Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Alzheimer's Agents
Parasympathomimetic (Cholinergic) Agents, AHFS Class 120400
Miscellaneous Central Nervous System Agents (N-methyl-D-aspartic acid [NMDA] Receptor Antagonist—Memantine), AHFS Class 289200
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I. Overview

Alzheimer's disease (AD) is a progressive disease that affects both cognition and behavior. AD is classified under Delirium, Dementia, and Amnestic and Other Disorders in the American Psychiatric Association's (APA's) *Diagnostic and Statistical Manual for Mental Disorders*, Text Revision, 4th edition (DSM-IV-TR).[1] It is defined as the development of multiple cognitive deficits manifested by memory impairment and one or more of the following: aphasia, apraxia, agnosia, and/or disturbance in executive functioning.[1] Pathophysiologic mechanisms behind the disease are not entirely understood, but a common pathologic finding is the accumulation of beta-amyloid proteins in the brain. Subsequently, inflammatory and free radical processes eventually result in neuron dysfunction and death. Although research is looking at preventing plaque formation or enhancing plaque removal, current drug therapies target symptom reduction and slow progression of cognitive and behavioral decline.

The course of the disease starts with mild cognitive impairment, progresses to more severe effects and, eventually, death, commonly due to pneumonia or aspiration. Predictors of mortality include severity at time of diagnosis, abnormal neurologic findings, and the presence of heart disease and diabetes.[2] AD is the most common of the dementias in the United States (US), accounting for more than 50% of all diagnosed dementias. It is estimated that in 2007 there are 5.1 million Americans with AD.[3]

By 2050, one in five people will be over age 65 years, and the number of Alzheimer's patients is projected to be 11-16 million.[4] It is predicted that in Alabama there will be an 8% increase in AD over the 10-year period 2000-2010 resulting in 91,000 individuals with AD.[3] Although there is no definitive diagnostic laboratory, clinical, or imaging tests available, neuropsychological testing and clinical evaluation is 90% accurate. Treatment consists of nonpharmacologic and pharmacologic therapies, with nonpharmacologic interventions as the primary mechanism for management of memory loss and behavioral symptoms of AD. Nonpharmacologic therapies consist of keeping a notepad in one's pocket to make reminders, posting lists and notes throughout the house, exercising one's brain through reading and crossword puzzles, and other strategies. Current pharmacotherapy is aimed at reducing the rate of cognitive decline. Behavioral conditions also show some improvement with this class of medications but, once again, treatment is geared towards reducing symptoms instead of curing or arresting the disease.

In the early 1980s, tacrine was the first drug evaluated as a means to enhance cholinergic activity in patients with AD. Due to an extensive adverse effect profile, use of tacrine has been replaced by more tolerable cholinesterase inhibitors. Also, due to a risk of hepatotoxicity, tacrine is contraindicated in patients with liver disease. Donepezil has specificity for inhibition of acetylcholinesterase compared to butyrylcholinesterase, which results in fewer side effects (eg, nausea, vomiting, and diarrhea) but may make it less effective in late stages of Alzheimer's disease since butyrylcholinesterase is more abundant than acetylcholinesterase in patients with late stages of the disease. Rivastigmine has central activity for acetylcholinesterase and butyrylcholinesterase, with low affinity at these sites in the periphery. The most recently approved cholinesterase inhibitor, galantamine, is specific for acetylcholinesterase and has activity as a nicotinic receptor modulator which results in acetylcholine binding more tightly to the receptor.

Memantine effects the transmission of glutamate by weakly and noncompetitively blocking cation channels on the glutamate neuron. This weak binding does not allow for chronic stimulation which may damage neurons but does allow for bursts of excitation which allows for appropriate signal transmission.[5] Abnormal glutamatergic activity, in addition to causing cognitive deficits, may cause neuronal toxicity thought to be involved in the destruction of

brain cells in AD patients. The drug appears to inhibit abnormal glutamatergic activity and slow the cognitive, functional, and global deterioration apparent in patients with moderate-to-severe AD.

The Alzheimer's agents that are included in this review are listed in Table 1. There are four cholinesterase inhibitor medications and one N-methyl-D-aspartate (NMDA) receptor antagonist. At this time, there are no generic alternatives to any of the Alzheimer's medications. This review encompasses all dosage forms and strengths.

Table 1. Alzheimer's Agents Included in this Review

Generic Name	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Parasympathomimetic (Cholinergic) Agents—Cholinesterase Inhibitors			
donepezil	orally disintegrating tablet, tablet	Aricept®, Aricept ODT®	none
galantamine	extended-release capsule, solution, tablet	Razadyne®, Razadyne ER®	none
rivastigmine	capsule, solution, transdermal patch	Exelon®, Exelon Patch®	Exelon®
tacrine	capsule	Cognex®	none
Miscellaneous Central Nervous System Agents—NMDA Receptor Antagonist			
memantine	solution, tablet	Namenda®	none

No generic products are available in this class.

II. Evidence-Based Medicine and Current Treatment Guidelines

Until recently, the cholinesterase inhibitors were the only drugs indicated for first-line treatment of cognitive symptoms in AD. It is believed that the memory loss in Alzheimer's disease is the result of a deficiency of cholinergic neurotransmission. Increasing cholinergic function is the primary mechanism of action of the cholinesterase inhibitors. Memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist, does not directly increase acetylcholine effects but seems to preserve neuronal function. Memantine is Food and Drug Administration (FDA) approved only for moderate-to-severe dementia and the cholinesterase inhibitors are indicated for mild-to-moderate disease with the exception of donepezil which also is indicated for moderate-to-severe disease. Rivastigmine has recently been given the additional indication of dementia associated with Parkinson's disease. Treatment guidelines that incorporate the Alzheimer's agents are summarized in Table 2.

Table 2. Treatment Guidelines Using the Alzheimer's Agents

Clinical Guideline	Recommendation(s)
American Academy of Neurology (AAN): **Practice Parameter: Management of Dementia (An Evidence-Based Review) (2003)**[6]	<u>Pharmacologic Treatment of Alzheimer's Disease</u> • Cholinesterase inhibitors should be considered in patients with mild-to-moderate AD, although studies suggest a small average degree of benefit. • Vitamin E (1,000 IU by mouth [PO] twice a day [BID]) 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. • Some patients with unspecified dementias may benefit from ginkgo biloba, but evidence-based efficacy data are lacking. <u>Pharmacologic Treatment for Noncognitive Symptoms of Dementia</u> • Antipsychotics should be used to treat agitation or psychosis in patients with dementia where environmental manipulation fails. Atypical agents may be better tolerated compared with traditional antipsychotics.

Clinical Guideline	Recommendation(s)
	• Selected antidepressants (eg, selective serotonin-reuptake inhibitors and tricyclics) should be considered in the treatment of depression in individuals with dementia with side effect profiles guiding the choice of agent. <u>Educational Interventions for Patients with Dementia and/or Caregivers</u> • Short-term programs directed toward educating family caregivers about AD should be offered to improve caregiver satisfaction. • Intensive long-term education and support services should be offered to caregivers of patients with AD to delay time to nursing home placement. • Staff of long-term care facilities should receive education about AD to reduce the use of unnecessary antipsychotics. • As part of this practice guideline, additional interventions other than education for patients and caregivers are available for functional behaviors, problem behaviors, and care environment alterations.
American Academy of Neurology (AAN): **Practice Parameter: Diagnosis of Dementia: An Evidence-Based Review (2004)**[5]	<u>Management of Dementia</u> • Cognitive symptoms of AD are treated with cholinesterase inhibitors and vitamin E. • Cholinesterase inhibitors have been proven effective in patients with mild-to-moderate AD and vitamin E may be considered to slow progression of AD. • Agitation, depression, and psychosis should be treated initially with environmental manipulation. If this is not effective, then antipsychotics may be used. Tricyclics, monoamine oxidase B (MAO-B) inhibitors, and selective serotonin-reuptake inhibitors should be considered to treat depression. • Caregiver participation in educational programs and support groups is recommended.
British Association for Psychopharmacology: **Clinical Practice with Anti-dementia Drugs: A Consensus Statement (2006)**[7]	• Cholinesterase inhibitors are effective in the treatment of mild-to-moderate Alzheimer's disease: type 1a evidence (obtained from meta-analysis of randomized controlled trials). • One cholinesterase inhibitor should be switched to another if the first is not tolerated or effective: type 2b evidence (obtained from at least one other type of well-designed quasi-experimental study). • Memantine is effective in the treatment of moderate-to-severe Alzheimer's disease: type 1a evidence. • Memantine may be added to a cholinesterase inhibitor: type 1b evidence (obtained from at least one randomized controlled trial). • Cholinesterase inhibitors may be used for the treatment of both dementia with Lewy bodies and Parkinson's disease dementia, including neuropsychiatric symptoms: type 1b evidence. • Cholinesterase inhibitors and memantine may be used for the treatment of cognitive impairment in vascular dementia, though effect sizes are small and may not be clinically significant: type 1b evidence. • No distinction is made between cholinesterase inhibitors in terms of efficacy.

III. Indications

Cholinesterase inhibitors should be used with caution in patients with asthma, chronic obstructive pulmonary disease, sick sinus syndrome, or other supraventricular cardiac conditions. In addition, due to the mechanism of action of the cholinesterase inhibitors, gastric acid secretion may be increased as a result of increased cholinergic activity. Therefore, special caution should be used in patients at increased risk of developing ulcers or those with a history of peptic ulcer disease.

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[8-15]

Drug	Mild-to-moderate dementia of the Alzheimer's type	Moderate-to-severe dementia of the Alzheimer's type	Mild-to-moderate dementia associated with Parkinson's disease
Parasympathomimetic (Cholinergic) Agents—Cholinesterase Inhibitors			
Donepezil	✔	✔	
Galantamine	✔		
Rivastigmine	✔		✔
Tacrine	✔		
Miscellaneous Central Nervous System Agents—NMDA Receptor Antagonist			
Memantine		✔	

IV. Pharmacokinetics

The pharmacokinetic parameters for each of the agents in this class vary in some respects. Galantamine and donepezil are metabolized primarily by cytochrome P450 (CYP) 2D6 and CYP3A4. Tacrine is metabolized by CYP but uses the isoenzyme 1A2. Rivastigmine is metabolized by plasma esterases and not the CYP group of isoenzymes. Memantine is generally eliminated unchanged through the kidneys.

Galantamine extended release (ER) is galantamine hydrochloride encased in a slow-release capsule. The pharmacokinetics of the two delivery methods are equal except for the time to maximum concentration, which occurs later, and peak levels, which are lower with the ER version. The clinical significance of this difference is not known.

Table 4 compares additional pharmacokinetic parameters for the drugs used to treat AD.

Table 4. Pharmacokinetic Parameters of the Alzheimer's Agents[8-15]

Drug	T_{max} (hours)	Bioavailability (%)	Protein Binding (%)	Metabolism	Elimination	Serum Half-Life (hours)
Parasympathomimetic (Cholinergic) Agents—Cholinesterase Inhibitors						
Donepezil	3-4	100	96	CYP2D6 and CYP3A4, and glucuronidation	Renal (57%)	70
Galantamine	1	90	18	CYP2D6 and CYP3A4	Primarily renal	7
Rivastigmine	1	36	40	Cholinesterase-mediated hydrolysis; minimal CYP involvement	Renal (97%)	1.4-1.7
Tacrine	1-2	17	55	CYP1A2	First-pass	2-4
Miscellaneous Central Nervous System Agents—NMDA Receptor Antagonist						
Memantine	3-7	100	45	Partially hepatic, non-CYP metabolism	Renal (48% unchanged in urine, remainder as inactive metabolites)	60-80

V. Drug Interactions

Rivastigmine is metabolized by esterases rather than CYP enzymes theoretically resulting in no drug interactions with drugs metabolized by the following isoenzymes: CYP1A2, CYP2D6, CYP3A4/5, CYP2E1, CYP2C9, CYP2C8, or CYP2C19.[16] Galantamine does not inhibit the metabolic pathways catalyzed by CYP1A2, CYP2A6, CYP3A4, CYP4A, CYP2C, CYP2D6, or CYP2E1. Potential changes in serum levels of galantamine exist when coadministered with fluoxetine, cimetidine, ketoconazole, erythromycin, paroxetine and other medications that

inhibit or induce CYP2D6 and CYP3A4. Significant drug interactions with the Alzheimer's agents are listed in Table 5.

Table 5. Significant Drug-Drug Interactions with the Alzheimer's Agents[15]

Drug(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

Historically, about 17% of patients who receive tacrine withdraw from treatment permanently due to adverse events.[12,13,15] Transaminase elevations were the most common reason for withdrawals, accounting for 8% of all tacrine-treated patients. Transaminase elevations occur infrequently with the other Alzheimer's agents. For this reason, tacrine use is disadvantageous compared to the other agents in this class. Discontinuations due to adverse events for rivastigmine, donepezil, and galantamine are low and similar to placebo. Gastrointestinal (GI) adverse events occur most frequently among the cholinesterase inhibitor agents. Donepezil frequently results in lower GI adverse events compared to the other agents. Additive risk of adverse events may be expected with coadministration of these drugs, or with inadequate washout periods between agents. One report of fatal aspiration pneumonia has been published after initiation of rivastigmine and discontinuation of donepezil with no washout period between therapies.[17] A washout period should be considered, and is usually recommended when switching between cholinesterase inhibitors. The most common adverse drug events reported with the Alzheimer's agents are noted in Table 6.

Table 6. Adverse Drug Events (%) Reported with the Alzheimer's Agents[8-15]

	Parasympathomimetic (Cholinergic) Agents—Cholinesterase Inhibitors					NMDA Receptor Antagonist
Adverse Event	**Donepezil**	**Galantamine**	**Rivastigmine (Oral)**	**Rivastigmine (Transdermal)**	**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

	Parasympathomimetic (Cholinergic) Agents—Cholinesterase Inhibitors					NMDA Receptor Antagonist
Adverse Event	**Donepezil**	**Galantamine**	**Rivastigmine (Oral)**	**Rivastigmine (Transdermal)**	**Tacrine**	**Memantine**
Agitation	≥1	-	≥1*	-	7	≥2
Anxiety	≥1	-	4-5	3	3	≥2
Aphasia	≥1	-	-	-	-	-
Bradykinesia	-	-	≥1*	-	-	-
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	-
Pruritis	≥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	-	-	-

	Parasympathomimetic (Cholinergic) Agents—Cholinesterase Inhibitors					NMDA Receptor Antagonist
Adverse Event	**Donepezil**	**Galantamine**	**Rivastigmine (Oral)**	**Rivastigmine (Transdermal)**	**Tacrine**	**Memantine**
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	-
Epigastric pain	≥1	-	-	-	-	-
Fecal incontinence	≥1	-	≥1	-	-	-
Flatulence	-	≥1	4	-	4	-
Gastritis	-	-	≥1	≥1	-	-
Gastroenteritis	≥1	-	-	-	-	-
Gastrointestional bleeding	≥1	-	-	-	-	-
Nausea	6-11	13-24	29-47	7-21	-	≥2
Nausea/vomiting	-	-	-	-	28	-
Vomiting	5-8	6-13	17-31	6-19	-	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	-
Lab Test Abnormalities						
Elevated alkaline phosphatase	≥1	-	-	-	-	≥1
Elevated creatinine	3	-	-	-	-	-
Elevated LDH	≥1	-	-	-	-	-
Elevated transaminase	-	-	-	-	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

	Parasympathomimetic (Cholinergic) Agents—Cholinesterase Inhibitors					NMDA Receptor Antagonist
Adverse Event	**Donepezil**	**Galantamine**	**Rivastigmine (Oral)**	**Rivastigmine (Transdermal)**	**Tacrine**	**Memantine**
Eye irritation	≥1	-	-	-	-	-
Respiratory						
Bronchitis	≥1	-	-	-	≥1	≥2
Cough increased	≥1	-	-	-	3	4
Dypsnea	≥1	-	≥1	-	≥1	2
Pharyngitis	≥1	-	-	-	≥1	-
Pneumonia	≥1	-	-	≥1	≥1	≥1
Rhinitis	-	4	4	-	8	-
Sinusitis	-	-	-	-	≥1	-
Upper respiratory tract infection	-	-	-	-	3	≥2
Other						
Accident	7-13	-	-	-	-	-
Accidental trauma	-	-	1-10	-	-	-
Allergy	-	-	≥1	-	-	-
Chills	-	-	-	-	≥1	-
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	-	-	-

✓ =Percent not specified
- Event not reported or incidence <1%
LDH=lactic dehydrogenase
*These central nervous system (CNS) adverse events were reported only in trials for Parkinson's disease–associated dementia.

VII. Dosing and Administration

Donepezil and galantamine extended release are the only agents approved for once daily dosing. Galantamine, memantine and rivastigmine, are available in a liquid dosage form and donepezil is available as an orally disintegrating tablet (ODT). Although studies indicate the clearance of donepezil and rivastigmine may be altered in renal and hepatic impairment, neither manufacturer has provided specific recommendations for dosing in patients with renal or hepatic disease. Galantamine use is not recommended in patients with severe hepatic or renal impairment, and caution should be used when the drug is given to patients with moderate hepatic or renal disease. Tacrine should be used with caution in patients with pre-existing liver disease, and in renal impairment, especially in the event of electrolyte disturbances from adverse gastrointestinal (GI) events. When given with food, the GI tolerability of the cholinesterase inhibitors may be improved.

The usual dosing regimens for the agents used to treat Alzheimer's disease are summarized in Table 7.

Table 7. Usual Dosing for the Alzheimer's Agents[8-15]

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
Parasympathomimetic (Cholinergic) Agents—Cholinesterase Inhibitors			
Donepezil	Tablet and orally disintegrating tablets (ODT): Initial: 5 mg every night at bedtime (QHS), with or without food	Safety and efficacy in children have not been established.	ODT: 5 mg 10 mg

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
	Maintenance: 5-10 mg every day (QD) Time between dosage adjustment: 4-6 weeks		Tablet: 5 mg 10 mg
Galantamine	Extended-release capsule: Initial: 8 mg QD Maintenance: 16-24 mg QD Time between dosage adjustment: 4 weeks Tablet: Initial: 4 mg twice a day (BID) with the morning and evening meals Maintenance: 8-16 mg BID Time between dosage adjustment: 4 weeks	Safety and efficacy in children have not been established.	Extended-release capsule: 8 mg 16 mg 24 mg Solution: 4 mg/mL Tablet: 4 mg 8 mg 12 mg
Rivastigmine	Capsule and solution: Initial: 1.5 mg BID with the morning and evening meals Maintenance: 3-6 mg BID Time between dosage adjustment: 2 weeks Transdermal patch: Initial: 4.6 mg/24 hours; dose can be titrated after a minimum of 4 weeks up to the maximum recommended dose of 9.5 mg/24 hours	Safety and efficacy in children have not been established.	Capsule: 1.5 mg 3 mg 4.5 mg 6 mg Solution: 2 mg/ml Transdermal patch: 4.6 mg/24 hours 9.5 mg/24 hours
Tacrine	Initial: 10 mg four times a day (QID) at least 1 hour before meals Maintenance: 20-40 mg QID Time between dosage adjustment: 4-6 weeks	Safety and efficacy in children have not been established.	Capsule: 10 mg 20 mg 30 mg 40 mg
Miscellaneous Central Nervous System Agents—NMDA Receptor Antagonist			
Memantine	Solution and tablet: Week 1: 5 mg QD Week 2: 10 mg/day (5 mg BID) Week 3: 15 mg/day (10 mg every morning, 5 mg every night) Week 4: maintenance dose, 20 mg/day (10 mg BID)	Safety and efficacy in children have not been established.	Solution: 10 mg/5 mL Tablet: 5 mg 10 mg 4 week titration pack

VIII. Effectiveness

Until recently, there were no head-to-head trials comparing the efficacy of the agents used to treat Alzheimer's disease. Limited comparative data is now available; however, data comparing memantine to other agents is not available. Memantine has been studied in combination with donepezil and galantamine. In addition, memantine has been studied in Europe during the last decade for the treatment of dementia, and was approved in the European Union in May of 2002 for the treatment of moderately severe and severe AD. In 2003, the FDA gave memantine approval for the treatment of moderate-to-severe AD but not for mild AD.

Kaduszkiewicz et al[18] conducted a systematic review of all randomized-controlled trials of donepezil, rivastigmine and galantamine published from 1989-2004. They found 22 trials which met the inclusion criteria: 12 for donepezil, 5 for rivastigmine and 5 for galantamine. The authors found that the differences in efficacy among the 3 medications vary by study and that the overall efficacy versus placebo is moderate. They concluded that "the scientific basis for recommendations of the cholinesterase inhibitors for Alzheimer's disease is questionable."

Clinical studies evaluating the safety and efficacy of the Alzheimer's agents are summarized in Table 8.

