day 4, 40% and 55% of patients receiving tolvaptan (SALT-1 and SALT-2, respectively) had normal serum sodium concentrations compared to 13% and 11% for placebo (P<0.001 for all comparisons). By day 30, 53% and 58% of patients receiving tolvaptan (SALT-1 and SALT-2, respectively) had normal serum sodium concentrations compared to 25% and 25% for placebo (P<0.001 for all comparisons). Scores on the Physical Component Summary did not differ significantly between groups. Scores for the Mental Component Summary improved in the tolvaptan group when the data from SALT-1 and SALT-2 were combined (P=0.02), as well as in SALT-1 (P=0.04). Scores improved significantly in the combined subgroup of patients with marked hyponatremia (P=0.04). There was no significant difference between the groups found in SALT-2 (P=0.14). Adverse event profiles in the two study groups were similar for all comparisons. The most common adverse events occurring during the study in the tolvaptan groups were thirst and dry mouth. Overall, there were 26

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			12) General Health Survey	serious adverse events potentially related to the study treatment in SALT-1 and SALT-2. The number of deaths in the two study groups was similar (14 deaths among 223 patients in the tolvaptan groups and 13 deaths among 220 patients in the placebo groups), and they occurred within the defined observation period. In 4 of the patients in the tolvaptan group, the desirable rates of sodium correction were exceeded during the first 24 hours of the study (>0.5 mmol/L per hour). In 4 patients (1.8%), the predefined serum sodium concentration (>146 mmol per liter) was exceeded.
Udelson et al.[7] (2008) Tolvaptan 15mg, 30 mg, or 60 mg administered as a single dose vs placebo	RCT, MC, DB, PC Patients ≥18 years of age with symptomatic heart failure (New York Heart Association functional class III or IV) of at least 3 months' duration caused by left ventricular ejection fraction <40%. Patients were also required to be on standard background therapy for heart failure for at least 1 month.	N=181 12 hours	Primary: Pulmonary capillary wedge pressure (PCWP) peak change from baseline within 3 to 8 h after treatment administration Secondary: Area under the curve (AUC) for the change from baseline PCWP and other hemodynamic parameters over an 8 hour evaluation period and renal and electrolyte parameters	Primary: The pairwise comparisons of 15, 30, and 60 mg tolvaptan versus placebo each showed a statistically significant decrease in peak change in PCWP from 3 to 8 hours post-dose (P=0.003, P=0.044, and P=0.033, respectively). Secondary: For the AUC0-8h, the 15 mg tolvaptan group was the only tolvaptan dose group that was statistically significantly different from placebo. All tolvaptan doses produced statistically significantly greater changes than placebo in peak change in pulmonary artery pressure (P<0.01 for 15 mg; P<0.05 for 30 mg and 60 mg). Tolvaptan 15- and 30 mg doses resulted in statistically significant reductions in peak change in right atrial pressure as compared with placebo (P<0.01 and P<0.05, respectively). No significant changes in cardiac index, pulmonary vascular resistance, and systemic vascular resistance were observed after tolvaptan administration compared with placebo. The single dose of tolvaptan produced a dose-dependent increase in urine output (P<0.0001 for all tolvaptan groups vs. placebo). Urine osmolality was significantly reduced by all doses of tolvaptan relative to placebo (P<0.0001 for all tolvaptan groups vs. placebo). Free water clearance was significantly greater for all tolvaptan doses relative to placebo at all time