Table 8. Comparative Clinical Trials Using the Alzheimer's Agents

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Alzheimer's Disease				
Geldmacher et al[19] Donepezil 5 mg/day; treatment duration varied	Observational Follow-up of patients previously enrolled in one of three randomized, double-blind, placebo-controlled trials of donepezil, and two subsequent open-label studies	N=1,115 Duration not specified	Primary: Time to nursing home placement Secondary: Not reported	Primary: Use of donepezil of 5 mg/day or more was associated with significant delays in nursing home placement. A cumulative dose-response relationship was observed between longer-term sustained donepezil use and delay of nursing home placement. When donepezil was taken at effective doses for at least 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. Secondary: Not reported
Courtney et al[20] Donepezil 5-10 mg/day vs	DB, R Patients with Alzheimer's disease	N=565 12 week run-in period; 156 weeks total	Primary: MMSE, BADLS, time to entering institution Secondary:	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 (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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo		duration	Not reported	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. Secondary: Not reported
Birks and Harvey[21] Donepezil 5-10 mg/day vs placebo	MA (24 trials) Patients diagnosed with Alzheimer's disease	N=5,796 12-60 weeks	Primary: ADAS-Cog, MMSE, CIBIC-Plus, ADL, withdrawals and adverse events Secondary: Not reported	Primary: Statistically 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). Statistically 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 to 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,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				and muscle cramps. Secondary: Not reported
Black et al[22] Donepezil 5 mg daily for 6 weeks, then 5 mg twice a day (10 mg daily) for 18 weeks thereafter vs placebo	DB, MC, PC, RCT Men or women aged at least 50 years who were ambulatory or ambulatory-aided (cane, walker, or wheelchair) diagnosed with probable AD consistent with the DSM-IV and the NINCDS-ADRDA criteria, MMSE score between 1 and 12 (inclusive), a modified Hachinski Ischemic score of ≤6, and a FAST score of ≥6	N=343 24 weeks	Primary: SIB is a comprehensive evaluation of cognitive dysfunction in patients with more advanced AD (lower scores indicating greater impairment); CIBIC-Plus (lower scores indicating improvement) Secondary: ADCS-ADL-sev, NPI, MMSE, CBQ, RUSP	Primary: Donepezil was more efficacious when compared to placebo on SIB score change from baseline to endpoint, as well as on CIBIC-Plus score ($P \leq 0.05$ 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 (P value not reported). The RUSP scores also had low average responses with little movement from baseline and no significant differences (P value not reported).
Winblad et al[23] Donepezil 5 mg for the first 30 days followed by daily donepezil 10 mg (or 5 mg if not well tolerated) for the next 5 months vs placebo	DB, PC, PG Patients 50 years or older with the ability to walk alone or with help, a MMSE score of 1-10, and a FAST rating of stage 5 (requires assistance in choosing proper clothing) to 7c (non-ambulatory-unable to walk without assistance), a diagnosis	N=248 6 months	Primary: Change from baseline to month 6 in the scores for the SIB and the Modified ADCS-ADL-severe Secondary: Change in scores at 6 months compared with screening for the MMSE	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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	of probable or possible AD consistent with the DSM-IV and the criteria of the NINCDS-ADRDA		baseline for the NPI, and scores at month 6 for the CGI-I	
Winblad et al[24] Donepezil 5 mg daily for the first 28 days and 10 mg/day thereafter, as per clinician's judgment for the next 11 months vs placebo All patients entering the 2-year, open-label phase receiving 5 mg of donepezil, once daily for the first 28 days, after which the dosage was increased to 10 mg/day, as per clinician's judgment.	DB, OL, PC Men and women aged between 40 and 90 years with a diagnosis of AD consistent with the DSM-IV criteria and the NINCDS-ADRDA criteria for possible or probable AD	N=286 52 week, randomized, double-blinded, placebo-controlled phase plus a 2-year, open-label continuation phase for a total of 3 years	Primary: GBS Secondary: MMSE, GDS, PDS, NPI	Primary: The GBS total scores indicate that both the continuous-treatment group and delayed-start groups had declined, with the difference between the two groups favoring the continuous-donepezil group, over the 3-year period (*P*=0.056). Secondary: The MMSE declined significantly less in the continuous-treatment group than in the delayed-start group over the course of the study (*P*=0.004, *P*=0.057, respectively). GDS declined significantly less over the 3-year study period in patients in the continuous-treatment group than in those in the delayed-start group (*P*=0.0231). There was a trend favoring continuous-donepezil treatment over delayed-start treatment on the PDS, although it was not statistically significant (*P*=0.091). NPI results showed no significant treatment differences between the groups (*P* value not reported).
Wallin et al[25] Donepezil 5-10 mg/day vs historical data	MC, PRO Patients 40 years of age and older with diagnosis of dementia and probable Alzheimer's disease	N=435 3 year	Primary: MMSE, ADAS-Cog, CIBIC, IADL Secondary: Not reported	Primary: For the MMSE (higher score=better function) patients had a mean score of 22.0 ± 4.6 at baseline and 19.1 ± 7.3 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: (higher score=lower function) patients had a mean score of 20.7 ± 10.0 at baseline and 26.1 ± 16.4 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				nontreatment (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. The IADL change from baseline at 6 months was 1.01±3.62, at 12 months 2.19±4.45 and at 36 months 6.18±5.54. Secondary: Not reported
Tariot et al[26] Donepezil (dose varied) and memantine 10 mg twice a day vs donepezil (dose varied) and placebo	DB, MC, PC, R Patients with moderate-to-severe Alzheimer's disease who received stable doses of donepezil	N=404 24 weeks	Primary: SIB, ADCS-ADL, CIBIC-Plus, BGP Secondary: Not reported	Primary: A significantly greater therapeutic effect was observed in the memantine group than in the placebo group on the ADCS-ADL, SIB, and CIBIC-Plus. Patients receiving memantine in combination with donepezil demonstrated significantly less decline in ADCS-ADL scores compared to patients receiving donepezil-placebo over the 24-week study period (*P*=0.02). Patients receiving memantine showed significantly less cognitive decline in SIB scores compared to patients receiving placebo. Therapy with memantine-donepezil resulted in sustained cognitive performance above baseline compared 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%. Secondary: Not reported
Cumming et al[27] Donepezil (dose varied)	DB, PC, PG, PRO Patients with moderate-	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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
and memantine 10 mg twice a day vs donepezil (dose varied) and placebo	to-severe Alzheimer's disease who received stable doses of donepezil		Secondary: Not reported	placebo group and decreased 2.5 points in the memantine group ($P<0.001$). At week 24, NPI scores increased 3.7 points (worsening behavior) in the placebo groups and the memantine group returned to baseline ($P=0.002$). Fewer patients developed delusions in the memantine treatment group than the placebo group ($P=0.011$). Secondary: Not reported
Rogers et al[28] Donepezil 5 mg daily vs donepezil 10 mg daily vs placebo	DB, MC, PC, R Patients with mild-moderate Alzheimer's disease	N=473 24 weeks	Primary: ADAS-Cog, CIBIC Secondary: Not reported	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. Secondary: Not reported
Raskind et al[29] Galantamine 24 mg/day vs placebo	DB, PC, R Patients with mild-moderate Alzheimer's disease	N=194 36 months	Primary: ADAS-Cog, adverse events Secondary: Not reported	Primary: Patients treated continuously with galantamine for 36 months increased a mean of 10.2 ± 0.9 points on the ADAS-Cog. This was a substantially smaller cognitive decline (approximately 50%) than that predicted for the placebo group. Patients discontinuing galantamine therapy before 36 months had declined 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				patients. Secondary: Not reported
Cummings et al[30] Galantamine 8, 16, or 24 mg/day vs placebo	DB, PC, R Patients with mild-moderate Alzheimer's disease	N=978 21 weeks	Primary: NPI, caregiver distress related to patients' behavior Secondary: Not reported	Primary: NPI scores worsened with placebo, whereas patients treated with 16 or 24 mg/day of galantamine had no change in NPI scores. Behavioral improvement in patients symptomatic at baseline ranged from 29% to 48%. Changes were evident in patients receiving 16 and 24 mg/day of galantamine. High-dose galantamine was associated with a significant reduction in caregiver distress. Secondary: Not reported
Loy and Schneider[31] Galantamine 8-36 mg/day vs placebo	MA (10 trials) Patients diagnosed with mild cognitive impairment or Alzheimer's disease	N=6,805 12 weeks-2 years	Primary: CIBIC-plus, ADAS-Cog, ADCS-ADL, DAD, NPI Secondary: Not reported	Primary: Statistically significant difference was seen on the global rating scales for 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 (*P* values not reported). Secondary: Not reported
Wilcock et al [32] Galantamine 24 mg vs	DB Patients with mild-moderate Alzheimer's disease	N=653 6 months	Primary: ADAS-Cog, adverse events Secondary:	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-

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
galantamine 32 mg vs placebo			Not reported	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. Secondary: Not reported
Dunbar et al[33] 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, R Patients with mild-to-moderate probable Alzheimer's disease according to NINCDS/ADRDA	N=965 7 months	Primary: Nausea and vomiting Secondary: Not reported	Primary: Nausea reports were as follows: 16.9% of the galantamine ER group, 13.8% of galantamine IR group, and 5% of placebo group. Vomiting reports were as follows: 6.6% of the galantamine ER groups, 8.6% of the galantamine IR group, and 2.2% of the placebo group. During dose titration, the area under the curve of daily percentage of patients reporting nausea or vomiting was significantly higher in the galantamine IR group compared to placebo (320.9 vs 102.9; *P*=0.01) but for galantamine ER versus placebo and galantamine ER versus galantamine IR no significant differences were seen ([173.5 vs 102.9; *P*=NS], [320.9 vs 173.5; *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. Secondary: Not reported
Brodaty et al[34] Galantamine 8-16 or 24 mg/day	AC, DB, MC, PC, PG, R Patients with mild-to-moderate probable	N=971 6 months	Primary: ADAS-cog/11, CIBIC-Plus Secondary:	Primary: Compared to placebo, galantamine PRC 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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs galantamine PRC 8-16 or 24 mg/day vs placebo	Alzheimer's disease according to NINCDS/ADRDA		ADCS-ADL, NPI, ADAS-cog/13, nonmemory ADAS-cog/ memory, ADAS-Cog	Galantamine also showed similar results when compared to placebo (OC mean change = –1.8 and 1.3, respectively; *P*<0.001; 95% CI: –4.17 to –2.08; LOCF mean change = –1.6 and 1.2, respectively; *P*<0.01; 95% CI: –3.70 to –1.86). Secondary: ADCS-ADL scores were significantly improved in the galantamine PRC 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 PRC and galantamine groups versus placebo, OC NPI scores were not statistically significant but instead numerically significant (OC, *P*=0.451; 95% CI: –2.77 to 1.23; LOCF, *P*=0.941; 95% CI, –1.85 to 1.82), (OC, *P*<0.205; 95% CI: –3.31 to 0.71; LOCF, *P*<0.102; 95% CI: –3.42 to 0.23). Statistical significance was found in cognition improvement from baseline for both galantamine groups compared to placebo based on ADAS-cog/13, non-memory ADAS-Cog, and memory ADAS-Cog scores.
Reisberg et al[35] Memantine 10 mg twice a 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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Winblad et al[36] Memantine 10 mg every day vs placebo	DB, PC Patients in Latvia with severe dementia, either Alzheimer's disease or vascular dementia	N=166 12 weeks	Primary: CGI-C and BGP Secondary: Safety	Primary: Significantly greater improvement was observed in the memantine group compared to the placebo group on the BGP and the CGI-C ($P<0.016$ and $P<0.001$, respectively). Separate analyses of the 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.
Winblad et al[37] Memantine 20 mg/day vs placebo	MA Four studies: memantine as mono-therapy, 2 studies of memantine vs placebo in patients already taking an acetylcholin-esterase inhibitor Patients diagnosed with moderate-to-severe Alzheimer's disease	N=1,826 in subgroup with moderate-to-severe Alzheimer's disease 24-28 weeks	Primary: CIBIC-Plus, SIB, ADAS-Cog, ADCS-ADL, NPI Secondary: Not reported	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 ($P=0.03$). Secondary: Not reported
Wilkinson and Andersen[38] Memantine 20 mg/day (10 mg twice a day or 20 mg daily) vs	MA Patients diagnosed with moderate-to-severe Alzheimer's disease	N=1,826 24-28 weeks	Primary: ADAS-Cog, SIB, CIBIC-Pus, ADCS-ADL Secondary: Not reported	Primary: Significantly more patients in the placebo group (21%) had marked clinical worsening, as demonstrated by deteriorating scores, than in the memantine group (11%; $P<0.001$). Significantly more patients in the placebo group (28%) compared to the memantine group (18%) had documentation of worsening in any outcome measure ($P<0.001$).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo				Secondary: Not reported
Ott et al[39] Continuation of memantine up to 20 mg/day vs placebo for 8 weeks then memantine 5-20 mg/day thereafter	DB, MC, OL, PG, R Patients at least 50 years old having probable Alzheimer's disease according to NINCDS/ADRDA, completed a lead-in trial that was multi-center, randomized, double-blind, placebo-controlled for 24 weeks with memantine in mild Alzheimer's disease	N=314 28 weeks	Primary: Safety and tolerability Secondary: Not reported	Primary: At least one adverse event was reported by 74.8% of patients during the 28 weeks with the most common adverse event being falls and other injuries (both 10.8%). 6.7% of patients withdrew from the study due to adverse events and the frequency was similar between the placebo-memantine group and the memantine-memantine group. Physical and lab exams were normal except for a significant increase in blood urea nitrogen levels with an incidence of 7% in the memantine-memantine group and 3.6% in the placebo-memantine group. Secondary: Not reported
Burns et al[40] Rivastigmine	RETRO Patients with moderately severe Alzheimer's disease/dementia	N=2,126 3 trials, each 6 months	Primary: Effectiveness Secondary: Not reported	Primary: Mean ADAS-Cog score declined by 6.3 points in the placebo group and increased by 0.2 points in the rivastigmine group ($P<0.001$). Clinical benefits were also observed with the MMSE, the six-item 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. Secondary: Not reported
Birks et al[41] Rivastigmine 6-12 mg/day vs	MA (8 trials) Patients diagnosed with Alzheimer's disease	N=3,660 12-52 weeks	Primary: ADAS-Cog, ADL, adverse events Secondary: Not reported	Primary: Statistically significant differences were seen in patients treated with rivastigmine at doses of 6-12 mg/day as compared to placebo for the following outcomes: ADAS-Cog (WMD -2.09, 95% CI: –2.65 to –1.54) and ADL (WMD -2.15, 95% CI: –3.16 to –1.13).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo				At 26 weeks, 55% of patient had severe dementia in the rivastigmine group as compared to 59% in the placebo group (OR 0.78, 95% CI: 0.64 to 0.94). Adverse events (nausea, vomiting, diarrhea, anorexia, headache, syncope, abdominal pain, and dizziness) were reported significantly more frequently in the rivastigmine group than with placebo. Secondary: Not reported
Rosler et al[42] Rivastigmine 1-4 mg/day vs rivastigmine 6-12 mg/day vs placebo	DB, MC, PC, RCT Patients 50-85 years of age and not able to bear children, all patients met criteria for Alzheimer's type dementia as described in the DSM-IV and criteria for probable AD according to criteria of the NINCDS/ADRDA, baseline MMSE 10-26	N=725 Dose titration over the first 12 weeks with a subsequent assessment period of 14 weeks, total of 26 weeks	Primary: Improvements in cognitive function and overall clinical status measured by the ADAS-Cog, CIBIC, PDS, MMSE and GDS Secondary: Safety and tolerability	Primary: Significant improvement in cognitive function assessed by the ADAS-Cog was observed with the higher dose group by ≥4 points compared to placebo ($P<0.05$). At week 26, significantly more patients in both rivastigmine groups had improved in global function as assessed by the CIBIC compared with those in the placebo group ($P<0.05$). Mean scores on the PDS improved from baseline in the higher dose group but fell in the placebo group ($P<0.05$). At week 26, mean scores in the MMSE and the GDS significantly improved in patients receiving rivastigmine 6-12 mg/day ($P<0.05$). Secondary: Discontinuation rates for any reason were significantly higher in the higher dose group than in the lower dose or placebo group (33% vs 14%). Adverse events related to treatment including nausea, vomiting, diarrhea, abdominal pain and anorexia, were generally mild and occurred most frequently during the dose escalation phase (23% in higher dose group, 7% in lower dose group and 7% in placebo group).
Winblad et al[43] Rivastigmine patch groups were up-titrated from a 5 cm² starting dose in 5 cm² steps to a	DB, DD, MC, PG Women or men aged 50-85 years with a diagnosis of dementia of the Alzheimer's type	N=1,195 24 weeks	Primary: ADAS-Cog, ADCS-CGIC Secondary: ADCS-ADL scale;	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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
maximum size of 20 cm² (target doses of 10 cm² or 20 cm² rivastigmine patch) vs rivastigmine capsule groups were up-titrated from 3 mg/day in steps of 3 mg/day to a maximum of 12 mg/day (target dose of 12 mg/day) vs placebo	according to the DSM-IV, and probable AD according to the criteria of the NINCDS/ ADRDA, and MMSE scores of 10-20 inclusive		NPI for behavior and psychiatric symptoms; MMSE for cognition; Ten Point Clock-drawing Test for assessment of visuospatial and executive functions; Trail Making Test Part A for assessment of attention, visual tracking and motor processing speed	10 cm² patch and capsule group (all $P<0.05$ vs placebo). The 20 cm² patch did not achieve statistical significance compared to placebo in the analysis ($P=0.054$). Secondary: Rivastigmine patches and capsule provided statistically significant benefits over placebo on the ADCS-ADL, MMSE and Trail-making Test A (all $P<0.05$ vs placebo). Changes from baseline on the NPI, NPI-distress subscale, and Ten-point Clock-drawing Test in the rivastigmine groups were not significantly different from those in the placebo groups (all $P>0.05$).
Winblad et al[44] 10 cm^2 rivastigmine patch (9.5 mg/24 hours) vs 20 cm^2 rivastigmine patch (17.4 mg/24 hours) vs rivastigmine 6 mg capsules twice daily vs placebo	DD, PC, RCT Patients aged 50-85 years with MMSE scores of 10-20 diagnosed with Alzheimer's disease, all patients were required to be living with someone or to be in daily contact with a caregiver	N=1,195 Dose titration in 4-week intervals over 16 weeks and maintained at their highest well-tolerated dose for a further 8 weeks, total of 24 weeks	Primary: ADAS-Cog subscale (assess orientation, memory, language, visuospatial and praxis function), ADCS-CGIC (assess single global rating) Secondary: ADCS-ADL, MMSE, NPI, Ten Point Clock-drawing Test, and Trail-making Test part A	Primary: Patients in all rivastigmine groups (patch and capsule) showed significant improvements compared with placebo at week 24 with respect to ADAS-Cog and the ADCS-CGIC (all $P<0.05$ vs placebo). Secondary: All rivastigmine groups (patch and capsule) showed statistically significant benefits over placebo on the ADCS-ADL, MMSE and Trail-making Test part A (all $P<0.05$ vs placebo). Statistically significant treatment effects were not attained on the NPI or Ten Point Clock-drawing Test (P value not reported).

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Blesa et al[45] 10 cm^2 rivastigmine patch (9.5 mg/24 hours) vs 20 cm^2 rivastigmine patch (17.4 mg/24 hours) vs rivastigmine 6 mg capsules twice daily vs placebo	DB, DD, PC 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 week	Primary: ADCPQ Secondary: Not reported	Primary: At 8 weeks, general preference was seen for the patch: 68% of caregivers preferred the patch over capsule form (*P*<0.0001). 70% of caregivers preferred the patch due to ease of schedule (*P*<0.0001). 55% of caregivers preferred the patch due to ease of use (*P*=0.0008). At 24 weeks, general preference was seen for the patch: 72% of caregivers preferred the patch over capsule form (*P*<0.0001). 74% of caregivers preferred the patch due to ease of schedule (*P*<0.0001). 64% of caregivers preferred the patch due to ease of use (*P*<0.0001). Caregivers preferred the patch over capsule dosage form, regardless of size of patch (*P*<0.0001). At 8 weeks, caregivers indicated greater satisfaction overall (*P*<0.0001), greater satisfaction with administration (*P*<0.0001), less interference with daily life with the patch than the capsule (*P*<0.01). Secondary: Not reported
Winblad, Kawata et al.[46] 10 cm^2 rivastigmine patch (9.5 mg/24 hours) vs 20 cm^2 rivastigmine patch (17.4 mg/24 hours) vs rivastigmine 6 mg capsules twice daily vs	DB, DD, PC Active controls included different size rivastigmine patches and rivastigmine capsules	N=1,059 24 week	Primary: ADCPQ Secondary: Not reported	Primary: At 8 weeks, general preference was seen for the patch: 68% of caregivers preferred the patch over capsule form (*P*<0.0001). 70% of caregivers preferred the patch due to ease of schedule (*P*<0.0001). 55% of caregivers preferred the patch due to ease of use (*P*=0.0008). At 24 weeks, general preference was seen for the patch: 72% of caregivers preferred the patch over capsule form (*P*<0.0001). 74% of caregivers preferred the patch due to ease of schedule (*P*<0.0001). 64% of caregivers preferred the patch due to ease of use (*P*<0.0001). Caregivers preferred the patch over capsule dosage form, regardless of size of patch (*P*<0.0001). At 8 weeks, caregivers indicated greater satisfaction overall (*P*<0.0001), greater satisfaction with administration (*P*<0.0001), less interference with daily life with the patch than the capsule (*P*<0.01). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo				Not reported
Dantoine et al[47] Rivastigmine 3-12 mg/day Addition of memantine 5-20 mg/day for non-responders of rivastigmine at end of week 16	MC, OL Patients at least 50 years old with probable Alzheimer's disease according to criteria of DSM-IV, baseline scores of <18 for MMSE or scores of >4 on GDS, previously treated for at least 6 months prior with donepezil 5-10mg/day or galantamine 16-24mg/day and considered not stabilized, current stabilized medications allowed	N=202 16 weeks of rivastigmine monotherapy (Phase 1) Additional 12 weeks of rivastigmine and memantine combination therapy for non-responders of rivastigmine monotherapy (Phase 2) Total 28 weeks	Primary: MMSE Secondary: MMSE, Mini-Zarit inventory, NPI, Ten-point Clock-drawing Test, D-KEFS verbal fluency test, CGI-C	Primary: Based on MMSE scores, 46.3% of patients improved or stabilized on rivastigmine monotherapy at the end of Phase 1. For those patients previously on donepezil or galantamine, responder rates were also similar (46.6% and 46.4%). At the end of Phase 2 with combination therapy of rivastigmine and memantine, according to MMSE scores, 77.9% of patients improved or stabilized. Patients switching to combination therapy from galantamine responded more significantly than those who switched from donepezil (84.2% vs 72.3%; P=0.047). Secondary: According to CGI-C data, no change or improvement was seen in 76.5% of patients who completed the study at the end of Phase 1. For the 82.6% who worsened from baseline at the end of Phase 1, 81.4% improved or had no change at the end of Phase 2 with the addition of memantine on the CGI-C. At the end of Phase 1, MMSE and NPI showed significant improvements (P<0.001 and P<0.05, respectively) while there was no change from baseline for Ten-point Clock-drawing Test and D-KEFS verbal fluency test scores and the Mini-Zarit interview. At the end of Phase 2, D-KEFS verbal fluency test, Mini-Zarit, and especially MMSE scores showed significant improvement (P<0.05, P<0.001, and P<0.001, respectively).
Farlow et al[48] Tacrine 20 mg a day for 6 weeks	DB, PC, PG Men and women at least 50 years of age with Alzheimer's	N=468 12 weeks	Primary: ADAS, CGI-C, adverse events Secondary:	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.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs tacrine 40 mg/day for 6 weeks vs placebo for 6 weeks For the second 6 weeks, half received the same treatment and half doubled their dose (placebo to 20 mg, 20 mg to 40 mg and 40 mg to 80 mg).	disease		Not reported	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. Other treatment related adverse events included nausea and/or vomiting (8%), diarrhea (5%), abdominal pain (4%), dyspepsia (3%), and rash (3%). Secondary: Not reported
Harry et al[49] Donepezil with doses ranging from 5-10 mg/day or galantamine with doses ranging from 8-36 mg/day vs placebo	MA Patients with mild-to-moderate Alzheimer's disease, and without diagnosis of any other psychiatric or neurological disorder	N=3,353 3 donepezil studies 5 galantamine studies Duration varied	Primary: ADAS-Cog or MMSE Secondary: Not reported	Primary: The majority of patients showed no difference compared to placebo. There was no significant difference in efficacy between the groups. Secondary: Not reported
Klatte et al[50] Donepezil at least 5 mg and vitamin E at least 1,000 IU	RETRO Patients with Alzheimer's disease Data was compared	N=130 1 year	Primary: MMSE Secondary: Not reported	Primary: Patients declined at a significantly lower rate as compared with the Consortium to Establish a Registry for Alzheimer's Disease data. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	with the Consortium to Establish a Registry for Alzheimer's Disease database for patients collected prior to the availability of these treatment options.			
Wilcock et al[51] Donepezil 10 mg/day vs galantamine 24 mg/day	MC, PG, R Patients with Alzheimer's disease	N=182 52 weeks	Primary: BrADL, MMSE, ADAS-Cog, NPI Secondary: Mot reported	Primary: BrADL total score showed no significant difference between treatment groups in mean change from baseline to week 52. In terms of cognition, galantamine patients' scores on the MMSE at week 52 did not differ significantly from baseline, whereas donepezil patients' scores deteriorated significantly from baseline ($P<0.0005$). The between group difference in MMSE change, which showed a trend for increased effectiveness of galantamine, 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. Secondary: Not reported
Jones et al[52] Donepezil up to 10 mg every day vs	OL, R Patients with Alzheimer's disease	N=120 12 weeks	Primary: Ease of use and tolerability, ADAS-Cog, effects on cognition and activities of daily	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.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
galantamine up to 12 mg twice a day			living Secondary: Not reported	Activities of daily living improved significantly in the donepezil group compared with the galantamine group at weeks 4 and 12 ($P<0.05$). 46% of galantamine patients reported gastrointestinal adverse events versus 25% of donepezil patients. Secondary: Not reported
Wilkinson et al[53] Donepezil up to 10 mg every day vs rivastigmine up to 6 mg twice a day	OL, R Patients with mild-moderate Alzheimer's disease	N=111 12 weeks	Primary: ADAS-Cog, tolerability Secondary: Not reported	Primary: More patients taking donepezil completed the study (89.3%) compared to the rivastigmine group (69.1%; $P=0.009$). 10.7% of the donepezil group and 21.8% of the rivastigmine group discontinued treatment due to adverse events. 87.5% of the donepezil patients and 47.3% of the rivastigmine patients remained on the maximum approved dose of each drug at the last study visit. Both groups showed comparable improvements in ADAS-Cog administered at weeks 4 and 12. Secondary: Not reported
Mossello et al[54] Donepezil 5-10 mg vs galantamine 16-24 mg vs rivastigmine 6-12 mg	OL, OS Patients with mild-to-moderate Alzheimer's disease; 63% were taking donepezil, 32% were taking rivastigmine, and 5% were taking galantamine	N=407 9 months (212 patients completed all 9 months)	Primary: MMSE, ADL and IADL Secondary: Not reported	Primary: There were no differences amongst the three groups in regards to any of the outcome measures (galantamine was not included in the MMSE comparison due to the small number of treated subjects). Discontinuation due to adverse effects was lower in those patients on donepezil (3%) vs rivastigmine (17%; $P=0.01$) and vs galantamine (21%; $P=0.01$). Secondary: Not reported
Aguglia et al[55]	OL	N=242	Primary: MMSE, ADAS-	Primary: There were no statistical differences on changes in the MMSE, ADAS-Cog,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Donepezil vs galantamine vs rivastigmine	Patients in Italy diagnosed with Alzheimer's disease	6 months	Cog, ADL and IADL Secondary: Not reported	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. Secondary: Not reported
Lopez-Pousa et al[56] Donepezil average dose 5.87 mg/day vs galantamine average dose 14.81 mg/day vs rivastigmine average 6.41 mg/day vs 45 historical controls	OL, PRO with historical controls Patients with mild-moderate Alzheimer's disease over 6 months	N=147 6 months	Primary: MMSE Secondary: Not reported	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). Secondary: Not reported
Trinh et al[57] Cholinesterase inhibitors (donepezil, eptastigmine*, galantamine metrifonate*,	MA Trials included outpatients with mild or moderate Alzheimer's disease who were treated for at least one	29 trials Duration varied	Primary: NPI, ADAS-noncog, ADL and IADL Secondary: Not reported	Primary: Cholinesterase inhibitors improved the NPI statistically better than placebo (95% CI: 0.87 to 2.57). Cholinesterase inhibitors improved the ADAS-noncog measure numerically but not statistically compared to placebo (95% CI: 0.0 to 0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
physostigmine patch*, rivastigmine, tacrine, velnacrine*) vs placebo	month with a cholinesterase inhibitor			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). Secondary: Not reported
Lanctot et al[58] Cholinesterase inhibitors (donepezil, galantamine, rivastigmine) vs placebo	MA Adult patients diagnosed with Alzheimer's disease	N=7,954 16 trials that varied in duration	Primary: Global responders, using CGI-C, CIBIC, adverse, events, dropouts Secondary: Not reported	Primary: For cholinesterase inhibitors the pooled mean proportion of global responders was in excess by 9% when compared to the placebo treatment (9%, 95% CI: 6 to 12). In the cholinesterase inhibitor treatment groups the rates of adverse events, dropout for any reason and dropout because of adverse events were higher compared to the placebo treatment groups (8%, 95% CI: 5 to 11; 8%, 95% CI: 5 to 11; and 7%, 95% CI: 3 to 10). The number needed to treat for 1 additional patient to benefit was 7 (95% CI: 6 to 9) for stabilization or better, 12 (95% CI: 9 to 16) for minimal improvement or better and 42 (95% CI: 26 to 114) for marked improvement. The number needed to treat for 1 additional patient to experience an adverse event was 12 (95% CI: 10 to 18). Secondary: Not reported
Birks et al[59] Donepezil 10 mg/day or galantamine 24 mg/day in two doses or rivastigmine 6-12 mg/day in 2 doses vs	MA Patients diagnosed with mild, moderate or severe dementia due to Alzheimer's disease	N=7,298 Minimum 6 months	Primary: CIBIC-Plus, GBS, GDS, ADAS-Cog, MMSE, SIB, NPI, ADL scored by PDS and DAD Secondary: Withdrawals prior to 6 months,	<u>Cholinesterase inhibitor vs placebo (12 trials)</u> Primary: Significant benefit was seen in CIBIC-Plus for patients treated with a cholinesterase inhibitor over placebo; more patients were scored as "showed improvement" than "showed decline/no change" (OR 1.56, 95% CI: 1.32 to 1.85; $P<0.00001$): 8 studies. No significant difference was seen in GBS between the cholinesterase inhibitor and placebo groups at 1 year (*P* value not reported): 1 trial.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo			adverse events	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): 10 studies. 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): 9 studies. Significant benefit was seen in ADL-PDS and DAD for patients treated with a cholinesterase inhibitor over placebo (MD, 2.40, 95% CI: 1.55 to 3.37, *P*<0.00001 for PDS; and MD, 4.39, 95% CI: 1.96 to 6.81, *P*=0.0004 for DAD). Significant benefit was seen in NPI for patients treated with a cholinesterase inhibitor over placebo (MD, –2.44, 95% CI: –4.12 to –0.76; *P*=0.004). Secondary: 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> Primary: There was no statistically significant difference between the treatment groups for cognitive function, ADL scales, behavior disturbances, and global assessment (*P* values not reported). Secondary: Significantly fewer patients in the donepezil group withdrew from treatment after 2 years than in the rivastigmine group (OR, 0.64, 95% CI: 0.50 to 0.83, *P*=0.0006). Adverse events that occurred significantly more frequently at 12-16 weeks of treatment in the rivastigmine group than in the donepezil group included: nausea (*P*<0.00001), vomiting (*P*<0.00001), falls (*P*=0.01), hypertension (*P*=0.01),

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				anorexia (*P*=0.0005) and weight loss (*P*=0.001), and after 16 weeks to 2 years of treatment: nausea (*P*=0.0002), vomiting (*P*<0.00001) and anorexia (*P*=0.02). No significant difference between treatment groups for serious adverse events was noted (*P* value not reported).
Brodaty et al[60] Galantamine 2 mg/day-50 mg/day, average dose 14-15 mg/day	OL, OS, PRO Patients diagnosed with mild-to-moderately severe dementia	N=345 intent-to-treat analysis (ITT) N= 229 for per protocol-analysis (PP) 6 month follow-up	Primary: MMSE, ADAS-Cog, CIBIC-Plus, IADL Secondary: Not reported	Primary: For the MMSE 65% of PP patients had an increased score at the 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. *P* values were not reported. For ADAS-Cog at 6 months, 86% of the PP patients and 33% of the ITT patients had a decrease in ADAS-Cog score. *P* value was not reported. For CIBIC-Plus at 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 .(*P* values not reported). 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 (*P* values not reported). Most PP patients had no change in IADL scores at 3 and 6 months (*P* value not reported). Most PP patients had no change in behavior scores at 3 and 6 months (*P* value not reported). Secondary: Not reported
Auchus et al[61] Galantamine 8-24 mg/day; average dose 16.4 ± 3.98	DB, PC, PG, R Patients meeting exact criteria for probable vascular dementia	N=786 26 weeks	Primary: ADAS-cog/11, ADCS-ADL Secondary:	Primary: At the end of 26 weeks, a significant improvement was shown for ADAS-cog/11 with galantamine compared to placebo (–1.8 vs –0.3; *P*<0.001). No significant differences were found on ADCS-ADL between galantamine and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mg/day vs placebo	defined by National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences		CIBIC-Plus, NPI, EXIT-25, ADAS-cog/13, ADAS-cog/10, ADAS-cog/memory	placebo (0.7 vs 1.3; *P*=0.783). Secondary: Galantamine did not show a significant improvement versus placebo in a global clinical assessment using the CIBIC-Plus (*P*=0.069). No differences were found in NPI between the two groups, galantamine and placebo. End Exit-25 scores showed a favorable response for galantamine compared to placebo (*P*=0.041). ADAS-cog/13, ADAS-cog/10, and ADAS-cog/memory had a significantly higher response rate and improvement with galantamine compared to placebo (*P*<0.001, *P*<0.01, and *P*<0.05, respectively).
McShane et al[62] Memantine 10-30 mg/day vs placebo	MA (12 trials) Patients diagnosed with mild-to-moderate, moderate-to-severe and mild-to-moderate vascular dementia	N=not specified Duration varied	Primary: CIBIC-Plus, SIB, ADAS-Cog, ADCS-ADL, NPI Secondary: Not reported	Primary: Significant improvement at 6 months was seen for patients with mild-to-moderate dementia treated with memantine on the ADAS-Cog scale (*P*=0.03); however, there was no significant difference seen for behavior and ADL scales. Significant improvement at 6 months was seen for patients with moderate-to-severe dementia treated with memantine for the following scales: CIBIC-Plus (*P*<0.00001), SIB (*P*<0.00001), ADCS-ADL (*P*=0.003), and NPI (*P*=0.004). Patients with vascular dementia treated with memantine had significant improvement in cognition scores and behavior scores but no significant change in global rating scales (ADAS-Cog *P*=0.0002, NPI *P*=0.03).
Mild-to-Moderate Dementia Associated with Parkinson's Disease				
Emre et al [63] Rivastigmine 3-12 mg/day; average dose 8.6 mg/day vs placebo	DB, MC, PC, R Patients at least 50 years old with mild-to-moderate dementia developed 2 years after the diagnosis of Parkinson's disease according to the	N=541 Dose titration over the first 16 weeks with a subsequent assessment period of 8	Primary: ADAS-Cog, ADCS-CGIC Secondary: ADCS-ADL, NPI-10, MMSE, CDR power of attention tests, D-KEFS	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 the rivastigmine group and 23.1% in the placebo group clinically worsened in the ADCS-CGIC scores (*P*=0.007).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	clinical diagnostic criteria of the United Kingdom Parkinson's Disease Society Brain Bank and DSM-IV	weeks Total of 24 weeks	verbal fluency test, Ten Point Clock-drawing Test	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] Rivastigmine 3-12 mg/day, average dose 8.6 mg/day vs placebo	DB, MC, PC, R Patients at least 50 years old with Parkinson's disease, according to clinical diagnostic criteria of United Kingdom Parkinson's Disease Society Brain Bank, and mild-to-moderately severe dementia due to Parkinson's disease, according to DSM-IV	N=487 24 weeks	Primary: Power of attention, continuity of attention, cognitive reaction time, reaction time variability Secondary: Not reported	Primary: At week 16, there was no statistical significance from baseline scores between rivastigmine and placebo for power of attention (*P*=0.11) but there was a significance at week 24 (*P*<0.01). By week 16, there was a significant improvement with continuity of attention (*P*=0.001) compared to placebo and this parameter continued to improve at week 24 (*P*=0.0001). Cognitive reaction time showed significant improvement by the end of week 24 (*P*<0.001) 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). Secondary: Not reported
Maidment et al[65] Rivastigmine (3-12 mg/day) vs placebo	MA Patients diagnosed with mild-to-moderately severe dementia, which developed at least 2 years after Parkinson's disease was diagnosed	N=541 (1 study) 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 (*P* values not reported). Secondary: Results for MMSE significantly favored patients treated with rivastigmine over

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				placebo (WMD, 1.00, 95% CI: 0.33 to 1.67, *P*=0.003). Results for ADCS-ADL significantly favored patients treated with rivastigmine over placebo (WMD, 2.50, 95% CI: 0.43 to 4.57, *P*=0.02). Results for NPI significantly favored patients treated with rivastigmine over placebo (WMD, –2.00, 95% CI: –3.91 to –0.09, *P*=0.04). For CDR no statistically significant difference was found (*P*=0.25). For D-KEFS, results significantly favored patients treated with rivastigmine over placebo (WMD, 2.80, 95% CI: 1.47 to 4.13, *P*<0.0001). Full UPDRS was not reported. No statistically significant difference was found for motor score, including tremor (*P*=0.83 and *P*=0.84). Significantly more patients in the rivastigmine group than the placebo group experienced one or more adverse events (*P*=0.0006). Adverse events included: nausea, vomiting, tremor, and dizziness. Significantly more patients treated with rivastigmine withdrew from treatment for any reason than those treated with placebo (*P*=0.02).

*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, 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
Diagnostic Criteria: 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: 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, 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, 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, PDS=Progressive Deterioration Scale, RUSP=Resource Utilization for Severe Alzheimer Disease Patients, SIB=Severe Impairment Battery, UPDRS=Unified Parkinson's Disease Rating Scale
Miscellaneous abbreviations: LOCF=last observed case forward, PRC=prolonged-release capsule

Additional Evidence

Dose Simplification

Little evidence is available on medication adherence in Alzheimer's disease. One study that looked at pharmacy claims data suggests the probability of a new user continuing donepezil at 90 days was 0.797 +/- 0.103 and at 180 days was 0.627 +/- 0.124.[66] Additionally, 13.9% of those who continued therapy for at least 180 days showed gaps in treatment of six weeks or more. A study by Jones et al[52] assessed physician's and caregiver's satisfaction with once-a-day donepezil versus twice-daily galantamine. They reported statistically significant greater total mean scores for donepezil versus galantamine, particularly on the dosing frequency item of the Physician's and Caregiver's Satisfaction Questionnaires; however, no difference in compliance was noted. The authors reported significantly greater improvement in cognition and activities of daily living with donepezil compared to galantamine at the end of the 12 week study; but it was not clear if the differences in clinical outcomes were due to dosing frequency or other factors.

Stable Therapy

The pharmacological differences among the cholinesterase inhibitors and evidence from comparative studies support a switch strategy when a patient is intolerant to one drug or when a therapeutic dose of one drug cannot be reached.[67] One study reported that when switched from donepezil to rivastigmine, about 50% of those who had side-effects or no efficacy with donepezil tolerated or responded well to rivastigmine.[68] Another study looked at switching donepezil to galantamine with either a 4-day washout period or a 7-day washout period.[69] The authors found that there was no difference in tolerability between the two methods of conversion. One analysis reviewed 3 comparative studies, donepezil vs rivastigmine,[53] galantamine vs donepezil,[51] and donepezil vs galantamine,[52] and assessed them for quality.[70] The authors concluded that these 3 studies were methodologically flawed to the point where the validity in the outcomes was questionable.

A post hoc analysis of a 5-month trial with galantamine showed that patients had similar efficacy outcomes, whether or not they had received prior anticholinesterase therapy, suggesting that a previous failure to respond to another cholinesterase inhibitor did not predict response to galantamine.[71] On the basis of available data, it is suggested that patients not tolerating or not responding to one particular cholinesterase inhibitor may still draw benefits upon switching to another.

There is only limited guidance in the literature on the safety of switching cholinesterase inhibitors. The maintenance of a therapeutic inhibition of acetylcholinesterase throughout the switching period is desirable and, for both galantamine and rivastigmine, time is needed to reach a therapeutic dose after the start of the titration. More research is needed to establish practice guidelines for switching cholinesterase inhibitors.

Maelicke has studied risks associated with switching from donepezil to galantamine and has created a theoretical model for switching.[72] He stated that galantamine does not cause any long-lived increases in the acetylcholinesterase inhibition produced by the first drug used. Preliminary findings suggest there does not seem to be an urgent need for a washout protocol. This means the same dose escalation profile used for first-time galantamine patients could be used for patients who were exposed previously to other cholinesterase inhibitors. Because the effects of galantamine are rapidly reversible, switching from a previously used cholinesterase inhibitor to galantamine should be easy. The most conservative switch protocols (for use if adverse events occur) suggest a 1 week washout, followed by a daily dose of galantamine 8 mg (4 mg twice daily) escalated to 16 mg a day (8 mg twice daily) after 4 weeks. Another study found that a 4-day washout of donepezil was equally well tolerated as compared to a 7-day washout when switching to galantamine.[69]

Duration of therapy with cholinesterase inhibitors or memantine is controversial. Although it is clear that responding patients will return to baseline in 9 months it has been shown that without treatment these patients would have worse cognitive skills. Open label extensions have shown benefit for up to 2 years on cognitive functioning. However, the AD2000 trial showed no benefit in time to institutionalization or progression of disability for patients treated with donepezil for up to 5 years.[19]

Impact on Physician Visits

Data is not available relating to Alzheimer's treatments and impact on utilization of physician services. However, some literature is available on Alzheimer's disease and utilization of services. One study by Fillenbaum et al

looked at the probability and frequency of outpatient visits of patients with Alzheimer's disease and assessed whether stage of illness or institutionalization had any impact.[73] In this Medicare population, the number of patients with AD and a Medicare-reimbursed outpatient visit ranged from 81% to 95% and was not related to stage of dementia or institutional status.[73] Whether AD patients compared to those without AD have more physician visits has not been clearly determined due to questions about diagnosis and identification on claims. Another study showed the onset of AD 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 evaluated a care consultation multicomponent 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[76] found that in moderate-to-severe Alzheimer's disease outpatients the use of memantine was associated with a significantly less amount of total caregiver time vs placebo (51.5 hours less for the memantine group per month, 95% CI: –95.27 to –7.17, P=0.02). There were fewer patients institutionalized at week 28 in the memantine group (1) compared to the placebo group (5) which was statistically significant (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	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Parasympathomimetic (Cholinergic) Agents—Cholinesterase Inhibitors				
donepezil	orally disintegrating tablet, tablet	Aricept®, Aricept ODT®	$$$$	N/A
galantamine	extended-release capsule, solution, tablet	Razadyne®, Razadyne ER®	$$$$	N/A
rivastigmine	capsule, solution, transdermal patch	Exelon®, Exelon Patch®	$$$$	N/A
tacrine	capsule	Cognex®	$$$$$	N/A
Miscellaneous Central Nervous System Agents—NMDA Receptor Antagonist				
memantine	solution, tablet	Namenda®	$$$$	N/A

No generic products are available in this class.
N/A=not available

X. Conclusions

All four cholinesterase inhibitors have the FDA-approved indication for mild-to-moderate Alzheimer's disease (AD) while donepezil has the added indication for moderate-to-severe AD. A review of the pharmacokinetic properties of each agent shows that rivastigmine is the single agent not metabolized by the cytochrome P450 enzyme system, theoretically resulting in less potential for pharmacokinetic drug interactions. Tacrine possesses significant disadvantages over other cholinesterase inhibitors due to its association with high rates of elevated liver transaminase levels, and its four times a day dosing schedule.

Efficacy data on cognitive function from trials comparing the cholinesterase inhibitors have shown that they are equally effective. The British Association for Psychopharmacology has determined that all cholinesterase inhibitors have shown equal efficacy and differ only in frequency of side effects.[7] Better designed head-to-head studies are needed between these agents to fully evaluate their comparative efficacy. Currently, the agents in this class (excluding tacrine) remain comparable in efficacy and all show a modest improvement in the rate of decline in cognitive function.[21] Rivastigmine is uniquely indicated for symptoms of dementia in Parkinson's disease patients. However, a review by Liepelt et al describes efficacy from donepezil similar to that of rivastigmine.[77] The Quality Standards Subcommittee of the American Academy of Neurology also reported comparable efficacy between rivastigmine and donepezil.[78]

A significant amount of literature supports use of the cholinesterase inhibitors as first-line agents for mild-moderate AD. Use of donepezil, galantamine or rivastigmine in the treatment of cognitive and neuropsychiatric complications of Alzheimer's disease provides comparable outcomes. Currently there are limited head-to-head trials comparing the efficacy of the cholinesterase inhibitors and no data comparing memantine to other agents used to treat Alzheimer's disease. Memantine is an NMDA receptor antagonist and has FDA approval for moderate-to-severe dementia of AD. It has also been studied as add-on therapy with donepezil and galantamine with results suggesting better tolerability than monotherapy. The addition of memantine to any current cholinesterase regimen may confer additional benefit, particularly in the area of tolerability and caregiver burden.

With the exception of tacrine, which possesses an extensive adverse effect profile and should not be used as a first-line agent, there is insufficient clinical evidence to conclude that one cholinesterase inhibitor is safer or more efficacious than another.

Therefore, all brand cholinesterase inhibitors within the class reviewed, with the exception of tacrine, are comparable to each other and to the generics and over-the-counter products in this class and offer significant clinical advantage over other alternatives in general use. Since memantine is only indicated to treat moderate-to-severe dementia of AD, it should be reserved for this patient population and it is advisable that this agent be managed through the existing medical justification portion of the prior-authorization process.

XI. Recommendations

Alabama Medicaid should work with manufacturers of brands of cholinesterase inhibitors, excluding tacrine, on cost proposals so that at least one brand cholinesterase inhibitor is selected as a preferred agent.

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

No brand NMDA receptor antagonist is recommended for preferred status, regardless of cost.