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				points. Plasma osmolality increased in all of the tolvaptan-treated groups compared with placebo. Serum sodium levels showed a dose-related increase compared with placebo (1.2 mEq/L, 3.3 mEq/L, 4.6 mEq/L, and -0.7 mEq/L for the tolvaptan 15 mg, 30 mg, 60 mg, and placebo groups, respectively). Potassium levels were not different from placebo in any of the tolvaptan dosing groups. No significant changes in serum creatinine, blood urea nitrogen, serum potassium, and vital signs were observed after study drug administration. Tolvaptan was well tolerated relative to placebo. Patient-reported adverse events in this short-term study occurred in 45.5%, 44.2%, 54.3%, and 33.3% of the 15-, 30-, and 60 mg tolvaptan and placebo groups, respectively.
Udelson et al.[8] (2007) Tolvaptan 30 mg daily vs placebo	RCT, MC, DB, PC Patients ≥18 years of age with congestive heart failure (New York Heart Association functional class II to III) with a left ventricular ejection fraction <30%. Patients were also required to be on standard background therapy for heart failure for at least for 3 months before enrollment.	N=240 55 weeks	Primary: Change from baseline in left ventricular end diastolic volume (LVEDV) index Secondary: Change from baseline in left ventricular end systolic volume (LVESV) index, comparison of the change from baseline in LVEDV index after drug withdrawal (week 55), and assessment of symptoms (using subject-assessed symptom scales	Primary: In the placebo group, there was no change in LVEDV index over the year of follow-up. After 1 year of tolvaptan therapy, there was a small reduction in LVEDV index; however, this was not significantly different from placebo (-1.8 ml/m^2; P=0.21 vs placebo). There was also no difference in the change of volumes from baseline at the week 55 study. Secondary: In the placebo group, LVEDV index decreased 0.4 ml/m^2 compared to a decrease of 3.3 ml/m^2 in the tolvaptan group (P=0.09). There was no difference in the change of LVESV index from baseline at week 55. Ejection fraction changes were small and similar in both treatment groups. Only minor changes in blood pressure and heart rate were observed over the course of the trial; there were no significant differences in the tolvaptan versus placebo groups. There were no significant between-group differences in serum sodium or potassium across the course of the trial. There were also no differences in renal function parameters (BUN and serum creatinine) across the year of therapy. No statistically significant differences were observed between the tolvaptan group and the placebo group for the change from baseline in Minnesota Living With Heart Failure Questionnaire score or for the Visual Analog Scale assessment of global status or respiratory status. More

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			and the Minnesota Living With Heart Failure Questionnaire)	subjects in the tolvaptan group reported a score of "better" in the subject-assessed overall treatment effect at each visit than did subjects in the placebo group; however, no statistically significant differences were observed between treatment groups. There were 6 deaths (5%) and 21 hospitalizations of patients with heart failure (18%) in the tolvaptan-treated group, compared with 11 deaths (9%) and 34 heart failure hospitalizations (28%) in the placebo-treated group (P<0.03 for the composite of death and heart failure hospitalizations). Adverse events including urinary frequency, thirst, and dry mouth occurred more frequently with tolvaptan than with placebo therapy. There was no difference in the number of patients withdrawn from the trial as the result of bothersome side effects between the 2 randomization groups.
Gheorghiade et al.[9] (2007) Tolvaptan 30 mg daily within 48 hours of admission vs placebo	RCT, MC, DB, PC (Results of 2 short-term trials; EVEREST) Patients ≥18 years of age with a history of chronic heart failure who had been hospitalized for worsening congestive heart failure and who had a left ventricular ejection fraction ≤40%. Patients also received conventional heart failure therapy.	N=2,048 (trial A) N=2,085 (trial B) 7 days	Primary: Composite score of changes from baseline in patient-assessed global clinical status and body weight at day 7 or discharge Secondary: Patient-assessed changes in dyspnea at day 1, global clinical status at day 7 or discharge, body weight at days 1 and 7 or discharge, and peripheral edema at day 7 or discharge	Primary: The composite score of changes from baseline in patient-assessed global clinical status and body weight at day 7 or discharge was greater with tolvaptan compared to placebo (trial A, mean 1.06 vs 0.99; P<0.001; trial B, mean 1.07 vs 0.97; P<0.001). Improvement in patient-assessed global clinical status (assessed alone), measured by a 100-point visual analog scale at day 7 or discharge, was similar between the tolvaptan and placebo groups (trial A, mean 18.25 vs 17.73; P=0.51; trial B, mean 18.72 vs 18.28; P=0.52). Mean body weight reductions at day 7 or discharge in the tolvaptan and placebo groups were 3.35 kg vs 2.73 kg, respectively, in trial A (P<0.001) and 3.77 kg vs 2.79 kg, respectively, in trial B (P<0.001). Secondary: More patients in the tolvaptan groups (76.74% in trial A and 72.06% in trial B) reported an improvement dyspnea at day 1 (for those patients with dyspnea at baseline) compared to placebo (70.61% in trial A and 65.32% in trial B; P<0.001 in both trials). There was no significant difference in global clinical status at day 7 or

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				discharge between the tolvaptan or placebo treatment groups (trial A, P=0.51; trial B, P=0.52). Changes in mean body weight were significantly greater with tolvaptan at day 1 (trial A, -1.71 kg; trial B -1.82 kg) than with placebo (trial A, -0.99 kg; trial B, 0.95 kg; P<0.001 in both trials). There was no difference in peripheral edema at inpatient day 7 or discharge with tolvaptan vs placebo in trial A. In trial B, 73.67% of patients experienced at least a 2-grade improvement in pedal edema with tolvaptan compared to placebo (P=0.02). An overall in-hospital mortality rate of 2.4% and 2.9% was observed in the tolvaptan and placebo groups, respectively. Through day 7 or discharge, adverse events were reported in 49.1% and 40.0% of patients in trial A, and in 55.9% and 47.9% of patients in trial B in the tolvaptan and placebo groups, respectively.
Konstam et al.[10] (2007) Tolvaptan 30 mg daily within 48 hours of admission vs placebo	RCT, MC, DB, PC (Results of a long-term outcome study; EVEREST) Patients ≥18 years of age with a history of chronic heart failure who had been hospitalized for worsening congestive heart failure and who had a left ventricular ejection fraction ≤40%. Patients also received conventional heart failure therapy.	N=4,133 ≥60 days	Primary: All-cause mortality and the composite of cardiovascular death or hospitalization for HF Secondary: Composite of cardiovascular mortality or cardiovascular hospitalization, incidence of cardiovascular mortality, incidence of clinical worsening of HF (death,	Primary: The median duration of follow-up was 9.9 months. A total of 537 patients in the tolvaptan group (25.9%) and 543 patients in the placebo group (26.3%) died (HR, 0.98; 95% CI, 0.87- 1.11; P=0.68). A total of 871 patients in the tolvaptan group (42.0%) and 829 patients in the placebo group (40.2%) died from cardiovascular causes or had a first hospitalization for HF (HR, 1.04; 95% CI, 0.95-1.14; P=0.55). Secondary: The composite of cardiovascular death or cardiovascular hospitalization, the incidence of cardiovascular mortality, and the incidence of clinical worsening of HF did not differ between the 2 treatment groups (P=0.52, P=0.67 and P=0.62, respectively). In patients with dyspnea at baseline, patient-assessed dyspnea scores significantly improved at day 1 in patients receiving tolvaptan compared with placebo (P<.001), with 74.3% of the tolvaptan group and 68.0% of the placebo group demonstrating an improvement in dyspnea score. Mean body weight at day 1 was reduced by 1.76 kg in the tolvaptan group