References

1. American Psychiatric Association: diagnostic and statistical manual of mental disorders, 4th ed, text revision. [monograph on the internet]. Washington: American Psychiatric Association, 2000 [cited 2007 Jul 16]. Available from: http://online.statref.com/Document/Document.aspx?DocID=1&StartDoc=1&EndDoc=1&FxID=37&offset=151&level=2&State=False&SessionId=9FD39DGSXWDOTZNU.
2. Larson EB, Shadlen MF, Wang L, McCormick WC, Bowen JD, Teri L, Kukull WA. Survival after initial diagnosis of Alzheimer disease. Ann Intern Med. 2004 Apr 6;140(7):501-9.
3. Alzheimer's Association. Alzheimer's disease Facts and Figures, 2007 [monograph on the internet]. Washington (DC): Alzheimer's Association; 2007 [cited 2007 Sep 10]. Available from: http://www.alz.org/national/documents/Report_2007FactsAndFigures.pdf.
4. Hebert LE, Scherr PA, Bienias JL, Bennett DA, Evans DA. Alzheimer disease in the US population: prevalence estimates using the 2000 census. Arch Neurol. 2003 Aug;60(8):1119-22.
5. Knopman DS, DeKosky ST, Cummings JL, Chui H, Corey-Bloom J, et al. Practice parameter: diagnosis of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2001 May 8;56(9):1143-53 [reaffirmed 2004 Feb 13; cited 2007 Jul 3]. Available from: http://www.aan.com/practice/guideline/index.cfm?fuseaction=home.date.
6. Doody RS, Stevens JC, Beck C, Dubinsky RM, Kaye JA, Gwyther L, et al. Practice parameter: management of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2001 May 8;56(9):1154-66 [reaffirmed 2003 Oct 18; cited 2007 Jul 3]. Available from: http://www.aan.com/practice/guideline/index.cfm?fuseaction=home.date.
7. Burns A, O'Brien J. Clinical practice with anti-dementia drugs: a consensus statement from British Association for Psychopharmacology. J Psychopharmacol. 2006 [cited 2007 Sep 30];20:732-55. Available from: http://www.bap.org.uk/consensus/anti-dementia_drugs.html.
8. Aricept® [package insert]. Woodcliff Lake (NJ): Eisai, Inc; 2006 Nov.
9. Razadyne® [package insert]. Titusville (NJ): Ortho-McNeil, Inc; 2007 Apr.
10. Namenda® [package insert]. St. Louis (MO): Forest Pharmaceuticals, Inc; 2007.Apr
11. Exelon® [package insert]. East Hanover (NJ): Novartis Pharmaceuticals Corporation; 2006 Jun.
12. Cognex® [package insert on the Internet]. Atlanta (GA): Sciele Pharma, Inc; 2007 Feb [cited 2007 Oct 5]. Available from: http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=3207.
13. Autonomic drugs 12:00, Parasympathomimetic (cholinergic) agents 12:04. In: McEvoy GK, editor; American Hospital Formulary Service. AHFS drug information 2007 [monograph on the Internet]. Bethesda (MD): American Society of Health-System Pharmacists; 2007 [cited 2007 Sep 15]. Available from: http://online.statref.com/document.aspx?fxid=1&docid=307.
14. Central nervous system agents 28:00, Central nervous system agents, miscellaneous 28:92, Memantine. In: McEvoy GK, editor; American Hospital Formulary Service. AHFS drug information 2007 [monograph on the Internet]. Bethesda (MD): American Society of Health-System Pharmacists; 2007 [cited 2007 Sep 15]. Available from: http://online.statref.com/document.aspx?fxid=1&docid=702.
15. Drug Facts and Comparisons 4.0 [database on the internet]. St. Louis: Wolters Kluwer Health, Inc.; 2007 [cited 2007 Jul 16]. Available from: http://online.factsandcomparisons.com.
16. Bentue-Ferrer D, Tribut O, Polard E, Allain H. Clinically significant drug interactions with cholinesterase inhibitors: a guide for neurologists. CNS Drugs. 2003;17(13):947-63.
17. Taylor AM, Hoehns JD, Anderson DM, Tobert DG. Fatal aspiration pneumonia during transition from donepezil to rivastigmine. Ann Pharmacother. 2002 Oct;36(10):1550-3.
18. Kaduszkiewicz H, Zimmermann T, Beck-Bornholdt HP, van den Bussche H. Cholinesterase inhibitors for patients with Alzheimer's disease: systematic review of randomised clinical trials. BMJ. 2005 Aug 6;331(7512):321-7.
19. Geldmacher DS, Provenzano G, McRae T, Mastey V, Ieni JR. Donepezil is associated with delayed nursing home placement in patients with Alzheimer's disease. J Am Geriatr Soc. 2003 Jul;51(7):937-44.
20. Courtney C, Farrell D, Gray R, Hills R, Lynch L, Sellwood E, Edwards S, Hardyman W, Raftery J, Crome P, Lendon C, Shaw H, Bentham P; AD2000 Collaborative Group. Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomised double-blind trial. Lancet. 2004 Jun 26;363(9427):2105-15.
21. Birks J, Harvey RD. Donepezil for dementia due to Alzheimer's disease. Cochrane Database Syst Rev. 2006 Jan 25;(1):CD001190. doi: doi: 10.1002/14651858.CD001190.pub2.
22. Black SE, Doody R, Li H, McRae T, Jambor KM, et al. Donepezil preserves cognition and global function in patients with severe Alzheimer disease. Neurology. 2007;69:459-69.

23. Winblad B, Kilander L, Eriksson S, Minthon L, Batsman S, Wetterholm AL Jansson-Blixt C, et al; Severe Alzheimer's Disease Study Group. Donepezil in patients with severe Alzheimer's disease: double-blind, parallel-group, placebo-controlled study. Lancet. 2006 Apr 1;367(9516):1057-65.
24. Winblad B, Wimo A, Engedal K, Soininen H, Verhey F, Waldemar G, et al. 3-year study of donepezil therapy in Alzheimer's disease: effects of early and continuous therapy. Dement Geriatr Cogn Disord. 2006;21(5-6):353-63.
25. Wallin A et al. Donepezil in Alzheimer's disease: what to expect after 3 years of treatment in a routine clinical setting. Dementia and Geriatric Cognitive Disorders. 2007;23:150-60.
26. Tariot PN, Farlow MR, Grossberg GT, Graham SM, McDonald S, Gergel I; Memantine Study Group. Memantine treatment in patients with moderate-to-severe Alzheimer disease already receiving donepezil: a randomized controlled trial. JAMA. 2004 Jan 21;291(3):317-24.
27. Cumming JL, Schneider E, Tariot P, et al. Behavioral effects of memantine in Alzheimer disease patients receiving donepezil treatment. Neurology. 2006;67:57-63.
28. Rogers SL, Farlow MR, Doody RS, Mohs R, Friedhoff LT. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. Donepezil Study Group. Neurology. 1998 Jan;50(1):136-45.
29. Raskind MA, Peskind ER, Truyen L, Kershaw P, Damaraju CV. The cognitive benefits of galantamine are sustained for at least 36 months: a long-term extension trial. Arch Neurol. 2004 Feb;61(2):252-6.
30. Cummings JL, Schneider L, Tariot PN, Kershaw PR, Yuan W. Reduction of behavioral disturbances and caregiver distress by galantamine in patients with Alzheimer's disease. Am J Psychiatry. 2004 Mar;161(3):532-8.
31. Loy C, Schneider L. Galantamine for Alzheimer's disease and mild cognitive impairment. Cochrane Database Syst Rev. 2006, Issue 1.Art.No.:CD001747. DOI: 10.1002/14651858.CD001747.pub3.
32. Wilcock GK, Lilienfeld S, Gaens E. Efficacy and safety of galantamine in patients with mild-to-moderate Alzheimer's disease: multicentre randomised controlled trial. Galantamine International-1 Study Group. BMJ. 2000 Dec 9;321(7274):1445-9.
33. Dunbar F, Zhu Y, Brashear H. Post hoc comparison of daily rates of nausea and vomiting with once- and twice-daily galantamine from a double-blind, placebo-controlled, parallel-group, 6-month study. Clin Ther. 2006 Mar;28(3):365-72.
34. Brodaty H, Corey-Bloom J, Potocnik F, Truyen L, Gold M, et al. Galantamine prolonged-release formulation in the treatment of mild-to-moderate Alzheimer's disease. Dementia and Geriatric Cognitive Disorders. 2005;20:120-32.
35. Reisberg B, Doody R, Stoffler A, Schmitt F, Ferris S, Mobius HJ; Memantine Study Group. Memantine in moderate-to-severe Alzheimer's disease. N Engl J Med. 2003 Apr 3;348(14):1333-41.
36. Winblad B, Poritis N. Memantine in severe dementia: results of the 9M-Best Study (benefit and efficacy in severely demented patients during treatment with memantine). Int J Geriatr Psychiatry. 1999 Feb;14(2):135-46.
37. Winblad B, Jones RW, Wirth Y, Stoffler A, Mobius HJ. Memantine in moderate-to-severe Alzheimer's disease: a meta-analysis of randomised clinical trials. Dement Geriatr Cogn Disord. 2007;24(1):20-7.
38. Wilkinson D and Andersen HF. Analysis of the effect of memantine in reducing the worsening of clinical symptoms in patients with moderate-to-severe Alzheimer's disease. Dementia and Geriatric Cognitive Disorders. 2007;24:138-45.
39. Ott BR, Blake L, Kagan E, Resnick M; for the Memantine MEM-MD-11AB Study Group. Open label, multicenter, 28-week extension study of the safety and tolerability of memantine in patients with mild-to-moderate Alzheimer's disease. Journal of Neurology. 2007;254:351-8.
40. Burns A, Spiegel R, Quarg P. Efficacy of rivastigmine in subjects with moderately severe Alzheimer's disease. Int J Geriatr Psychiatry. 2004 Mar;19(3):243-9.
41. Birks J, Grimely EJ, Iakovidou V, Tsolaki M. Rivastigmine for Alzheimer's disease. Cochrane Database Syst Rev. 2000, Issue 4. Art. No.: CD001191. DOI: 10.1002/14651858.CD001191.
42. Rosler M, Anand R, Cicin-Sain A, Gauthier S, et al. Efficacy and safety of rivastigmine in patients with Alzheimer's disease: international randomized controlled trial. BMJ. 1999;318:633-40.
43. Winblad B, Cummings J, Andreasen N, Grossberg G, et al. A six-month double-blind, randomized, placebo-controlled study of a transdermal patch in Alzheimer's disease-rivastigmine patch versus capsule. International Journal of Geriatric Psychiatry. 2007;22:456-67.
44. Winblad B, Grossberg G, Frolich L, Farlow M, et al. IDEAL: a 6 month, double-blind, placebo-controlled study of the first skin patch for Alzheimer disease. Neurology. 2007;69(Suppl1):S14-S22.
45. Blesa R, et al. Caregiver preference for rivastigmine patches versus capsules for the treatment of Alzheimer disease. Neurology. 2007;69(Suppl 1):S23-S28.
46. Winblad B, Kawata AK, Beusterien KM, Thomas SK, Wimo A, Lane R, et al. Caregiver preference for rivastigmine patch relative to capsules for treatment of probable Alzheimer's disease. Int J Geriatr Psychiatry. 2007 May;22(5):485-91.

47. Dantoine T, Auriacombe S, Sarazin M, et al. Rivastigmine monotherapy and combination therapy with memantine in patients with moderately severe Alzheimer's disease who failed to benefit from previous cholinesterase inhibitor treatment. International Journal of Clinical Practice. 2006;60(1):110-8.
48. Farlow M, Gracon SI, Hershey LA, Lewis KW, Sadowsky CH, Dolan-Ureno J. A controlled trial of tacrine in Alzheimer's disease. The Tacrine Study Group. JAMA. 1992 Nov 11;268(18):2523-9.
49. Harry RD, Zakzanis KK. A comparison of donepezil and galantamine in the treatment of cognitive symptoms of Alzheimer's disease: a meta-analysis. Hum Psychopharmacol. 2005 Apr;20(3):183-7.
50. Klatte ET, Scharre DW, Nagaraja HN, Davis RA, Beversdorf DQ. Combination therapy of donepezil and vitamin E in Alzheimer disease. Alzheimer Dis Assoc Disord. 2003 Apr-Jun;17(2):113-6.
51. Wilcock G, Howe I, Coles H, Lilienfeld S, Truyen L, Zhu Y, Bullock R, Kershaw P; GAL-GBR-2 Study Group. A long-term comparison of galantamine and donepezil in the treatment of Alzheimer's disease. Drugs Aging. 2003;20(10):777-89.
52. Jones RW, Soininen H, Hager K, Aarsland D, Passmore P, Murthy A, Zhang R, Bahra R. A multinational, randomised, 12-week study comparing the effects of donepezil and galantamine in patients with mild-to-moderate Alzheimer's disease. Int J Geriatr Psychiatry. 2004 Jan;19(1):58-67.
53. Wilkinson DG, Passmore AP, Bullock R, Hopker SW, Smith R, Potocnik FC, Maud CM, Engelbrecht I, Hock C, Ieni JR, Bahra RS. A multinational, randomised, 12-week, comparative study of donepezil and rivastigmine in patients with mild-to-moderate Alzheimer's disease. Int J Clin Pract. 2002 Jul-Aug;56(6):441-6.
54. Mossello E, Tonon E, Caleri V, Tilli S, Cantini C, Cavallini MC, Bencini F, Mecacci R, Marini M, Bardelli F, Sarcone E, Razzi E, Biagini CA, Masotti G. Effectiveness and safety of cholinesterase inhibitors in elderly subjects with Alzheimer's disease: a "real world" study. Arch Gerontol Geriatr Suppl. 2004;(9):297-307.
55. Aguglia E, Onor ML, Saina M, Maso E. An open-label, comparative study of rivastigmine, donepezil and galantamine in a real-world setting. Curr Med Res Opin. 2004 Nov;20(11):1747-52.
56. Lopez-Pousa S, Turon-Estrada A, Garre-Olmo J, Pericot-Nierga I, Lozano-Gallego M, Vilalta-Franch M, Hernandez-Ferrandiz M, Morante-Munoz V, Isern-Vila A, Gelada-Batlle E, Majo-Llopart J. Differential efficacy of treatment with acetylcholinesterase inhibitors in patients with mild and moderate Alzheimer's disease over a 6-month period. Dement Geriatr Cogn Disord. 2005;19(4):189-95.
57. Trinh NH, Hoblyn J, Mohanty S, Yaffe K. Efficacy of cholinesterase inhibitors in the treatment of neuropsychiatric symptoms and functional impairment in Alzheimer disease: a meta-analysis. JAMA. 2003 Jan 8;289(2):210-6.
58. Lanctôt K, Herrmann N, Yau K, Khan L, Liu B et al. Efficacy and safety of cholinesterase inhibitors in Alzheimer's disease: a meta-analysis. CMAJ. 2003 Sept 16;(6) 2003;169.
59. Birks J. Cholinesterase inhibitors for Alzheimer's disease. Cochrane Database Syst Rev. 2006, Issue1.Art.No.:CD005593.DOI: 10.1002/14651858.CD005593.
60. Brodaty H et al. A Naturalistic Study of Galantamine for Alzheimer's disease. CNS Drugs. 2006;20(11):935-46.
61. Auchus AP, Brashear HR, Salloway S, et al. Galantamine treatment of vascular dementia: A randomized trial. Neurology. 2007;69:448-58.
62. McShane R, Areosa Sastre A, Minakaran N. Memantine for dementia. Cochrane Database of Systematic Reviews 2006, Issue 2.Art.No.:CD003154. DOI: 10.1002/14651858.CD003154.pub5.
63. Emre M, Aarsland D, Albanese A, et al. Rivastigmine for dementia associated with Parkinson's disease. NEJM. 2004;351(24):2509-18.
64. Wesnes KA, McKeith I, Edgar C, Emre M, Lane R. Benefits of rivastigmine on attention in dementia associated with Parkinson disease. Neurology. 2005;65:1654-6.
65. Maidment I, Fox C, Boustani M. Cholinesterase inhibitors for Parkinson's disease dementia. Cochrane Database Syst Rev. 2006, Issue 1.Art. No.: CD004747. DOI: 10.1002/14651858.CD004747.pub2.
66. Roe CM, Anderson MJ, Spivack B. How many patients complete an adequate trial of donepezil? Alzheimer Dis Assoc Disord. 2002 Jan-Mar;16(1):49-51.
67. Scarpini E, Scheltens P, Feldman H. Treatment of Alzheimer's disease: current status and new perspectives. Lancet Neurol. 2003 Sep;2(9):539-47.
68. Gauthier S, Emre M, Farlow MR, Bullock R, Grossberg GT, Potkin SG. Strategies for continued successful treatment of Alzheimer's disease: switching cholinesterase inhibitors. Curr Med Res Opin. 2003;19(8):707-14.
69. Wilkinson DG, Howe I. Switching from donepezil to galantamine: a double-blind study of two wash-out periods. Int J Geriatr Psychiatry. 2005 May;20(5):489-91.
70. Hogan DB, Goldlist B, Naglie G, Patterson C. Comparison studies of cholinesterase inhibitors for Alzheimer's disease. Lancet Neurol. 2004 Oct;3(10):622-6.
71. Emre M. Switching cholinesterase inhibitors in patients with Alzheimer's disease. Int J Clin Pract Suppl. 2002 Jun;(127):64-72.

72. Maelicke A. Pharmacokinetic rationale for switching from donepezil to galantamine. Clin Ther. 2001;23 Suppl A:A8-12.
73. Fillenbaum G, Heyman A, Peterson BL, Pieper CF, Weiman AL. Use and cost of outpatient visits of AD patients: CERAD XXII. Neurology. 2001 Jun 26;56(12):1706-11.
74. Leibson C, Owens T, O'Brien P, Waring S, Tangalos E, Hanson V, Plevak M, Kokmen E. Use of physician and acute care services by persons with and without Alzheimer's disease: a population-based comparison. J Am Geriatr Soc. 1999 Jul;47(7):864-9.
75. Clark PA, Bass DM, Looman WJ, McCarthy CA, Eckert S. Outcomes for patients with dementia from the Cleveland Alzheimer's Managed Care Demonstration. Aging Ment Health. 2004 Jan;8(1):40-51.
76. Wimo A, Winblad B, Stoffler A, Wirth Y, Mobius HJ. Resource utilization and cost analysis of memantine in patients with moderate-to-severe Alzheimer's disease. Pharmacoeconomics. 2003;21(5):327-40.
77. Liepelt I, Maetzler W, Blaicher HP, et al. Treatment of dementia in Parkinsonian syndromes with cholinesterase inhibitors. Dement Geriatr Cogn Disord. 2007;23:351–67.
78. Miyasaki JM, Shannon K, Voon V, et al. Practice Parameter: Evaluation and treatment of depression, psychosis, and dementia in Parkinson disease (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2006;66:996-1002.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Antidepressants
AHFS Class 281604
November 14, 2007

I. Overview

Antidepressants are used in the management of a variety of psychiatric disorders including mood disorders, eating disorders, premenstrual dysphoric disorders, and anxiety disorders. Anxiety disorders include obsessive-compulsive disorder, panic disorder, social anxiety disorder, and posttraumatic stress disorder. A mood disorder is defined as a disturbance in mood that is severe enough to impair a person's social, academic, or occupational functioning for a specific duration of time.[1] Major depressive disorder and dysthymic disorder are two examples of mood disorders. Some antidepressants have also been used in nonpsychiatric conditions, such as diabetic peripheral neuropathy and nocturnal enuresis in children.

Treatment for psychiatric disorders includes psychotherapy, pharmacotherapy, or the combination of the two. The decision to implement psychotherapy is dependent upon patient willingness and severity of illness. Despite the variety of pharmacologic options available, all antidepressants appear to be equally efficacious for mood disorders. Therefore, initial treatment should depend on the individual's overall medical condition and current medication profile.[2] Pharmacology, tolerability, and safety profiles differ among these classes and among individual agents. However, for all antidepressants, the Food and Drug Administration (FDA) requires manufacturers to include a black-box warning notifying prescribers of the potential for antidepressants to increase suicidal thoughts in children and adults.[3]

The antidepressants can be classified in several ways, such as by chemical structure and/or presumed mechanism of activity. The agents included in this review belong to the following American Hospital Formulary Service (AHFS) categories:[4]

Monoamine Oxidase Inhibitors (MAOIs)
Selective Serotonin- and Norepinephrine-reuptake Inhibitors (SNRIs)
Selective Serotonin-reuptake Inhibitors (SSRIs)
Serotonin Modulators
Tricyclics and Other Norepinephrine-reuptake Inhibitors
Miscellaneous Antidepressants
Miscellaneous Central Nervous System Agents—Monoamine Oxidase Inhibitors

Table 1 lists the agents included in this review. This review encompasses all dosage forms and strengths.

Table 1. Antidepressants Included in this Review

Generic Name	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Antidepressants—Monoamine Oxidase Inhibitors			
isocarboxazid	tablet	Marplan®	none
phenelzine	tablet	Nardil®	none
tranylcypromine	tablet	Parnate®*	tranylcypromine
Antidepressants—Selective Serotonin- and Norepinephrine-reuptake Inhibitors			
duloxetine	delayed-release capsule	Cymbalta®	none
venlafaxine	sustained-release capsule, tablet	Effexor®*, Effexor XR®	venlafaxine
Antidepressants—Selective Serotonin-reuptake Inhibitors			
citalopram	solution, tablet	Celexa®*	citalopram
escitalopram	solution, tablet	Lexapro®	Lexapro®

Generic Name	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
fluoxetine	capsule, delayed-release capsule, solution, tablet	Prozac®*, Prozac Weekly®, Sarafem®	fluoxetine
fluoxetine and olanzapine	capsule	Symbyax®	none
fluvoxamine	tablet	Luvox®*†	fluvoxamine
paroxetine hydrochloride	oral suspension, sustained-release tablet, tablet	Paxil®*, Paxil CR®	Paxil CR®, paroxetine
paroxetine mesylate	tablet	Pexeva®	Pexeva®
sertraline	oral concentrate, tablet	Zoloft®*	sertraline
Antidepressants—Serotonin Modulators			
nefazodone	tablet	Serzone®*†	nefazodone
trazodone	tablet	Desyrel®*	trazodone
Antidepressants—Tricyclics and Other Norepinephrine-reuptake Inhibitors			
amitriptyline	tablet	Elavil®*†	amitriptyline
amitriptyline and chlordiazepoxide	tablet	Limbitrol®*, Limbitrol DS®*	amitriptyline and chlordiazepoxide
amitriptyline and perphenazine	tablet	Etrafon A 4-10®*†	amitriptyline and perphenazine
amoxapine	tablet	Asendin®*†	amoxapine
clomipramine	capsule	Anafranil®*	clomipramine
desipramine	tablet	Norpramin®*	desipramine
doxepin	capsule, oral concentrate	Sinequan®*†	Sinequan®*†, doxepin
imipramine	capsule, tablet	Tofranil®*, Tofranil-PM®*	imipramine
maprotiline	tablet	Ludiomil*†	maprotiline
nortriptyline	capsule, solution	Pamelor®*	nortriptyline
protriptyline	tablet	Vivactil®	none
trimipramine	capsule	Surmontil®*	Surmontil®*, trimipramine
Miscellaneous Antidepressants			
bupropion	sustained-release tablet, sustained-release tablet 24 hours, tablet	Wellbutrin®*, Wellbutrin SR®*, Wellbutrin XL®*	bupropion
mirtazapine	orally disintegrating tablet, tablet	Remeron®*	mirtazapine
Miscellaneous Central Nervous System Agents—Monoamine Oxidase Inhibitors			
selegiline	transdermal patch	Emsam®‡	none

*Generic is available in at least one dosage form or strength.
†Brand is no longer available.
‡Generic is available in other dosage forms, but is not indicated for the treatment of depression.

II. Evidence Based Medicine and Current Treatment Guidelines

Treatment guidelines that incorporate the antidepressants are summarized in Table 2.