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			hospitalization for HF, or unscheduled visit for HF), changes from baseline in body weight at day 1, serum sodium level at day 7 or discharge, edema score at day 7 or discharge, patient-assessed dyspnea at day 1, and Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score at outpatient week 1	and by 0.97 kg in the placebo group (P<0.001). Among patients with baseline serum sodium levels less than 134 mEq/L, mean serum sodium concentrations increased by 5.49 mEq/L at day 7 or discharge with tolvaptan compared with 1.85 mEq/L in the placebo group (P<0.001). This effect was observed as early as day 1 and was maintained through 40 weeks of treatment. In patients with baseline pedal edema, edema scores significantly improved at day 7 or discharge in patients receiving tolvaptan compared with placebo (P=0.003), with 73.8% of tolvaptan patients and 70.5% of placebo patients manifesting improvement in edema by at least 2 grades. A significant improvement in physician assessed pedal edema was observed as early as day 1 and continued through post discharge week 4. No significant changes were observed at outpatient week 1 in the KCCQ overall summary score. Statistically significant changes favoring tolvaptan were observed at the time of the last scheduled on-treatment assessment at study end for the quality-of life domain (P=0.003), the social limitation domain (P=0.05), and the overall summary score (P=0.02). The other domains (clinical summary, physical limitation, total symptom, symptom frequency, symptom burden, symptom stability, and self-efficacy) did not reach significance at the time of the last on-treatment assessment. Adverse events occurred in 89.0% of tolvaptan patients and 86.1% of placebo patients.
Gheorghiade et al.[13] (2004) Tolvaptan 30 mg, 60 mg, or 90 mg daily vs	RCT, MC, DB, PC (ACTIV in CHF) Patients ≥18 years of age admitted for worsening congestive heart failure with left ventricular ejection fraction <40%	N=319 Inpatient: 10 days Outpatient: 7 weeks	Primary: Change in body weight at 24 hours after the administration of the first dose of study drug; worsening heart failure at 60 days	<u>Inpatient Phase</u> Primary: A greater median reduction in body weight was found in patients treated with tolvaptan compared to placebo 24 hours after the administration of the first dose of study drug (−1.80, −2.10, −2.05, and −0.60 kg for tolvaptan 30, 60, and 90 mg, and placebo, respectively; P=0.002, P=0.002, and P=0.009 for the 3 tolvaptan groups compared with the placebo group). Secondary: The median body weight reductions from baseline to discharge were

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo	within 1 year of admission and systemic congestion (jugular venous distention [JVD], rales, or peripheral edema after initial in-hospital therapy for heart failure). Patients also received conventional heart failure therapy.		Secondary: Changes in dyspnea, JVD, rales, edema, body weight, urine output, serum electrolyte levels, length of hospital stay after randomization, use of diuretics, and patient/physician-assessed symptom scales	greater in the tolvaptan groups compared with the placebo group (−3.30, −2.80, −3.20, and −1.90 kg in the groups receiving tolvaptan 30, 60, and 90 mg, and placebo, respectively; P=0.006, P=0.002, and P=0.06 for the 3 tolvaptan groups compared with placebo). The mean urine output at 24 hours was 4056.2, 4175.2, 4127.3, and 2296.5 mL for the tolvaptan 30, 60, and 90 mg, and placebo groups, respectively (P =0.02, P<0.001, and P<0.001 for the 3 tolvaptan groups compared with the placebo group). Signs and symptoms of heart failure improved in all patients during the period of hospitalization. There were no significant differences in JVD, and peripheral edema between the treatment groups (dyspnea P=0.04). Global assessment scales did not show a significant difference among the treatment groups. The median length of time between randomization and discharge was 4 days in both treatment groups. <u>Outpatient Phase</u> Primary: There was no significant difference in worsening heart failure between the tolvaptan groups and the placebo group. Secondary: Diuretic use decreased in all patients after discharge. There was no significant difference in mean dose reduction between the treatment groups. Adverse events occurred in 85% of patients. Tolvaptan did not appear to cause hypotension, tachycardia, worsening renal function, or abnormalities in serum potassium levels. One hundred thirty patients discontinued therapy prior to completing the 7-week outpatient treatment period.
Gheorghiade et al.[14] (2003)	RCT, DB, MC, PC Patients ≥18 years	N=254 25 days	Primary: Changes in body weight	Primary: Mean decreases from baseline in body weight were observed on the first day of tolvaptan treatment at all doses and maintained throughout the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Tolvaptan 30 mg, 45 mg, or 60 mg daily vs placebo	of age with a diagnosis of congestive heart failure irrespective of left ventricular ejection fraction. Patients also received conventional heart failure therapy.		Secondary: Ankle edema measurements, urine sodium excretion, urine volume, urine osmolality, and safety	study (P<0.001 vs placebo). The decrease in body weight was similar in all tolvaptan-treated patients irrespective of the LVEF. Patients receiving placebo experienced an increase in body weight from baseline. Secondary: Improvements in ankle edema scores were significantly better with tolvaptan 45 mg compared to placebo (P<0.05). None of the other doses studies differed significantly from placebo. Tolvaptan-treated patients had significantly greater mean total urinary sodium excretions (339.9, 373.0, and 355 mEq for the 30-, 45-, and 60 mg tolvaptan groups, respectively) than placebo-treated patients (193.7 mEq; P<0.05). Urine volumes were greater in tolvaptan-treated patients (3909, 4232, and 4597 mL for the 30-, 45-, and 60 mg tolvaptan groups, respectively) than in placebo-treated patients (2328 mL; P<0.05). At day 1, urine osmolality decreased by 15.5, 52.4, and 118.8 mOsm/kg in the 30-, 45-, and 60 mg tolvaptan groups, respectively compared to an increase of 135.8 mOsm/kg in the placebo group (P<0.05 for all comparisons). No significant differences were found between the tolvaptan groups and the placebo group in the quality-of-life assessment. No changes in heart rate or systolic or diastolic blood pressure, supine or standing, were observed in the tolvaptan groups during the study. Dry mouth, thirst, and polyuria, including urinary frequency, were higher in the tolvaptan-treated patients.