Table 2. Treatment Guidelines Using the Antidepressants

Clinical Guideline	Recommendation
American Psychiatric Association (APA): **Practice Guideline for the Treatment of Patients with Major Depressive Disorder**	• The following are recommendations for the treatment of patients older than 18 years of age and who have been diagnosed with major depressive disorder, for which other causes have been eliminated. • 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

Clinical Guideline	Recommendation
(2000)[5]	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 (if partial response), changing the antidepressant, adding psychotherapy or electroconvulsive therapy (ECT). • Switching to a different non-MAOI antidepressant to another 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 Association (APA): **Guideline Watch: Practice Guideline for the Treatment of Patients with Major Depressive Disorder, 2nd Edition (2005)** [6]	• 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. Continued 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 an SSRI approved for the acute and maintenance treatment of major depressive disorder and has shown comparable efficacy and tolerability to other antidepressants, including citalopram and venlafaxine. • Duloxetine is a selective serotonin- and norepinephrine-reuptake inhibitor (SNRI), approved for the treatment of depression, that has shown comparable efficacy to SSRIs.

Clinical Guideline	Recommendation
	• 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 Academy of Child and Adolescent Psychiatry (AACAP): **Practice Parameters for the Assessment and Treatment of Children and Adolescents with Depressive Disorders (2007)**[7]	<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.
National Institute for Health and Clinical Excellence (NICE): **Management of Depression in Primary and Secondary Care (2004)** [8]	<u>Mild depression</u> • Due to a low risk-benefit ratio, antidepressants are not recommended for the initial treatment of mild depression. • Antidepressants may be used when mild depression is resistant to other interventions, when depression is associated with psychosocial or medical problems, or in patients with a past history of moderate-to-severe depression. <u>Moderate-to-severe depression</u> • Patients at risk of harming themselves or others should be immediately referred to a specialist. • Antidepressants should be routinely offered to patients with moderate depression before psychological interventions are attempted. <u>Pharmacological treatment of Major Depressive Disorder (MDD)</u> • Therapy should be continued for at least 6 months following remission; longer treatment duration may be appropriate for some patients. • SSRIs are recommended as the initial treatment of depression. If agitation occurs early into treatment, BZDs may be used for management of this adverse event.

Clinical Guideline	Recommendation
	• In case of an inadequate response to the standard dose of an SSRI, gradual dose escalation may be appropriate. • Lack of response after 1 month of therapy may warrant switching to another antidepressant. Decision to switch therapy may be postponed for 6 weeks after initiation of drug if the patient is experiencing a partial response to the medication. • Recommended choices for a second antidepressant include a different SSRI, mirtazapine, and TCAs. • SSRIs should not be discontinued abruptly due to the risk of withdrawal symptoms and a gradual reduction of the dose over a 4-week period is appropriate (fluoxetine may be stopped sooner). <u>Pharmacological treatment of atypical depression</u> • SSRIs should be used to treat atypical depression. • Phenelzine may be considered in women who cannot tolerate or failed to achieve an adequate response with an SSRI. <u>Chronic depression</u> • Combination of pharmacological and cognitive behavioral therapy (CBT) is appropriate. <u>Treatment-resistant depression</u> • Combination of pharmacological and cognitive behavioral therapy (CBT) is appropriate. • Augmentation with lithium or another antidepressant (i.e. mirtazapine) may be considered for patients failing several antidepressants. • Augmentation with carbamazepine, lamotrigine, buspirone, pindolol, valproate, or thyroid medication is not recommended. • Augmentation with BZDs is not recommended due to insufficient evidence. • Venlafaxine may be considered after an adequate trial of 2 other antidepressants. <u>Recurrent depression</u> • Patients with a history of at least 2 recent severe depressive episodes should continue antidepressant therapy for 2 years. • Lithium is not recommended for the prevention of recurrent depressive episodes. <u>Psychotic depression</u> • Augmentation with antipsychotic should be considered.

International Consensus Group on Depression and Anxiety: **Consensus Statement on Generalized Anxiety Disorder (GAD) (2001)**[9]	<u>General Considerations</u>
	• Chronic worrying and the effects of chronic tension are the specific features that define GAD; duration of symptoms is an important factor differentiating GAD from other anxiety disorders. For a diagnosis of GAD, the symptoms of anxiety and worry should have been present for 6 months.
	• Cognitive behavioral therapy (CBT) techniques are recommended as the preferred form of psychotherapy in GAD.
	• When GAD is comorbid with depression, as it commonly is, medication is often indicated.
	
	<u>Treatment of Choice</u>
	• Antidepressants are recommended as first-line treatment of GAD. The following classes of antidepressants can be used:
	  o Selective serotonin-reuptake inhibitors (SSRIs)
	  o Serotonin- and norepinephrine-reuptake inhibitors (SNRIs)
	  o Nonsedating tricyclic antidepressants (TCAs)
	• Benzodiazepines may be used as adjunct agents in acute exacerbations of GAD or for sleep disturbances during the initiation of antidepressant therapy. Patients should be stabilized on antidepressant therapy for >4 weeks before benzodiazepines are slowly tapered off (over 4 to 8 weeks).
	• For patients with a long-term condition, with several comorbid conditions, and in

Clinical Guideline	Recommendation
	patients with an increased risk of suicide, an SSRI or SNRI is indicated. Other Therapeutic Options • Buspirone has demonstrated efficacy in GAD in most clinical trials, although it has not shown efficacy against comorbid conditions and therefore is not recommended as first-line treatment for GAD. Additional Pertinent Considerations • The guideline indicates that the only first-line use of benzodiazepines is an acute anxiety reaction, with an expected duration of 2 to 6 weeks; benzodiazepines are not appropriate for first-line treatment of GAD, which is a condition requiring appropriate long-term treatment. • Benzodiazepines are appropriate for intermittent or episodic use. • Benzodiazepines may have a role as adjunctive therapy in acute exacerbation of GAD or in sleep disturbances during the initiation of antidepressant therapy. • GAD is frequently comorbid with depressive disorders, for which benzodiazepines are not desirable, or with other anxiety disorders, for which benzodiazepine therapy is not usually favored as first-line. • The use of benzodiazepines may be a problem in the long term, due to the risk of withdrawal reactions, or in patients with a history of drug abuse or alcoholism. • The guideline indicates that hydroxyzine is used in acute anxiety states, in which it is targeting symptoms rather than treating the condition itself. • The use of hydroxyzine is similar to that of benzodiazepines; however, hydroxyzine does not cause dependence. • Hydroxyzine has no demonstrated efficacy in depression, panic disorder, social phobia, or obsessive-compulsive disorder. • Neuroleptics are not appropriate for the treatment of GAD as there is almost no clinical evidence to support their use, and they may be associated with tardive dyskinesia even in low doses.

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 (2004)**[10]	Panic Disorder General Considerations
	• Benzodiazepines are associated with a less effective outcome in the long term and should not be prescribed for panic disorder. More effective options are outlined below.
	• Sedating antihistamines or antipsychotics should not be prescribed for panic disorder.
	
	Panic Disorder Treatment Options
	Interventions with evidence for the longest duration of effect are listed in descending order, where preference of the patient should be taken into account:
	  • Psychological therapy (ie, cognitive behavioral therapy, structured problem solving, psychoeducation)
	  • Pharmacological therapy: antidepressants
	  • Self-help interventions (ie, bibliotherapy, support groups, exercise, cognitive behavioral therapy via a computer interface)
	
	Panic Disorder Additional Considerations for Pharmacologic Therapy
	• 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 (eg, paroxetine, fluvoxamine, citalopram) licensed in the United Kingdom (UK) for panic disorder should be offered; if an SSRI is not suitable, the TCAs imipramine or clomipramine may be considered.

Clinical Guideline	Recommendation

	• Side effects with the initiation of antidepressants may be minimized by starting at a low dose and increasing the dose slowly until a satisfactory therapeutic response is achieved.
	• 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, imipramine or clomipramine may be considered, or another form of therapy may be offered.
	
	<u>Generalized Anxiety Disorder General Considerations</u>
	• Benzodiazepines may be used for acute treatment, but they should not usually be used beyond 2 to 4 weeks.
	
	<u>Generalized Anxiety Disorder Treatment Options</u>
	Interventions with evidence for the longest duration of effect are listed in descending order, where preference of the patient should be taken into account:
	  • Psychological therapy (eg, cognitive behavioral therapy, structured problem solving, psychoeducation)
	  • Pharmacological therapy: antidepressants
	  • Self-help interventions (eg, bibliotherapy, support groups, exercise, cognitive behavioral therapy via a computer interface)
	
	<u>Generalized Anxiety Disorder Additional Considerations for Pharmacologic Therapy</u>
	• Unless otherwise indicated, an SSRI should be offered; if one SSRI is not suitable, another SSRI should be offered.
	• Side effects with the initiation of antidepressants may be minimized by starting at a low dose and increasing the dose slowly until a satisfactory therapeutic response is achieved.
	• 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.
	• If venlafaxine is being considered, an initial electrocardiogram (ECG) and blood pressure measurement should be undertaken and the dose should be no higher than 75 mg per day; treatment should be initiated and managed under the supervision of specialist mental health medical practitioners and regular monitoring of cardiac status is advised.
	• A number of different drugs are considered for the treatment of GAD in the guideline, including SSRIs (eg, paroxetine, fluvoxamine, citalopram), TCAs (eg, imipramine, clomipramine), benzodiazepines (eg, diazepam, alprazolam, clonazepam, lorazepam), sedating antihistamines (eg, hydroxyzine), SNRIs (eg, venlafaxine), and buspirone.
	• Antidepressants are preferred over benzodiazepines due to the potential for abuse and because antidepressants may treat comorbid depression.

International Consensus Group on Depression and Anxiety: **Consensus Statement on Panic Disorder (1998)**[11]	<u>General Considerations</u> • The goal of treatment is full remission across the syndrome: panic attacks, anxiety, phobias, well-being, and disability. • The strongest evidence for clinical efficacy exists for selective serotonin-reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), and benzodiazepines. • Monoamine oxidase inhibitors (MAOIs) have demonstrated efficacy, though the

Clinical Guideline	Recommendation
	quality of evidence is less extensive. • There is limited evidence for the use of anticonvulsants, and recommended use of valproate is confined to treatment-resistant patients. • β-Blockers should be considered an ineffective therapeutic option in panic disorder. <u>Treatment of Choice</u> • SSRIs are recommended as first-line treatment of panic disorder. • SSRI treatment is to be initiated at a low dose and increased slowly, as tolerated, to the target dose. • Effective treatment may be continued for 12 to 24 months with consideration for stopping only when the patient is well and in a stable life situation, after which treatment may be discontinued slowly over the course of 4 to 6 months; treatment should never be stopped abruptly. • Concomitant use of a benzodiazepine for a limited period (<8 weeks) may be used to help initiate treatment with an SSRI in some patients. <u>Second-line Treatment</u> • Second-line treatment is needed when a patient fails to respond to an adequate trial (8 to 12 weeks) of an SSRI at the maximum tolerated dose. • If partial response was observed and the SSRI was well tolerated, switch to another SSRI. • If an SSRI was not tolerated, initiate a trial of a benzodiazepine or a TCA. <u>Third-line Treatment</u> • An MAOI or valproate may be tried. <u>Additional Pertinent Considerations</u> • SSRIs are generally preferable to benzodiazepines or TCAs based on a review of long-term treatment data. • SSRIs may be administered in a once-daily dosing regimen (except fluvoxamine); clomipramine may be given as a single dose at bedtime; however, other TCAs require multiple dosing as do benzodiazepines. • Patients with panic disorder and a recent history of alcoholism should, except in some instances, not be prescribed benzodiazepines. • Patients who have panic disorder and a history of suicidal ideation or temporal lobe epilepsy should not be prescribed TCAs. • SSRIs are an appropriate choice of treatment for patients with panic disorders who also have concomitant depression, high suicidality, or concomitant medical illness. • SSRIs should be the preferred therapeutic option for panic disorder comorbid with other anxiety disorders (eg, obsessive-compulsive disorder) or alcoholism. • Benzodiazepines are generally well tolerated but may cause unwanted sedative effects, poor coordination, and memory problems; may potentiate the effects of alcohol; and are associated with the risk of dependence with long-term use as well as potential difficulties with withdrawal symptoms. • TCAs are associated with poor tolerability due to their anticholinergic effects, may cause weight gain, and have the potential to cause seizures as well as other safety concerns. • SSRIs have an improved tolerability over traditional TCAs and most side effects resolve over time; some SSRIs may cause initial jitteriness.
International Consensus Group on Depression and Anxiety: **Consensus Statement on Social Anxiety Disorder (SAD)**	<u>General Considerations</u> • SAD appears to predispose individuals to the development of other psychiatric disorders, most notably depression. • There is some evidence for the effectiveness of cognitive behavioral treatment in

Clinical Guideline	Recommendation
(1998)[12]	SAD; however, this is based on relatively small trials as compared to that for pharmacotherapy. <u>Treatment of Choice</u> • Selective serotonin-reuptake inhibitors (SSRIs) are recommended as first-line treatment of SAD, with most efficacy evidence for SSRIs derived from well-controlled studies with paroxetine. • The appropriate dosage regimen for paroxetine has been defined: it should be initiated at 20 mg/day for 2 to 4 weeks, and then increased as necessary. • An adequate trial of treatment with an SSRI is 6 to 8 weeks, and if effective, treatment should be continued for at least 12 months. • Long-term treatment is indicated if symptoms are unresolved, if the patient has a comorbidity or a history of relapse, or if there was an early onset of SAD. • SSRIs are also recommended for treating patients who have failed to respond to other treatments for SAD. <u>Other Therapeutic Options</u> • Phenelzine, a monoamine oxidase inhibitor (MAOI), has less evidence for efficacy in SAD and is associated with concerns about its tolerability and safety, which make it an inappropriate option for first-line treatment. • The benzodiazepine clonazepam has limited but well-controlled data for the treatment of SAD; alprazolam was shown to be significantly less effective than clonazepam for SAD, and there is no evidence that benzodiazepines as a class are effective in SAD. <u>Additional Pertinent Considerations</u> • β-Blockers do not have a place in the management of SAD; despite the benefit of their use with normal performance anxiety, there is no controlled evidence to show that β-blockers are advantageous for the pathologic anxiety of generalized SAD. Furthermore they may have harmful effects, especially in patients with asthma. • In contrast with their efficacy in panic disorder, there are no controlled data for the efficacy of tricyclic antidepressants (TCAs) in SAD. • There is no evidence for the efficacy of buspirone in SAD.
American Psychiatric Association: **Practice Guideline for the Treatment of Patients with Obsessive-Compulsive Disorder (2007)**[13]	• 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. • 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.

Clinical Guideline	Recommendation
	• 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.
The Expert Consensus Guidelines: **Treatment of Obsessive-Compulsive Disorder (1997)**[14]	• CBT and SRI therapy are recommended as first-line treatment strategies for OCD. • Fluoxetine, fluvoxamine, clomipramine, sertraline, and paroxetine are all recommended as first-line SRI options. • The dose of SRI may be increased within 4-8 weeks of initiation if the patient is not fully responding. • Experts consider 8-13 weeks to be an adequate medication trial. If patients are not responding within 8-13 weeks, medication therapy may be switched or augmented. • Venlafaxine, MAOIs and clonazepam are considered third line and may be tried when SRI therapy has not proven successful.
Obsessive-Compulsive Disorder in Children and Adolescents**:** **Treatment Guidelines (1999)**[15]	• The timely and appropriate use of medications in children and adolescents with OCD is very important. • Clomipramine has the most data to supports its use in the treatment of OCD. • Selective serotonin-reuptake inhibitors (SSRIs) seem to be better tolerated for long-term use. • Clomipramine should generally be reserved for children whose symptoms are refractory to SSRIs or in whom SSRIs are not fully efficacious. • All SSRIs seem to be equally efficacious for the treatment of OCD.
National Institute for Health and Clinical Excellence (NICE): **Obsessive-Compulsive Disorder (2005)**[16]	• 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 can not 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): **Practice Guideline for the Treatment of Patients with Acute Stress Disorder and Posttraumatic Stress Disorder (PTSD) (2004)** [17]	• 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

Clinical Guideline	Recommendation
	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.
International Consensus Group on Depression and Anxiety: **Consensus Statement Update on Posttraumatic Stress Disorder (2004)** [18]	• Trauma experienced early in life is a significant risk factor for developing a psychiatric illness later in life. • Treatment with an SSRI or cognitive behavior therapy should begin within 3-4 weeks of symptom onset, and the trial should last 2-3 months minimum. • SSRIs have the best evidence supporting their use for PTSD. • If response after 8 weeks is not optimal, consider changing the dose or switching to a different SSRI, venlafaxine or mirtazapine. • Benzodiazepines have not been proven to be effective for PTSD. • Treatment should be continued for at least one year.
American College of Obstetricians and Gynecologists (ACOG): **Practice Bulletin: Premenstrual Syndrome (2000)**[19]	• 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 (2006)**[20]	• Evidence supports the use of SSRIs as first-line therapy for severe PMS and premenstrual dysphoric disorder (PMDD). • Continuous and intermittent dosing of SSRIs appear 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 (2006)**[21]	• Patients with eating disorders should be treated with nutritional rehabilitation. • Psychosocial therapy should be used in the treatment of anorexia. • SSRIs may be considered in the treatment of anorexia. • Bupropion, tricyclic antidepressants, and monoamine oxidase inhibitors should be avoided in patients with eating disorders. • Atypical antipsychotics may be used in patients with severe symptoms. • SSRIs may be considered in patients with bulimia.

III. Indications

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[22-89]

Generic Name	Bulimia Nervosa	Depression*	GAD	Mixed Anxiety and Depressive Disorder	OCD	Panic Disorder	PMDD	PTSD	Seasonal Affective Disorder	Social Anxiety Disorder	Other
Antidepressants—Monoamine Oxidase Inhibitors											
Isocarboxazid		✔									
Phenelzine		✔ †									
Tranylcypromine		✔									
Antidepressants—Selective Serotonin- and Norepinephrine-reuptake Inhibitors											
Duloxetine		✔	✔								Diabetic Peripheral Neuropathic Pain
Venlafaxine		✔	✔ (SR)			✔ (SR)				✔ (SR)	
Antidepressants—Selective Serotonin-reuptake Inhibitors											
Citalopram		✔									
Escitalopram		✔	✔								
Fluoxetine	✔	✔			✔	✔	✔				
Fluoxetine and olanzapine		✔ ‡									
Fluvoxamine					✔						
Paroxetine hydrochloride		✔	✔ (IR)		✔ (IR)	✔	✔ (SR)	✔ (IR)		✔	
Paroxetine mesylate		✔			✔	✔					
Antidepressants—Serotonin Modulators											
Nefazodone		✔									
Trazodone		✔									
Antidepressants—Tricyclics and Other Norepinephrine-reuptake Inhibitors											
Amitriptyline		✔									
Amitriptyline and				✔							

Generic Name	Bulimia Nervosa	Depression*	GAD	Mixed Anxiety and Depressive Disorder	OCD	Panic Disorder	PMDD	PTSD	Seasonal Affective Disorder	Social Anxiety Disorder	Other
chlordiazepoxide											
Amitriptyline and perphenazine		✔ §		✔							
Amoxapine		✔ ‖									
Clomipramine					✔						
Desipramine		✔									
Doxepin		✔ ¶									(Note: Topical Product Approved for Pruritus)
Imipramine		✔									Pediatric Nocturnal Enuresis (IR)
Maprotiline		✔ #									
Nortriptyline		✔									
Protriptyline		✔									
Trimipramine		✔									
Miscellaneous Antidepressants											
Bupropion		✔							✔ (SR 24 hours)		Smoking Cessation
Mirtazapine		✔									
Miscellaneous Central Nervous System Agents—Monoamine Oxidase Inhibitors											
Selegiline		✔									

GAD=generalized anxiety disorder, IR=immediate release, OCD=obsessive-compulsive disorder, PMDD=premenstrual dysphoric disorder, PTSD=posttraumatic stress disorder, SR=sustained release

*Includes major depressive disorder

† Includes depressed patients clinically characterized as "atypical," "nonendogenous," or "neurotic", also patients with mixed anxiety and depression and phobic or hypochondriacal features

‡ Depressive episodes associated with bipolar disorder

§Includes patients with moderate-to-severe anxiety and/or agitation and depressed mood; patients with depression in whom anxiety and/or agitation are moderate or severe; patients with anxiety and depression associated with chronic physical disease; patients in whom depression and anxiety cannot be clearly differentiated; schizophrenic patients who have associated symptoms of depression

‖ Includes relief of symptoms of depression in patients with neurotic or reactive depressive disorders as well as endogenous and psychotic depressions, and also depression accompanied by anxiety or agitation

¶ Includes treatment of psychoneurotic patients with depression and/or anxiety, depression and/or anxiety associated with alcoholism or organic disease, psychotic depressive disorders with associated anxiety including involutional depression and manic-depressive disorders

Includes depressive neurosis (dysthymic disorder) and manic-depressive illness, major depressive disorder and anxiety associated with depression

IV. Pharmacokinetics

As a group, the tricyclic antidepressants are extensively metabolized in the liver by CYP450. Multiple pathways of CYP450 are involved with 2D6 and 1A2 playing the most prominent role and 2C19 playing a lesser role. Of note is the fact that amitriptyline is metabolized to nortriptyline and imipramine is metabolized into desipramine. Other members of this class with active metabolites are clomipramine, amoxapine, doxepin, and maprotiline. The pharmacokinetic parameters for the antidepressants are summarized in Table 4.

Table 4. Pharmacokinetic Parameters of the Antidepressants[22-89]

Drug	Bioavailability (%)	Protein binding (%)	Metabolism	Active metabolites	Elimination	Half-Life (hours)
Antidepressants—Monoamine Oxidase Inhibitors						
Isocarboxazid	Not reported	Not reported	Hepatic	Phenylacetic acid, Parahydroxyphenyl acetic acid	Renal	Not reported
Phenelzine	Not reported	Not reported	Hepatic	phenylacetic acid, parahydroxyphenylacetic acid and N(2)-acetylphenelzine	Renal	11
Tranylcypromine	Not reported	Not reported	Not reported	Not reported	Renal	1.5-3.5
Antidepressants—Selective Serotonin- and Norepinephrine-reuptake Inhibitors						
Duloxetine	Not Reported	>90	Hepatic	4-hydroxy duloxetine glucoronide, 5-hydroy, 6-methoxy duloxetine sulfate	Renal (70%), Feces (20%)	8-17
Venlafaxine	100	25-29	Hepatic	O-desmethylvenlafaxine	Renal	3-7
Antidepressants—Selective Serotonin-reuptake Inhibitors						
Citalopram	≈80	≈80	Hepatic	Demethylcitalopram, didemethylcitalopram, citalopram-N-oxide, deaminated propionic acid derivative	Renal (20%)	35
Escitalopram	≈80	≈56	Hepatic	S-demethylcitalopram, S-didmethylcitalopram	Renal (7%)	27-32
Fluoxetine	Not Reported	≈94.5	Hepatic	Norfluoxetine	Hepatic	24-384
Fluoxetine and olanzapine	Not Reported/ >57	≈94.5/ 93	Hepatic/ Hepatic	Norfluoxetine	Hepatic/ Renal (57%), Feces (30%)	24-384/ 21-54
Fluvoxamine	53	≈80	Hepatic	Not reported	Renal (94%)	15.6
Paroxetine hydrochloride	100	≈93-95	Hepatic	Not reported	Renal	21
Paroxetine mesylate	100	≈93-95	Hepatic	Not reported	Renal (65&0, Feces (36%)	3-65
Sertraline	Not Reported	98	Hepatic	N-desmethylsertraline	Renal (40-455), Feces (40-45%)	26; active metabolite 62-104
Antidepressants—Serotonin Modulators						
Nefazodone	≈20	>99	Hepatic	Hydroxynefazodone, meta-chlorophenylpiperazine, triazole-dione	Renal (55%), Feces (20-30%)	2-4
Trazodone	65	85-95	Hepatic	m-chlorophenylpiperazine	Renal, Feces	7-8

Drug	Bioavailability (%)	Protein binding (%)	Metabolism	Active metabolites	Elimination	Half-Life (hours)
Antidepressants—Tricyclics and Other Norepinephrine-reuptake Inhibitors						
amitriptyline	100	90-95	Hepatic	Nortriptyline	Renal (18%)	9-27
amitriptyline and chlordiazepoxide	100	90-98	Hepatic/ Hepatic	Nortriptyline/ desmethyldiazepam	Renal (18%)/ Renal	9-27/6.6-25
amitriptyline and perphenazine	100/20		Hepatic/ Hepatic	nortriptyline	Renal (18%)/ Renal, Feces	9-27/ 9-12
amoxapine	18-54	80	Hepatic	8-hydroxyamoxapine	Renal	11-16
clomipramine	20-78	97	Hepatic	Desmethylclomipramine		20-30
desipramine			Hepatic	2-hydroxydesipramine	Renal (70%)	4-6
doxepin		80-85	Hepatic	Desmethyldoxepin	Renal	6-8
imipramine	94-96	89	Hepatic	Desipramine	Renal	6-18
maprotiline	100	88	Hepatic	Desmethylmaprotiline, Maprotiline-N-oxide	Renal (70%), Feces (30%)	27-53
nortriptyline	60	93-95	Hepatic	10-hydroxynortriptyline, E-10-hydroxynortriptyline, Z-10-hydroxynortriptyline	Renal, Feces	28-31
protriptyline		92	Hepatic	Protriptyline 10,11-epoxide, 10-hydroxy protriptyline, 10,11-dihydroxy protriptyline	Renal	54-92
trimipramine	18-63	95	Hepatic		Renal	16-40
Miscellaneous Antidepressants						
bupropion	Not reported	84	Hepatic	Hydroxybupropion, threohydrobupropion, erythrohydrobupropion	Renal (87%), Feces (10%)	Terminal Phase 14; chronic dosing 21; active metabolites 20, 37, 33
mirtazapine	50	≈85	Hepatic	8-hydroxy metabolite, N-desmethyl metabolite, N-oxide metabolite	Renal (75%), feces (15%)	20-40
Miscellaneous Central Nervous System Agents—Monoamine Oxidase Inhibitors						
selegiline	25-30	≈90	Hepatic	N-desmethylselegiline, amphetamine, methamphetamine	Renal, Feces	18-25

V. Drug Interactions

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

Table 5. Significant Drug-Drug Interactions with the Antidepressants[23]

Drug(s)	Significance Level	Interaction	Mechanism
Antidepressants—Monoamine Oxidase Inhibitors (MAOIs)			
MAOIs (isocarboxazid, phenelzine, and tranylcypromine)	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

Drug(s)	Significance Level	Interaction	Mechanism
			are possible. Coadministration is contraindicated. After discontinuing an MAO inhibitor, allow at least 2 weeks before administering atomoxetine. Conversely, allow at least 2 weeks after discontinuing atomoxetine before administering an MAO inhibitor.
MAOIs (all)	1	Bupropion	Risk of acute bupropion toxicity may be increased, although the exact mechanism is unknown. Coadministration of bupropion and MAO inhibitors is contraindicated. Allow at least a 14-day window to elapse between discontinuing an MAOI and starting bupropion.
MAOIs (all)	1	Carbamazepine	A theoretical risk of severe side effects (eg, hyperpyrexia, hyper-excitability, muscle rigidity, seizures) exists, albeit by an unknown mechanism. On theoretical grounds, coadministration of carbamazepine and an MAOI is contraindicated. Discontinuation of MAOI therapy for at least 14 days prior to administration of carbamazepine is recommended.
MAOIs (all)	1	Dexmethylphenidate, and methylphenidate	The risk of hypertensive crisis exists. The precise mechanism of this interaction is unknown. Close monitoring of blood pressure during combined MAOI and methylphenidate use is recommended. Dexmethylphenidate is contraindicated in patients receiving concomitant MAOI therapy, and also for a minimum of 14 days after discontinuation of an MAOI.
MAOIs (all)	1	Dextromethorphan	Hyperpyrexia, abnormal muscle movement, hypotension, coma, and death have been associated with coadministration of these agents. This interaction may represent a "serotonin syndrome" resulting from decreased serotonin metabolism (MAO inhibitor) and decreased synaptic reuptake of serotonin (dextromethorphan). Due to the potential severity of reaction, avoid coadministration.
MAOIs (all)	1	Meperidine	Coadministration of these agents could result in adverse reactions that may result in, agitation, seizures, diaphoresis, and fever; with the potential to progress to coma, apnea, and death. Reactions may be delayed and ultimately occur several weeks following withdrawal of MAO inhibitors, although the mechanism is unknown. Avoidance of this drug combination is recommended.
MAOIs (all)	1	Selective 5-HT_1 receptor agonists (sumatriptan, rizatriptan, zolmitriptan)	Serum concentrations of certain selective 5-HT_1 receptor agonists may be elevated, increasing the risk of cardiac toxicity (eg, coronary artery vasospasm, transient myocardial ischemia), due to the inhibition of metabolism via monoamine oxidase, subtype A (MAO-A). Use of certain selective 5-HT_1 receptor agonists concomitantly or within 2 weeks following the discontinuation of an MAOI is contraindicated. If concomitant therapy is necessary, naratriptan appears to be less likely to cause this interaction.

Drug(s)	Significance Level	Interaction	Mechanism
MAOIs (all)	1	Serotonin-reuptake inhibitors (citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, nefazodone, paroxetine, sertraline, venlafaxine)	A serotonin syndrome (eg, altered consciousness, CNS irritability, myoclonus, shivering) may occur as a result of rapid, excessive accumulation of serotonin. These agents should not be coadministered. Allow at least 5 days after stopping duloxetine, 1 week after stopping nefazodone or venlafaxine, 2 weeks after stopping citalopram, escitalopram, fluvoxamine, paroxetine, or sertraline, and 5 weeks after stopping fluoxetine before initiating an MAO inhibitor. After stopping an MAO inhibitor, allow at least 2 weeks before giving any serotonin-reuptake inhibitor.
MAOIs (all)	1	Sibutramine	A "serotonin syndrome," including CNS irritability, motor weakness, shivering, myoclonus and altered consciousness, may occur, as the serotonergic effects of these agents may be additive. Concomitant administration of these agents is contraindicated. Allow at least 2 weeks after stopping MAO inhibitor therapy before starting treatment with sibutramine. Similarly, allow at least 2 weeks after stopping sibutramine therapy before starting treatment with an MAO inhibitor.
MAOIs (all)	1	Sympathomimetics (brimonidine, dopamine, ephedrine, isometheptene mucate, mephentermine, metaraminol, phenylephrine, pseudoephedrine)	Coadministration of an MAO inhibitor and an indirect- or mixed-acting sympathomimetic agent may cause hypertensive crisis. Direct-acting agents may interact minimally. When MAO is inhibited, norepinephrine accumulates and is released by indirect- and mixed-acting sympathomimetics, producing an increased pressor response at receptor sites. The coadministration of these agents should be avoided. If used together and hypertension develops, administer phentolamine. Brimonidine is contraindicated in patients receiving MAO inhibitors.
MAOIs (all)	1	Tricyclic antidepressants (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)	Hyperpyretic crises, convulsions, and death have occurred as a result of this interaction, although the exact mechanism is unclear. Tricyclic antidepressants (TCAs) should not be used with or within 2 weeks of MAO inhibitor therapy.
MAOIs (all)	2	Insulin	Coadministration of MAO inhibitors may potentiate the hypoglycemic response to insulin and delay recovery from hypoglycemia. It is believed that this interaction may be the result of stimulation of insulin secretion and inhibition of gluconeogenesis. Blood glucose concentrations should be monitored closely and insulin dosage requirements should be adjusted as necessary.
MAOIs (all)	2	Sulfonylureas (chlorpropamide, glimepiride, glipizide, glyburide, tolazamide, tolbutamide)	MAO inhibitors enhance the hypoglycemic action of sulfonylureas through an unknown mechanism. If a patient develops hypoglycemia while taking both medications, dosing adjustments should be made to achieve euglycemia.

Drug(s)	Significance Level	Interaction	Mechanism
Antidepressants—Selective Serotonin- and Norepinephrine-reuptake Inhibitors			
Venlafaxine	1	Sibutramine	A "serotonin syndrome," including CNS irritability, motor weakness, shivering, myoclonus, and altered consciousness, may occur, as the serotonergic effects of these agents may be additive. Concomitant administration of these agents is not recommended by the manufacturer. If concurrent use cannot be avoided, careful patient monitoring for adverse effects is advised. The serotonin syndrome requires immediate medical attention if encountered.
Duloxetine and venlafaxine	1	Linezolid	Serotonin syndrome (eg, agitation, altered consciousness, ataxia, myoclonus, overactive reflexes, shivering) may occur, possibly due to excessive accumulation of serotonin. Coadminister linezolid and SRIs with caution. Because linezolid has MAOI activity, allow at least 2 weeks between stopping linezolid and starting an SRI.
Duloxetine and venlafaxine	1	Selective 5-HT_1 receptor agonists (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan)	Serotonin syndrome, including agitation, overactive reflexes, ataxia, shivering, myoclonus, and altered consciousness, may occur in some patients, as a result of rapid accumulation of serotonin in the CNS. If coadministration of these agents is indicated, start with low dosages and closely monitor patients for adverse events. Be prepared to provide supportive care, stop the serotonergic agent, and give an antiserotonergic agent (eg, cyproheptadine) if warranted.
Duloxetine and venlafaxine	1	Thioridazine	Thioridazine plasma concentrations may be elevated, increasing the risk of life-threatening ventricular arrhythmias and sudden death as a result of the inhibition of thioridazine metabolism by duloxetine via the CYP2D6 system. Do not coadminister thioridazine with duloxetine.
Duloxetine and venlafaxine	1	Tramadol	Serotonin syndrome (eg, agitation, altered consciousness, ataxia, myoclonus, overactive reflexes, shivering) may occur, as the serotonergic effects of these agents may be additive. Closely monitor patients for adverse reactions. Serotonin syndrome requires immediate medical attention, including withdrawal of the serotonergic agent and supportive care.
Duloxetine	2	Propafenone	Plasma propafenone levels may be elevated, increasing the pharmacologic effects and potential adverse reactions. Certain SRIs may inhibit the metabolism (CYP2D6) of propafenone, thus careful monitoring of cardiac function is warranted when coadministration is necessary. Citalopram does not inhibit CYP2D6 and may be a safer alternative.
Venlafaxine	2	Azole antifungals (fluconazole, itraconazole, ketoconazole, voriconazole)	Venlafaxine plasma levels may become elevated, increasing the potential for adverse effects. While CYP2D6 is the major pathway for venlafaxine metabolism, CYP3A4 inhibition by azole antifungal agents may be an important factor in poor

Drug(s)	Significance Level	Interaction	Mechanism
			metabolizers. In patients receiving venlafaxine, closely observe the clinical response when starting or stopping azole antifungal agents, as the therapeutic response to venlafaxine may be altered. Be prepared to adjust therapy as needed.
Venlafaxine	2	Cyproheptadine	Decreased pharmacologic effects of SRIs 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.
Venlafaxine	2	Sympathomimetics (amphetamine, amphetamine/ dextroamphetamine, benzphetamine, dextroamphetamine, diethylpropion, methamphetamine, phendimetrazine, phentermine)	Increased sensitivity to sympathomimetic effects and increased risk of serotonin syndrome may result through an unknown mechanism. If these agents must be used concurrently, monitor for increased CNS effects and adjust therapy as needed.
Antidepressants—Selective Serotonin-reuptake Inhibitors (SSRIs)			
Fluoxetine	1	Phenothiazines (chlorpromazine, thioridazine)	Phenothiazine plasma concentrations may be elevated, increasing the risk of life-threatening cardiac arrhythmias, including torsades de pointes. Fluoxetine may inhibit the metabolism of phenothiazines through the CYP2D6 system. Thioridazine is contraindicated in patients already receiving fluoxetine. Closely monitor ECGs when coadministering fluoxetine and a phenothiazine.
Paroxetine	1	Digoxin	Digoxin serum concentrations may be elevated, increasing the pharmacologic and toxic effects. Inhibition of renal tubular P-glycoprotein excretion of digoxin by paroxetine is suspected, therefore, patients receiving digoxin, closely monitor digoxin serum levels and observe the patient for signs of digitalis toxicity when paroxetine is coadministered. Adjustment of the digoxin dose should be altered as needed. Since citalopram and venlafaxine have less of an effect on P-glycoprotein, they may be less likely to interact with digoxin.
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. Clozapine dose adjustments should be made as needed.
SSRIs (citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, nefazodone, paroxetine, sertraline, venlafaxine)	1	Linezolid	Serotonin syndrome (eg, agitation, altered consciousness, ataxia, overactive reflexes, shivering) may occur as a result of excessive accumulation of serotonin. The coadministration of linezolid and SRIs should be handled with caution. Since linezolid has MAOI activity, allow at least 2 weeks between stopping linezolid and starting an SSRI.

Drug(s)	Significance Level	Interaction	Mechanism
SSRIs (citalopram, sertraline)	1	Pimozide	The risk of life-threatening cardiac arrhythmias, including torsades de pointes, may be increased, although the precise mechanism is unknown. The concurrent administration of pimozide with citalopram or sertraline is contraindicated.
SSRIs (citalopram, duloxetine, fluoxetine, fluvoxamine, nefazodone, paroxetine, sertraline, venlafaxine)	1	Selective 5-HT_1 receptor agonists (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan)	Serotonin syndrome, including agitation, overactive reflexes, ataxia, shivering, myoclonus, and altered consciousness, may occur in some patients as a result of rapid accumulation of serotonin in the CNS. If coadministration of these agents is indicated, lower starting dosages and close monitoring is recommended. Readiness to provide supportive care, stop the serotonergic agent, and give an antiserotonergic agent (eg, cyproheptadine) is necessary.
SSRIs (fluoxetine, fluvoxamine, nefazodone, paroxetine, sertraline, venlafaxine)	1	Sibutramine	A "serotonin syndrome," including CNS irritability, motor weakness, shivering, myoclonus, and altered consciousness, may occur, since the serotonergic effects of these agents may be additive. Concomitant administration of these agents is not recommended by the manufacturer. If concurrent use cannot be avoided, carefully monitor the patient for adverse effects. The serotonin syndrome requires immediate medical attention.
SSRIs (fluoxetine, paroxetine, sertraline)	1	Risperidone	Risperidone plasma concentrations may be elevated, increasing the risk of side effects. Serotonin syndrome (eg, altered consciousness, CNS irritability, increased muscle tone, myoclonus) 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. Close observation of the clinical response to risperidone when starting, stopping, or changing the dose of fluoxetine or paroxetine, or when giving high sertraline doses (more than 100 mg/day) should be employed. Dose adjustments of risperidone should be managed as needed.
SSRIs (citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, nefazodone, paroxetine, sertraline, venlafaxine)	1	Tramadol	Serotonin syndrome (eg, agitation, altered consciousness, ataxia, myoclonus, overactive reflexes, shivering) may occur, as the serotonergic effects of these agents may be additive. Close monitoring for adverse reactions is advised. Serotonin syndrome requires immediate medical attention, including withdrawal of the serotonergic agent and supportive care.
Fluoxetine	2	Carbamazepine	Serum carbamazepine levels may be increased, producing possible toxicities by an unknown mechanism. However, fluoxetine is known to inhibit the metabolism of other drugs, suggesting that this may be a potential mechanism involved in the interaction. The close monitoring of serum carbamazepine levels during concurrent administration of fluoxetine is recommended. Adjustment of carbamazepine dose advised.

Drug(s)	Significance Level	Interaction	Mechanism
Fluoxetine	2	Hydantoins (ethotoin, fosphenytoin, phenytoin)	Serum hydantoin concentrations may be elevated, producing an increase in the pharmacologic and toxic effects, possibly by the inhibition of hydantoin metabolism by fluoxetine. Close monitoring of hydantoin levels and observing patients for toxicity or loss of therapeutic activity if fluoxetine is started or stopped is advised. Adjustment of the hydantoin dose as needed is recommended.
Fluoxetine	2	Ritonavir	The area under the curve (AUC) of ritonavir may be increased. Serotonin syndrome (eg, CNS irritability, increased muscle tone, myoclonus, and altered consciousness) may occur as a result of coadministration. Fluoxetine and ritonavir may inhibit the CYP2D6 metabolism of each other, resulting in the need for close monitoring of adverse effects. Serotonin syndrome requires immediate medical attention, including withdrawal of fluoxetine and supportive care.
Fluvoxamine	2	Methadone	Increased serum methadone concentrations with possible toxicity may result. Fluvoxamine may inhibit the hepatic metabolism of methadone. As a result the starting and stopping of fluvoxamine therapy should be handled with caution in patients receiving methadone maintenance treatment.
Fluvoxamine	2	Ropivacaine	Ropivacaine plasma concentrations may be elevated, potentially prolonging the pharmacologic effects and increasing the risk of toxicities. Fluvoxamine may inhibit the metabolism of ropivacaine via the CYP1A2 system. In patients receiving fluvoxamine, administer ropivacaine with caution and monitor for ropivacaine toxicities regularly. Adjust the dose of ropivacaine as needed.
Fluvoxamine	2	Tacrine	Plasma tacrine concentrations may be elevated, increasing the pharmacologic and adverse effects, possibly by the CYP1A2 inhibition of tacrine metabolism by fluvoxamine. If this combination cannot be avoided, monitor for side effects, including hepatotoxicity, when fluvoxamine is initiated in patients receiving tacrine or if both drugs are started concomitantly. Other selective serotonin-reuptake inhibitors that are not metabolized by CYP1A2 might be safer alternatives.
Fluvoxamine	2	Theophyllines (aminophylline, theophylline)	Increased theophylline serum concentrations with possible toxicities. Fluvoxamine inhibits the hepatic metabolism (CYP1A2) of theophylline, so close monitoring of theophylline levels is warranted when fluvoxamine therapy is started or stopped. Adjustments to the theophylline dosing should be manipulated as needed. A 33% reduction in theophylline dose has been recommended when starting theophylline in patients receiving fluvoxamine.

Drug(s)	Significance Level	Interaction	Mechanism
Fluvoxamine	2	Tizanidine	Tizanidine plasma concentrations may be elevated, increasing the pharmacologic and adverse reactions (eg, hypotension). Inhibition of tizanidine metabolism (CYP1A2) by fluvoxamine is suspected as a potential mechanism. Coadministration of tizanidine and fluvoxamine is contraindicated.
Paroxetine	2	Phenothiazines (chlorpromazine, fluphenazine, methotrimeprazine, perphenazine, prochlorperazine, promethazine, thiethylperazine, thioridazine, trifluoperazine)	Phenothiazine plasma levels may be elevated, increasing the pharmacologic and adverse effects, including the risk of life-threatening cardiac arrhythmias with thioridazine, secondary to the decreased metabolism (CYP2D6) of the phenothiazine. Thioridazine is contraindicated in patients receiving paroxetine, and it may be necessary to decrease the usual starting dose of other phenothiazines in patients whose paroxetine therapy is at steady-state. In patients receiving a phenothiazine, careful observation of the clinical response when starting, stopping, or changing the dose of paroxetine is necessary. Adjust the phenothiazine dose as needed.
SSRIs (fluoxetine, fluvoxamine, paroxetine, sertraline)	2	Cyclosporine	Serotonin-reuptake inhibitors may increase cyclosporine concentrations via the CYP3A4 inhibition of cyclosporine metabolism, resulting in various toxicities. Close monitoring of cyclosporine trough whole blood concentrations when adding or discontinuing a serotonin-reuptake inhibitor is warranted, with the subsequent adjustment of the cyclosporine dose as needed.
SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, nefazodone, paroxetine, sertraline, venlafaxine)	2	Cyproheptadine	Decreased pharmacologic effects of SRIs 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 (fluoxetine, paroxetine)	2	Metoclopramide	Metoclopramide plasma concentrations may be elevated, secondary to the inhibition of metoclopramide metabolism (CYP2D6) by certain serotonin-reuptake inhibitors, increasing the risk of adverse reactions. Close monitoring for adverse reactions to metoclopramide during coadministration of certain serotonin-reuptake inhibitors is warranted. Adjustment of the metoclopramide dose as needed is recommended.
SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline)	2	Nonsteroidal anti-inflammatory drugs (diclofenac, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamate, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, piroxicam, sulindac, tolmetin)	The risk of upper gastrointestinal (GI) bleeding may be increased, although the specific mechanism is unknown. If coadministration of these agents cannot be avoided, consider shortening the nonsteroidal anti-inflammatory drug (NSAID) treatment duration, decreasing the dose, or replacing the NSAID with acetaminophen, or the SSRI with a tricyclic antidepressant (TCA). If GI adverse reactions occur, consider interventional therapy (eg, proton pump inhibitor) or discontinuing the SSRI or NSAID and giving an alternative therapy.