Study abbreviations: AC=active control, CI=confidence interval, DB=double-blind, HR=hazard ratio, MA=meta-analysis, MC=multicenter, NS=not significant, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RR=relative risk, SB=single-blind, SC=single center

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 branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

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

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

Rx=prescription

Table 10. Relative Cost of Tolvaptan

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Tolvaptan	tablet	Samsca®	$$$$$	N/A

N/A=Not available

X. Conclusions

Tolvaptan, an oral vasopressin V_2 receptor antagonist, is approved for the treatment of clinically significant euvolemic and hypervolemic hyponatremia (serum sodium <125 mEq/L or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction).[1] The management of hyponatremia depends on the clinical presentation and duration of the disease. Treatment must be approached carefully as overly rapid correction of hyponatremia (>12 mEq/L per 24 hours) may cause osmotic demyelination.

There are limited guidelines available that discuss the management of hyponatremia. An expert panel provided treatment recommendations in 2007, which includes fluid restriction, sodium chloride administration and diuresis.[5] The panel concluded that the optimal use of the vasopressin receptor antagonists has not been determined and further studies are needed.

Three short-term studies were conducted in a small number of patients with euvolemic or hypervolemic hyponatremia.[11-12] The results demonstrated significant improvements in serum sodium concentrations compared

to fluid restriction or placebo. Several other studies have evaluated the use of tolvaptan in patients with congestive heart failure as add-on therapy to conventional treatments.[7-10,13-14] Significant changes in body weight have been observed; however, the long-term use of tolvaptan (median duration 9.9 months) failed to demonstrate any improvements in mortality or hospitalizations for worsening heart failure.[10]

Data supporting the use of tolvaptan are limited. It has not been established that raising serum sodium with tolvaptan provides a symptomatic benefit to patients.[1] Patients requiring intervention to raise serum sodium urgently should not be treated with tolvaptan.[1] Hospitalization is required for initiation and reinitiation of tolvaptan therapy so that serum sodium can be monitored closely.[1]

At this time, there is insufficient evidence to conclude that tolvaptan offers a significant clinical advantage over other alternatives in general use. Since tolvaptan is not indicated as first-line therapy for the management of hyponatremia, it should be managed through the medical justification portion of the prior authorization process.

XI. Recommendations

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

XII. References

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