Drug(s)	Significance Level	Interaction	Mechanism
SSRIs (fluoxetine, fluvoxamine, nefazodone)	2	Phosphodiesterase type 5 inhibitors (sildenafil, tadalafil, vardenafil)	Phosphodiesterase Type 5 (PDE5) inhibitor plasma levels may be elevated as a result of the inhibition of PDE5 inhibitor metabolism (CYP3A4) by certain SRIs, thus increasing the risk of adverse reactions. Until more clinical data are available, administer PDE5 inhibitors with caution to patients receiving certain SRIs. Consider reducing the initial dose of the PDE5 inhibitor if coadministration cannot be avoided.
SSRIs (duloxetine, fluoxetine, paroxetine, sertraline)	2	Propafenone	Plasma propafenone levels may be elevated, increasing the pharmacologic and adverse reactions. Certain SRIs may inhibit the metabolism (CYP2D6) of propafenone, so careful monitoring of cardiac function if SRIs are coadministered with propafenone. Citalopram does not inhibit CYP2D6 and may be a safer alternative.
SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine, venlafaxine)	2	Sympathomimetics (amphetamine, amphetamine/ dextroamphetamine, benzphetamine, dextroamphetamine, diethylpropion, methamphetamine, phendimetrazine, phentermine)	Increased sensitivity to sympathomimetic effects and increased risk of serotonin syndrome are possible, through an unknown mechanism. If these agents must be used concurrently, monitor for increased CNS effects and adjust therapy as needed.
Antidepressants—Serotonin Modulators			
Nefazodone	1	Carbamazepine	Elevated serum carbamazepine levels with possible increase in side effects and lower nefazodone levels with 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	1	Cisapride	Increased cisapride plasma concentrations with cardiotoxicity may occur. Nefazodone may inhibit the hepatic metabolism (CYP3A4) of cisapride. The coadministration of cisapride and nefazodone is contraindicated.
Nefazodone	1	Eplerenone	Elevated eplerenone plasma concentrations, which may increase the risk of hyperkalemia and associated serious, sometimes fatal, arrhythmias, may result as nefazodone inhibits the metabolism (CYP3A4) of eplerenone. Coadministration of eplerenone and nefazodone is contraindicated.
Nefazodone	1	HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin)	With certain HMG-CoA reductase inhibitors, the risk of rhabdomyolysis and myositis may be increased secondary to nefazodone inhibiting the metabolism of HMG-CoA reductase inhibitors metabolized by CYP3A4. If coadministration of these agents cannot be avoided, advise patients to report any unexplained muscle pain, tenderness, or weakness. Since

Drug(s)	Significance Level	Interaction	Mechanism
			CYP3A4 is not the principal isozyme responsible for fluvastatin or pravastatin metabolism, these drugs may be less likely to interact and may be safer alternatives.
Nefazodone	1	Linezolid	Serotonin syndrome (eg, agitation, altered consciousness, ataxia, myoclonus, overactive reflexes, shivering) may occur, secondary to excessive accumulation of serotonin. Coadministration of linezolid and SRIs should be handled with caution. Since linezolid has MAOI activity, allow at least 2 weeks between stopping linezolid and starting an SRI.
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	Selective 5-HT_1 receptor agonists (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan)	Serotonin syndrome, including agitation, overactive reflexes, ataxia, shivering, myoclonus, and altered consciousness, may occur in some patients due to a rapid accumulation of serotonin in the CNS. If coadministration of these agents is indicated, start with low dosages and closely monitor patients. Readiness to provide supportive care, stop the serotonergic agent, and give an antiserotonergic agent (eg, cyproheptadine) is necessary.
Nefazodone	1	Sibutramine	A "serotonin syndrome," including CNS irritability, motor weakness, shivering, myoclonus, and altered consciousness, may occur, as the serotonergic effects of these agents may be additive. Concomitant administration of these agents is not recommended by the manufacturer. If, however, concurrent use cannot be avoided, careful monitoring of the patient for adverse effects is advised, as serotonin syndrome requires immediate medical attention.
Nefazodone	1	Tramadol	Serotonin syndrome (eg, agitation, altered consciousness, ataxia, myoclonus, overactive reflexes, shivering) may occur, as the serotonergic effects of these agents may be additive Close monitoring of patients for adverse reactions is advised, as serotonin syndrome requires immediate medical attention, including withdrawal of the serotonergic agent and supportive care.
Nefazodone	2	Corticosteroids (dexamethasone, hydrocortisone, methylprednisolone)	The pharmacologic and adverse effects of certain corticosteroids may be enhanced. Inhibition of corticosteroid metabolism (CYP3A4) and increased duration of cortisol suppression are suspected mechanisms for this interaction. A reduction in the dose of certain corticosteroids may be warranted when nefazodone is started and a dose increase may be warranted when nefazodone is discontinued.
Nefazodone	2	Cyclosporine	Cyclosporine concentrations and toxicities may be increased as nefazodone may inhibit the metabolism

Drug(s)	Significance Level	Interaction	Mechanism
			(CYP3A4) of cyclosporine. Close monitoring of cyclosporine trough whole blood concentrations when nefazodone is started or stopped is recommended. Dosage adjustments of cyclosporine as needed are advised.
Nefazodone	2	Cyproheptadine	Decreased pharmacologic effects of SRIs 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.
Nefazodone	2	Phosphodiesterase type 5 inhibitors (sildenafil, tadalafil, vardenafil)	Phosphodiesterase Type 5 (PDE5) inhibitor plasma levels may be elevated, increasing the risk of adverse reactions, secondary to the inhibition of PDE5 inhibitor metabolism (CYP3A4) by certain SRIs. Until more clinical data are available, administer PDE5 inhibitors with caution to patients receiving SRIs. Consider reducing the initial dose of the PDE5 inhibitor if coadministration cannot be avoided.
Trazodone	2	Protease inhibitors (amprenavir, atazanavir, fosamprenavir, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir, saquinavir)	Trazodone plasma concentrations may be elevated, increasing the pharmacologic and adverse effects. The suspected mechanism of this interaction is caused by the inhibition of trazodone metabolism (CYP3A4) by protease inhibitors. Monitor the patient for a change in trazodone effect if a protease inhibitor is started or stopped. Dosage adjustments of trazodone as needed are recommended.
Trazodone	2	Warfarin	The hypoprothrombinemic effect of warfarin may be decreased, potentially resulting in suboptimal anticoagulation with possible disease exacerbations occurring. The exact mechanism of this interaction is unknown. Close and frequent monitoring of anticoagulant parameters when starting or stopping trazodone is advised, and preparedness to adjust anticoagulant dose is necessary. As needed use of trazodone in patients receiving anticoagulants should be avoided.
Antidepressants—Tricyclics and Other Norepinephrine-reuptake Inhibitors			
Tricyclic antidepressants (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)	1	Cisapride	The risk of life-threatening cardiac arrhythmias, including torsades de pointes, may be increased, due to the possible additive prolongation of the QT interval. Cisapride is contraindicated in patients receiving tricyclic antidepressants.
Tricyclic antidepressants (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)	1	Clonidine	Loss of blood pressure control and possibly life-threatening elevations in blood pressure may result, possibly by the inhibition of the central alpha$_2$-adrenergic receptors by the tricyclic antidepressants. The combination of clonidine and tricyclic antidepressants should be avoided by using other antihypertensive agents or non-tricyclic antidepressants, if possible.
Tricyclic antidepressants (amitriptyline, amoxapine,	1	Quinolones (gatifloxacin, levofloxacin,	The risk of life-threatening cardiac arrhythmias, including torsades de pointes, may be increased,

Drug(s)	Significance Level	Interaction	Mechanism
clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)		moxifloxacin, sparfloxacin)	although the exact mechanism is unknown. Sparfloxacin is contraindicated in patients receiving drugs that prolong the QTc interval (eg, tricyclic antidepressants). Levofloxacin should be avoided, while gatifloxacin and moxifloxacin should be used with caution. Other quinolone antibiotics that do not prolong the QTc interval or are not metabolized by the CYP3A4 isozyme may be suitable alternatives.
Tricyclic antidepressants (amitriptyline, imipramine, nortriptyline)	2	Azole antifungals (fluconazole, ketoconazole)	Serum tricyclic antidepressant levels may be elevated, resulting in an increase in therapeutic and adverse effects, including cardiac arrhythmias. The inhibition of tricyclic antidepressant metabolism (CYP2C9 by fluconazole; CYP3A4 by ketoconazole) is a suspected mechanism for this interaction. Close monitoring of the patient's clinical response and tricyclic antidepressant serum concentrations when starting or stopping azole antifungal agents is recommended. Adjusting the dose of the tricyclic antidepressants as needed is advised.
Tricyclic antidepressants (amitriptyline, desipramine, doxepin, imipramine, nortriptyline)	2	Carbamazepine	Serum carbamazepine (CBZ) levels may be elevated, increasing pharmacologic and toxic effects, while tricyclic antidepressants (TCA) levels may be decreased. TCAs may compete with CBZ for hepatic microsomal enzyme metabolism, and CBZ may induce the hepatic metabolism of TCAs. Monitoring of CBZ and TCA levels is advised. Patients should be observed for signs of toxicity or loss of therapeutic effect when either drug is added to or discontinued from the treatment regimen. Dosage adjustments as needed are advised.
Tricyclic antidepressants (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)	2	Cimetidine	Increased serum concentrations of the tricyclic antidepressants (TCA) may occur (mild symptoms have been noted) as a result of the interference with the metabolism of the TCA and decreased first-pass effects. The result of this interaction may yield an increased bioavailability and elevated serum concentrations. Tricyclic antidepressant serum concentrations should be monitored when cimetidine is used, and for several days after cimetidine is started or stopped. Reductions in TCA doses as needed may be warranted.
Tricyclic antidepressants (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)	2	Dicumarol	Tricyclic antidepressants (TCAs) may increase the half-life or bioavailability of dicumarol, possibly resulting in increased anticoagulation actions. The TCA may possibly impairment dicumarol's liver degradation. Increased dicumarol absorption may also be involved. Close monitoring of prothrombin times is recommended, and patients should be observed for signs of bleeding. The dose of dicumarol may need to be decreased.
Tricyclic antidepressants (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine,	2	Fluoxetine	The pharmacologic and toxic effects of tricyclic antidepressants (TCAs) may be increased, as fluoxetine may inhibit the TCA's hepatic metabolism. Patients should be observed for signs of

Drug(s)	Significance Level	Interaction	Mechanism
nortriptyline, protriptyline, trimipramine)			TCA toxicity and the monitoring of TCA levels is advised. Dosage adjustments should be altered as necessary. When adding fluoxetine, it may be necessary to decrease the TCA dose by as much as 75% due to this interaction. It is recommended to start with lower than usual TCA doses when giving the drugs concomitantly and up to several weeks after fluoxetine therapy is discontinued.
Tricyclic antidepressants (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)	2	Fluvoxamine	The pharmacologic and toxic effects of tricyclic antidepressants (TCAs) may be increased, as fluvoxamine may inhibit the oxidative metabolism (CYP2D6) of the TCA. If this combination cannot be avoided, the dose of the TCA may need to be reduced during coadministration with fluvoxamine. Careful observation of clinical response and serum TCA concentrations are advised when concurrent therapy is started or stopped. The use of a TCA that does not undergo oxidative metabolism, such as desipramine, may avoid this interaction.
Tricyclic antidepressants (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)	2	Guanethidine	The hypotensive action of guanethidine is blocked. The mechanism by which this occurs is thought to be the inhibition of the uptake of guanethidine into the nerve terminal, its site of action. Close monitoring of blood pressure or the utilization of an alternative antihypertensive therapy is advised.
Tricyclic antidepressants (amitriptyline, desipramine, imipramine, nortriptyline)	2	Paroxetine	The pharmacologic and toxic effects of certain tricyclic antidepressants (TCAs) may be increased. Paroxetine may inhibit the metabolism of certain TCAs (eg, desipramine) in some patients (eg, extensive metabolizers of sparteine) and may increase metabolism in some patients (eg, poor metabolizers of sparteine). Observation of the patient for signs of TCA toxicity and TCA plasma level monitoring is advised. Adjustment of the TCA dose as necessary when starting or stopping paroxetine may be necessary. Careful evaluation for signs of "serotonin syndrome" (eg, altered mental status, autonomic dysfunction, neuromuscular abnormalities) are advised, and preparedness to discontinue TCA therapy and treat as indicated is recommended.
Tricyclic antidepressants (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)	2	Rifamycins (rifabutin, rifampin)	Tricyclic antidepressants (TCA) levels may be decreased, resulting in a decrease in pharmacologic effects, as the hepatic metabolism of TCAs may be increased. Considerations to monitor TCA concentrations when starting, discontinuing, or altering the dose of rifampin is advised. Dose adjustments to the TCA may be warranted.
Tricyclic antidepressants (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)	2	Sertraline	The pharmacologic and toxic effects of tricyclic antidepressants (TCAs) may be increased. "Serotonin syndrome" has been reported, probably due to the inhibition of TCA hepatic metabolism (CYP2D6). If this combination cannot be avoided, observe the patient for signs of TCA toxicity and monitor TCA plasma levels accordingly. Adjustment of the TCA

Drug(s)	Significance Level	Interaction	Mechanism
			dose when starting or stopping sertraline may be necessary. Careful evaluation for signs of "serotonin syndrome" (eg, altered mental status, autonomic dysfunction, neuromuscular abnormalities) are advised, and preparedness to discontinue TCA therapy and treat as indicated is recommended.
Tricyclic antidepressants (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)	2	Sympathomimetics (dobutamine, dopamine, ephedrine, epinephrine, metaraminol, norepinephrine, phenylephrine, neo-synephrine)	Tricyclic antidepressants potentiate the pressor response of the direct-acting sympathomimetics, potentially resulting in arrhythmias. The pressor response to the indirect-acting sympathomimetics is decreased by the tricyclic antidepressants, as they may inhibit the reuptake of the sympathomimetics in the neuron, increasing or decreasing their sensitivity at the receptor. If these agents must be used concurrently, a dosage adjustment of the sympathomimetic may be necessary. Close monitoring for arrhythmias and hypertension is advised.
Tricyclic antidepressants (amitriptyline, desipramine, imipramine, nortriptyline)	2	Terbinafine	The pharmacologic and toxic effects of tricyclic antidepressants (TCAs) may be increased, due to the suspected inhibition of TCA metabolism (CYP2D6) by terbinafine. Close monitoring for signs of TCA toxicity if terbinafine is coadministered is advised and dose adjustments of the TCA dose may be necessary.
Tricyclic antidepressants (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)	2	Valproic acid (divalproex sodium, valproate sodium, valproic acid)	Plasma concentrations and side effects of the tricyclic antidepressants (TCA) may be increased, due to the decreased first-pass metabolism and inhibition of hepatic metabolism of the TCA. Close monitoring of the plasma TCA concentrations and clinical response of the patient when valproic acid is started or stopped is recommended. In patients stabilized on valproic acid, it may be prudent to start with a conservative dose of the TCA, and adjust the dose as needed.
Miscellaneous Antidepressants			
Bupropion	2	Carbamazepine	Serum concentrations of bupropion may be decreased, reducing its pharmacologic effects, since carbamazepine increases the hepatic metabolism (CYP3A4) of bupropion. Close monitoring of clinical response and adjustments in therapy is advised.
Bupropion	2	Rifampin	Bupropion plasma concentrations may be reduced, decreasing its therapeutic effect, since an increased metabolism of bupropion (CYP2B6) is suspected. In patients receiving bupropion, close monitoring of clinical efficacy is advised when rifampin is coadministered. Preparedness to adjust the bupropion dose as needed is advised.
Bupropion	2	Ritonavir	Large increases in serum bupropion concentrations may occur, increasing the risk of bupropion toxicity, as ritonavir may inhibit the metabolism of bupropion. Ritonavir is contraindicated in patients receiving bupropion.

Drug(s)	Significance Level	Interaction	Mechanism
Mirtazapine	2	Hydantoins (ethotoin, fosphenytoin, phenytoin)	Mirtazapine plasma concentrations may be reduced, decreasing its pharmacologic effects, since the induction of mirtazapine metabolism (CYP3A3/4) by hydantoins is suspected. In patients receiving mirtazapine, close monitoring of clinical response when starting, stopping, or changing the hydantoin dose is recommended. Adjustment of mirtazapine therapy as needed may be warranted.
Miscellaneous Central Nervous System Agents—Monoamine Oxidase Inhibitors			
Selegiline	1	Bupropion	Risk of acute bupropion toxicity may be increased, although the exact mechanism is unknown. Coadministration of bupropion and MAOIs is contraindicated. At least a 14-day window should be allowed to elapse between discontinuing an MAOI and starting bupropion.
Selegiline	1	Meperidine	Coadministration could result in adverse reactions that may include agitation, seizures, diaphoresis, and fever, which may progress to coma, apnea, and death. Reactions may occur several weeks following withdrawal of MAO inhibitors by an unknown mechanism. Avoidance of this concomitant drug combination is advised.
Selegiline	1	Serotonin-reuptake inhibitors (citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, nefazodone, paroxetine, sertraline, venlafaxine)	A serotonin syndrome (eg, altered consciousness, CNS irritability, myoclonus, shivering) may occur as a possible result of rapid, excessive accumulation of serotonin. Coadministration should be avoided. Allow at least 5 days after stopping duloxetine, 1 week after stopping nefazodone or venlafaxine, 2 weeks after stopping citalopram, escitalopram, fluvoxamine, paroxetine, or sertraline, and 5 weeks after stopping fluoxetine before giving an MAO inhibitor. After stopping an MAO inhibitor, at least 2 weeks should elapse before administering any SRI.
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, thus it may be necessary to reduce the dose of selegiline if concurrent use of these agents cannot be avoided. Close monitoring of clinical response, and preparedness to alter therapy as needed is advised.

Significance Level 1: Major severity
Significance Level 2: Moderate severity

VI. Adverse Drug Events

The Food and Drug Administration (FDA) requires manufacturers to include a black-box warning notifying prescribers of the potential of antidepressants to increase suicidal thoughts in children and adolescents.[3] In addition, the FDA issued a public health advisory cautioning that adults being treated with antidepressant medications, particularly those being treated for depression, should be watched closely for worsening of depression and for increased suicidal thinking or behavior (Table 7).

Nefazodone carries a "black box warning" due to reports of life-threatening hepatic failure.[23,41] 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 (Table 8). The package insert for the combination product fluoxetine and olanzapine also contains a black box (Table 9) and the prescribing information has recently been adjusted to include new warnings for weight gain, hyperlipidemia and hyperglycemia and notes that this agent may have a greater association with hyperglycemia than other second generation antipsychotics.[34] The most common adverse drug events reported with the antidepressants are noted in Tables 6a–6g.

Table 6a. Adverse Drug Events (%) Reported with the Antidepressants—Monoamine Oxidase Inhibitors[24-26]

Adverse Event	Isocarboxazid	Phenelzine	Tranylcypromine
Cardiovascular			
Cardiovascular depression, transient	-	✔ *	-
Edema	-	-	✔
Orthostatic hypotension	4	-	-
Palpitation	2	-	✔
Postural hypotension	-	✔	-
Syncope	2	-	-
Tachycardia	-	-	✔
Central Nervous System			
Agitation	-	-	✔
Akathisia	✔	-	-
Anxiety	2	✔ †	✔
Ataxia	✔	✔	✔
Blurred vision	-	✔	✔
Confusion	-	-	✔
Chills	2	-	✔
Convulsions	-	✔	-
Disorientation	-	-	✔
Dizziness	15-29	✔	✔
Drowsiness	4	✔	✔
Euphoria	✔	✔	-
Fatigue	-	✔ ‡	-
Fever	-	✔	-
Hallucinations	✔	-	-
Headache	6-15	✔	✔
Hyperreflexia	-	✔	-
Hypersomnia	-	✔	-
Insomnia	4-6	✔	✔
Jitteriness	-	✔	-
Lethargy	2	-	-
Manic symptoms	-	✔	✔
Neuritis	✔	-	-
Numbness	-	-	✔
Nystagmus	-	✔	-
Palilalia	-	✔	-
Paresthesia	2	✔	✔
Restlessness	-	-	✔
Sedation	2	-	-
Sleep disturbance	2-5	✔	-
Tinnitus	-	-	✔
Twitching	-	✔	-
Weakness	-	✔	✔
Dermatological			
Cystic acne flare-up	-	-	✔
Photosensitivity	✔	-	-
Pruritis	-	✔	-

Adverse Event	Isocarboxazid	Phenelzine	Tranylcypromine
Rash	-	✔	✔
Endocrine and Metabolic			
Hepatitis	-	-	✔
Hypermetabolic syndrome	-	✔	-
Hypernatremia	-	✔	-
Jaundice, reversible	-	✔	-
Necrotizing hepatocellular damage	-	✔	-
Serum transaminase elevation	-	✔ §	-
Weight gain	-	✔	-
Gastrointestinal			
Abdominal pain	-	-	✔
Constipation	4-7	✔	✔
Diarrhea	2	-	✔
Dry mouth	6-9	✔	✔
Gastrointestinal disturbances	-	✔	-
Nausea	4-6	-	✔
Genitourinary			
Dysuria	✔	-	-
Incontinence	✔	-	-
Urinary frequency	2	-	-
Urinary hesitancy	1-4	-	-
Urinary retention	✔	✔	✔
Hematologic			
Agranulocytosis	-	-	✔
Anemia	-	-	✔
Hematologic changes	✔	-	-
Leukopenia	-	✔	✔
Thrombocytopenia	-	-	✔
Musculoskeletal			
Heavy feeling	2	-	-
Myoclonic jerks/movements	2	✔	✔
Tremor	4	✔	✔
Respiratory			
Edema of the glottis	-	✔	-
Respiratory depression, transient	-	✔ *	-
Other			
Alopecia	-	-	✔
Anorexia	-	-	✔
Anorgasmia	-	✔	-
Black tongue	✔	-	-
Coma	✔	✔ **	-
Ejaculation disturbances	-	✔	✔
Forgetfulness	2	-	-
Glaucoma	-	✔	-
Hyperactive	2	-	-
Impaired water secretion	✔	-	✔
Impotence	2	✔	✔
Lupus-like syndrome	-	✔	-
Precipitation of schizophrenia	-	✔	-
Sexual disturbances	✔	✔	-
Spider telangiectases	✔	-	-
Sweating	2	✔	-

Adverse Event	Isocarboxazid	Phenelzine	Tranylcypromine
Toxic amblyopia	✔	-	-
Toxic delirium	-	✔	-

✔ =Percent not specified
- Event not reported or incidence <1%
* Following ECT
† Acute anxiety reaction
‡ Associated with increased muscle tone
§ Without accompanying signs and symptoms
** Shock-like coma

Table 6b. Adverse Drug Events (%) Reported with the Antidepressants—Selective Serotonin- and Norepinephrine-reuptake Inhibitors[64-65]

Adverse Event	Duloxetine	Venlafaxine
Cardiovascular		
Aneurysm	-	<1
Angina pectoris	-	<1
Arrhythmia	-	<1
Atrial fibrillation	<1	-
Atrioventricular (AV) block	-	<1
Bigeminy	-	<1
Bradycardia	-	<1
Bundle branch block	<1	<1
Cardiovascular disorder	-	<1
Chest pain	-	2
Congestive heart failure	<1	<1
Coronary artery disease	-	<1
Edema	-	✔
EKG abnormalities	-	<1
Extrasytoles	-	<1
Heart arrest	-	<1
Hypertension, dose related	-	3-13
Hypertensive crisis	<1	-
Hypotension	-	<1
Myocardial infarct	<1	<1
Orthostatic hypotension	<1	-
Palpitation	1	3
Peripheral edema	<1	-
Postural hypotension	-	1
Syncope	<1	<1
Tachycardia	<1	2
Vasodilation	-	3-4
Central Nervous System		
Abnormal dreams	-	3-7
Abnormal thinking	-	2
Agitation	<1	2-4
Amnesia	-	✔
Anxiety	3	5-6
Ataxia	<1	<1
Blurred vision	4	4-6
Bradykinesia	-	<1
Chills	-	3
Confusion	-	2
Delusions	-	<1
Dementia	-	<1

Adverse Event	Duloxetine	Venlafaxine
Depersonalization	-	1
Depression	-	1-3
Diplopia	<1	-
Disorientation	<1	-
Dizziness	1-14	11-20
Fatigue	2-10	-
Fever	1-2	✔
Hostility	-	<1
Hypoesthesia	1	-
Headache	13	25-34
Hypoesthesia	-	✔
Insomnia	8-11	15-23
Irritability	1	-
Lethargy	1	-
Loss of consciousness	-	<1
Mania	<1	-
Migraine	-	✔
Mood swings	<1	-
Nervousness	1	6-13
Neuropathy	-	<1
Neutropenia	-	<1
Nightmares	1	-
Paresthesia	-	2-3
Photopsia	<1	-
Photosensitivity	<1	-
Restlessness	1	-
Seizure	<1	<1
Sleep disorder	1	-
Somnolence	7-15	12-23
Vertigo	1	✔
Yawning	1	3-5
Dermatological		
Acne	<1	-
Bruising	-	✔
Eczema	<1	-
Erythema	<1	-
Erythema multiforme	-	<1
Exfoliative dermatitis	-	<1
Hyperhydrosis	6	-
Maculopapular rash	-	<1
Miliaria	-	<1
Pruritis	1	1
Rash	1	3
Skin atrophy	-	<1
Stevens-Johnson syndrome	<1	<1
Toxic epidermal necrolysis	-	<1
Urticaria	<1	-
Endocrine and Metabolic		
Bilirubin increased	<1	-
Blood urea nitrogen (BUN) increased	-	<1
Cholesterol increased	<1	-
Creatinine increased	-	<1

Adverse Event	Duloxetine	Venlafaxine
Diabetes mellitus	-	<1
Dyslipidemia	<1	-
Electrolyte abnormalities	-	<1
Hepatic steatosis	<1	-
Hepatitis	<1	<1
Hot flushes	2	-
Hypercalcinuria	-	<1
Hypercholesterolemia	<1	<1
Hyperglycemia	-	<1
Hypertriglyceridemia	<1	-
Hyperlipidemia	<1	<1
Hyperthyroidism	-	<1
Hyperuricemia	-	<1
Hypocholesterolemia	-	<1
Hypoglycemia	1	<1
Hyponatremia	<1	<1
Hypothyroidism	-	<1
Jaundice	<1	<1
Kidney function abnormal	-	<1
Liver enzymes increased	-	<1
Transaminase elevation	1	-
Gastrointestinal		
Abdominal pain	<1	4
Anorexia	-	8-20
Appetite decreased	3-8	-
Appetite increased	-	✔
Bloody stools	<1	-
Cholelithiasis	-	<1
Colitis	<1	-
Constipation	5-11	8-15
Diarrhea	8-13	6-8
Diverticulitis	<1	-
Dyspepsia	4	5
Eructation	<1	-
Esophageal stenosis	<1	-
Flatulence	-	3-4
Gastric emptying impaired	<1	-
Gastric irritation	<1	-
Gastric ulcer	<1	<1
Gastritis	1	-
Intestinal obstruction	-	<1
Irritable bowel syndrome	<1	-
Loose stools	2-3	-
Melena	<1	-
Nausea	4-22	21-37
Vomiting	1-6	3-6
Xerostomia	5-15	12-22
Genitourinary		
Crystalluria	-	<1
Dysuria	1	-
Micturation urgency	<1	-
Nocturia	<1	-

Adverse Event	Duloxetine	Venlafaxine
Pollakiuria	1-3	-
Prostatic disorder	-	✔
Pyelonephritis	-	<1
Pyuria	-	<1
Urinary frequency	-	3
Urinary retention	<1	1
Urinary symptoms	1	-
Urination impaired	-	2
Hematologic		
Agranulocytosis	-	<1
Anemia	<1	-
Aplastic anemia	-	<1
Bleeding time increased	-	<1
Leukocytosis	-	<1
Leukoderma	-	<1
Leukopenia	<1	<1
Pancytopenia	-	<1
Thrombocytopenia	<1	<1
Thrombophlebitis	-	<1
Musculoskeletal		
Arthralgia	-	✔
Dysarthria	<1	-
Extrapyramidal symptoms	-	<1
Hypertonia	-	3
Malaise	<1	-
Muscle cramp	4-5	-
Muscle tightness	1	1-2
Muscle twitching	1	<1
Myalgia	1-3	-
Myasthenia	-	<1
Myopathy	-	<1
Neck pain/rigidity	-	✔
Neuroleptic malignant-like syndrome	-	<1
Rhabdomyolysis	-	<1
Rheumatoid arthritis	-	<1
Rigors	1	-
Tendon rupture	-	<1
Tremor	1-3	4-5
Weakness	2-4	8-17
Respiratory		
Asthma	-	<1
Atelectasis	-	<1
Cough	3-6	✔
Dyspnea	-	✔
Nasopharyngitis	7-9	-
Pharyngitis	-	7
Pharyngolaryngeal pain	1-3	-
Pleurisy	-	<1
Pneumonia	-	<1
Sinusitis	-	2
Other		
Alopecia	<1	-

Adverse Event	Duloxetine	Venlafaxine
Anaphylactic reaction	<1	<1
Angioneurotic edema	<1	-
Anorgasmia	1	-
Aphthous stomatitis	<1	-
Arteritis	-	<1
Bacteremia	-	<1
Basophilia	-	<1
Bilirubinemia	-	<1
Bruxism	<1	-
Carcinoma	-	<1
Cataract	-	<1
Catatonia	-	<1
Cellulites	-	<1
Cerebral ischemia	-	<1
Cyanosis	-	<1
Deafness	-	<1
Deep vein thrombosis (DVT)	-	<1
Dehydration	<1	<1
Diaphoresis increased	6	10-14
Dysphagia	<1	-
Dystonia	-	<1
Ecchymosis	<1	-
Ejaculation delayed	3	-
Ejaculatory dysfunction	3	2-16
Embolus	-	<1
Eosinophilia	-	<1
Erectile dysfunction	1-4	-
Facial edema	<1	-
Facial paralysis	-	<1
Fasciitis	-	<1
Flu-like syndrome	<1	6
Gingivitis	<1	-
Glaucoma	<1	<1
Guillain-Barre syndrome	-	<1
Hematemesis	-	<1
Hemorrhage	-	<1
Homicidal ideation	-	<1
Hyperacusis	-	<1
Hypoproteinemia	-	<1
Impotence	-	4-10
Infection	-	6
Keroconjunctivitis sicca	<1	-
Larynx edema	-	<1
Libido decreased	3-6	3-9
Lymphadenopathy	<1	<1
Lymphocytosis	-	<1
Macular degeneration	<1	-
Maculopathy	<1	-
Menstrual abnormalities	-	<1
Moniliasis	-	<1
Multiple myeloma	-	<1
Mydriasis	-	2

Adverse Event	Duloxetine	Venlafaxine
Nephropathy	<1	-
Night sweats	1	-
Orgasm abnormality	3-4	2-16
Oropharyngeal edema	<1	-
Osteoporosis	-	<1
Phlebitis	<1	-
Retinal detachment	<1	-
Serotonin syndrome	-	<1
Stomatitis	<1	-
Suicidal ideation/attempt	<1	<1
Syndrome of inappropriate antidiuretic hormone (SIADH)	-	<1
Thirst	<1	-
Tinnitus	-	2
Trauma	-	2
Trismus	-	✔
Visual disturbance	<1	-
Weight gain	<1	✔
Weight loss	1-2	1-4
Withdrawal syndrome	<1	<1

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

Table 6c. Adverse Drug Events (%) Reported with the Antidepressants—Selective Serotonin-reuptake Inhibitors[22,66-72]

Adverse Event	Citalo-pram	Escitalo-pram	Fluoxetine	Fluoxetine and olanzapine	Fluvox-amine	Parox-etine	Sertraline
Cardiovascular							
Angina	-	-	<1	-	-	-	-
Arrhythmia	-	-	<1	-	-	-	-
Atrial arrhythmia	-	-	-	-	-	-	<1
Atrial fibrillation	-	<1	-	-	-	-	-
AV block	-	-	-	-	-	-	<1
Bradycardia	-	<1	-	-	-	-	<1
Chest Pain	-	1-10	1-10	-	-	3	1-10
Chest tightness	-	<1	-	-	-	-	-
Congestive heart failure	-	-	<1	-	-	-	-
ECG abnormal	-	<1	-	-	-	-	-
Hemorrhage	-	-	1-10	-	<1	-	-
Hypertension	-	1-10	1-10	-	-	✔	-
Hypotension	-	-	-	-	-	-	-
Myocardial infarct	-	-	<1	-	-	-	-
Orthostatic hypotension	-	-	-	✔	-	-	-
Palpitation	-	1-10	1-10	-	-	2-3	1-10
Peripheral vascular collapse	-	-	-	-	-	-	-
Postural hypotension	-	-	<1	-	-	-	-
Pulmonary hypertension	-	-	-	-	-	-	<1
QT_c prolongation	<1	<1	<1	-	-	-	<1
Syncope	-	<1	<1	-	-	-	-
Tachycardia	-	<1	-	-	-	✔	-
Torsades de pointes	<1	<1	<1	-	-	-	<1
Vasculitis	-	-	-	-	-	-	<1
Vasodilation	-	-	1-5	-	-	2-4	-
Ventricular arrhythmia	<1	<1	-	-	-	-	-

Adverse Event	Citalo-pram	Escitalo-pram	Fluoxetine	Fluoxetine and olanzapine	Fluvox-amine	Parox-etine	Sertraline
Ventricular tachycardia	-	-	<1	-	-	-	<1
Central Nervous System							
Abnormal dreams	-	1-10	1-5	-	-	3-4	-
Abnormal thinking	-	-	2	-	-	-	-
Aggression	-	<1	-	-	-	-	-
Agitation	<10	-	1-10	-	16	3-5	1-10
Amnesia	-	-	1-10	-	-	-	-
Anxiety	<10	<1	6-15	-	5	5	1-10
Apathy	-	<1	-	-	-	-	-
Asthenia	-	-	-	-	14	-	-
Ataxia	-	-	-	-	-	-	-
Auditory hallucination	-	<1	-	-	-	-	-
Blurred vision	-	1-10	-	-	-	-	-
Chills	-	-	1-10	-	-	>1	-
Concentration impaired	-	1-10	-	-	-	3-4	-
Confusion	-	<1	1-10	-	-	>1	-
Central nervous system depression	-	-	-	-	-	-	-
Central nervous system excitation	-	-	-	-	-	-	-
Delirium	<1	<1	-	-	-	-	-
Depersonalization	-	<1	-	-	-	3	-
Depression	-	<1	-	✔	<1	-	-
Dizziness	-	5	9	-	11	6-14	>10
Drowsiness	-	-	-	-	-	-	-
Emotional lability	-	<1	1-10	-	-	>1	-
Euphoria	-	-	<1	-	-	-	-
Excitability	-	<1	-	-	-	-	-
Faint feeling	-	-	-	-	-	-	-
Fatigue	-	5-8	-	-	-	-	>10
Fever	-	1-10	2	-	-	-	-
Grand mal seizure	-	<1	-	-	-	-	-
Hallucinations	-	<1	<1	-	-	-	<1
Hangover effect	-	-	-	-	-	-	-
Headache	-	24	21	-	22	17-18	>10
Hypoesthesia	-	-	-	-	-	-	1-10
Hypomania	-	-	-	-	<1	-	-
Impaired cognition	-	-	-	✔	-	-	-
Insomnia	>10	9-12	10-33	-	21	11-24	>10
Irritability	-	1-10	-	-	-	-	-
Lethargy	-	1-10	-	-	-	-	-
Lightheadedness	-	1-10	-	-	-	-	-
Malaise	-	<1	-	-	-	-	1-10
Mania	-	-	-	✔	<1	-	-
Mental depression	-	-	-	-	-	-	-
Migraine	-	1-10	-	-	-	-	-
Nervousness	-	-	8-14	-	12	4-9	1-10
Nystagmus	-	<1	-	-	-	-	-
Panic reaction	-	<1	-	-	-	-	-
Paresthesia	-	1-10	-	-	-	-	1-10
Psychiatric disturbances	-	-	-	-	-	-	<1
Seizure	-	-	-	✔	<1	-	-

Adverse Event	Citalo-pram	Escitalo-pram	Fluoxetine	Fluoxetine and olanzapine	Fluvox-amine	Parox-etine	Sertraline
Sleep disorder	-	-	1-10	-	-	-	-
Somnolence	>10	6-13	5-17	-	22	15-24	>10
Tremors	-	-	-	-	4	-	>10
Vertigo	-	1-10	-	-	-	>1	-
Dermatological							
Angioedema	-	-	-	-	-	-	<1
Epidermal necrolysis	<1	<1	-	-	-	-	-
Erythema multiforme	<1	<1	-	-	-	-	-
Erythema nodosum	-	-	<1	-	-	-	-
Exfoliative dermatitis	-	-	<1	-	-	-	-
Injection site reaction	-	-	-	-	-	-	-
Pain at injection site	-	-	-	-	-	-	-
Photosensitivity	-	-	<1	-	-	-	<1
Pruritis	<10	-	4	-	-	>1	-
Rash	<10	1-10	2-6	-	-	2-3	1-10
Stevens-Johnson syndrome	-	-	<1	-	-	-	<1
Urticaria	-	-	-	-	-	-	-
Endocrine and Metabolic							
Galactorrhea	-	-	-	-	-	-	<1
Gynecomastia	-	-	-	-	-	5	<1
Hepatic failure	-	-	<1	-	-	-	<1
Hepatic necrosis	<1	<1	<1	-	-	-	-
Hepatitis	-	<1	-	-	-	-	<1
Hepatomegaly	-	-	-	-	-	-	<1
Hot flashes	-	1-10	-	-	-	-	-
Hypercholesterolemia	-	<1	-	-	-	-	-
Hyperglycemia	-	<1	-	✔	-	-	<1
Hyperprolactinemia	-	-	<1	-	-	-	<1
Hyponatremia	-	-	<1	✔	<1	-	-
Hypothyroidism	-	-	-	-	-	-	<1
Jaundice	-	-	<1	-	-	-	<1
Liver damage	-	-	-	-	-	-	-
Prolactinemia	-	<1	-	-	-	-	-
Transaminase elevation	-	-	-	-	-	-	<1
Gastrointestinal							
Abdominal cramps	-	1-10	-	-	-	-	-
Abdominal pain	<10	2	-	-	-	4	<1
Cholelithiasis	-	-	<1	-	-	-	-
Colitis	-	-	<1	-	-	-	-
Constipation	-	3-5	5	-	10	5-16	1-10
Cramping	-	-	-	-	-	-	-
Diarrhea	<10	8	8-18	-	11	9-12	>10
Dyspepsia	<10	-	6-10	-	-	2-5	1-10
Flatulence	-	1-10	3	-	-	4	1-10
Gastroenteritis	-	1-10	-	-	-	-	-
Gastroesophageal reflux	-	1-10	-	-	-	-	-
Heartburn	-	1-10	-		-	-	-
Indigestion	-	3	-	-	10	-	-
Nausea	>10	15	12-29	-	40	19-26	>10
Pancreatitis	<1	<1	<1	-	-	-	<1
Rectal bleeding	-	-	-	-	-	-	-
Vomiting	<10	1-10	3	-	5	2-3	1-10

Adverse Event	Citalo-pram	Escitalo-pram	Fluoxetine	Fluoxetine and olanzapine	Fluvox-amine	Parox-etine	Sertraline
Xerostomia	>10	6-9	4-12	-	14	9-18	>10
Genitourinary							
Micturition disorders	-	-	-	-	-	-	<1
Oliguria	-	-	-	-	-	-	-
Urinary frequency	-	1-10	1-10	-	-	2-3	-
Urinary tract infection (UTI)	-	1-10	-	-	-	2	-
Hematologic							
Agranulocytosis	-	-	-	-	-	-	<1
Anemia	-	<1	-	-	-	-	-
Aplastic anemia	-	-	-	-	-	-	<1
Bilirubin increased	-	<1	-	-	-	-	<1
Hemolytic anemia	<1	<1	<1	-	-	-	-
Increased bleeding	-	-	-	-	-	-	<1
Leukopenia	-	-	-	-	-	-	<1
Megaloblastic anemia	-	-	-	-	-	-	-
Pancytopenia	-	-	<1	-	-	-	-
Prothrombin decreased	-	<1	-	-	-	-	-
Thrombosis	-	<1	-	-	-	-	-
Thrombocytopenia	-	<1	<1	-	-	-	<1
Thrombocytopenic purpura	-	-	<1	-	-	-	-
Thrombophlebitis	-	-	-	-	-	-	-
Musculoskeletal							
Akathisia	-	<1	-	-	-	-	-
Arthralgia	<10	1-10	-	-	-	>1	-
Back pain	-	-	-	-	-	3	1-10
Choreothetosis	-	<1	-	-	-	-	-
Dyskinesias	<1	-	<1	✔	-	-	-
Dystonia	-	-	-	-	-	-	<1
Extrapyramidal symptoms	-	-	<1	-	-	-	<1
Hyperkinesia	-	-	-	-	-	-	-
Hyperreflexia	-	<1	-	-	-	-	-
Hypertonia	-	-	-	-	-	-	1-10
Involuntary muscle contractions	-	<1	-	-	-	-	-
Limb pain	-	1-10	-	-	-	-	-
Muscle cramp	-	1-10	-	-	-	-	-
Myalgia	<10	1-10	-	-	-	2-4	1-10
Neck/shoulder pain	-	1-10	-	-	-	-	-
Neuroleptic malignant syndrome	<1	-	<1	✔	-	-	-
Rhabdomyolosis	<1	<1	-	-	-	-	-
Rigidity	-	-	-	-	-	-	-
Tics	-	<1	-	-	-	-	-
Tremor	<10	1-10	3-13	-	-	4-11	-
Weakness	-	<1	7-21	-	-	12-22	1-10
Respiratory							
Apnea	-	-	-	-	-	-	-
Asthma	-	-	<1	-	-	-	-
Bronchitis	-	1-10	-	-	-	-	-
Cough	<10	1-10	-	-	-	-	-
Dyspnea	-	-	-	✔	-	-	-

Adverse Event	Citalo-pram	Escitalo-pram	Fluoxetine	Fluoxetine and olanzapine	Fluvox-amine	Parox-etine	Sertraline
Esosinophilic pneumonia	-	-	<1	-	-	-	-
Hypoventilation	-	-	-	-	-	-	-
Laryngospasm	-	-	<1	-	-	-	-
Nasal congestion	-	1-10	-	-	-	-	-
Pharyngitis	-	-	3-11	✔	-	4	-
Pulmonary embolism	-	<1	<1	-	-	-	-
Pulmonary fibrosis	-	-	<1	-	-	-	-
Pulmonary hypertension	-	-	<1	-	-	-	-
Respiratory depression	-	-	-	-	-	-	-
Rhinitis	<10	5	-	-	-	3	1-10
Sinus headache	-	1-10	-	-	-	-	-
Sinusitis	<10	3	1-6	-	-	4	-
Upper respiratory infection	-	-	-	-	4	7	-
Other							
Abnormal vision	-	-	-	-	-	-	1-10
Acute renal failure	<1	<1	<1	-	-	-	<1
Allergic reaction	-	<1	-	-	-	-	<1
Allergy	-	1-10	<1	-	-	-	-
Alopecia	-	-	<1	-	-	-	-
Anaphylaxis	<1	<1	<1	-	-	-	<1
Angioedema	<1	<1	-	-	-	-	-
Anorexia	<10	-	4-11	-	-	5-9	>10
Anorgasmia	-	2-6	-	-	2	>1	-
Appetite decreased	-	3	-	-	4	-	-
Appetite increased	-	1-10	1-10	-	-	-	1-10
Blindness	-	-	-	-	-	-	<1
Carbohydrate craving	-	<1	-	-	-	-	-
Cataract	-	-	<1	-	-	-	<1
Complex sleep-related behavior	-	-	-	-	-	-	-
Dependence	-	-	-	-	-	-	-
Diaphoresis	>10	4-5	2-8	-	7	5-14	>10
Dysphagia	-	-	<1	-	-	-	-
Ear ache	-	1-10	1-10	-	-	-	-
Ecchymosis	-	<1	-	-	-	-	-
Ejaculation disorder	-	9-14	<7	-	7	10-28	>10
Esophagitis	-	-	<1	-	-	-	-
Flu-like syndrome	-	5	3-10	-	-	-	-
Gout	-	-	<1	-	-	-	-
Gum hyperplasia	-	-	-	-	-	-	<1
Hypersensitivity reaction	-	-	-	-	-	-	-
Impotence	-	3	<7	-	-	2-9	1-10
Libido decreased	-	3-7	1-11	-	-	3-15	>10
Lupus-like syndrome	-	-	<1	-	-	-	<1
Menstrual cramps	-	1-10	-	-	-	-	-
Menstrual disorder	-	1-10	-	-	-	-	-
Neuroleptic malignant syndrome	-	-	-	-	-	-	<1
Oculogyric crisis	-	-	-	-	-	-	<1
Optic neuritis	-	-	<1	-	-	-	<1
Pain	-	-	-	-	-	-	1-10
Priapism	<1	<1	<1	-	-	-	<1

Adverse Event	Citalo-pram	Escitalo-pram	Fluoxetine	Fluoxetine and olanzapine	Fluvox-amine	Parox-etine	Sertraline
Serotonin syndrome	<1	<1	<1	-	<1	-	<1
Serum sickness	-	-	-	-	-	-	<1
Sexual dysfunction	<10	-	-	✔	-	-	-
Spontaneous abortion	-	<1	-	-	-	-	-
Suicidal tendency	-	<1	-	✔	<1	-	-
Syndrome of inappropriate antidiuretic hormone secretion (SIADH)	<1	<1	-	-	-	-	<1
Taste alteration	-	<1	1-10	-	2	2	-
Tinnitus	-	1-10	1-10	-	-	>1	1-10
Tooth ache	-	1-10	-	-	-	-	-
Vasculitis	-	-	<1	-	-	-	-
Visual difficulty	-	<1	2	-	-	2-4	1-10
Weight gain	<10	1-10	1-10	✔	-	>1	1-10
Weight loss	-	1-10	2	-	✔	-	-
Withdrawal syndrome	<1	<1	-	-	-	-	-
Yawning	<10	1-10	<11	-	2	2-4	1-10

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

Table 6d. Adverse Drug Events (%) Reported with the Antidepressants—Serotonin Modulators[73-74]

Adverse Event	Nefazodone	Trazodone
Cardiovascular		
Atrioventricular (AV) 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	-
Blurred vision	9	>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	-
Headache	>10	>10
Incoordination	1-10	1-10
Insomnia	>10	-
Lightheadedness	1-10	-
Memory impairment	1-10	-
Paresthesia	1-10	-

Adverse Event	Nefazodone	Trazodone
Psychomotor retardation	1-10	-
Sedation	-	>10
Seizure	<1	<1
Speech impairment	-	<1
Dermatological		
Photosensitivity	<1	-
Pruritis	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	-
Liver function tests abnormal	<1	-
Gastrointestinal		
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		
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	-
Rhabdomyolosis	<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		
Abnormal vision	7	-
Allergic reaction	<1	<1
Alopecia	-	<1
Angioedema	<1	-
Appetite increased	1-10	-

Adverse Event	Nefazodone	Trazodone
Breast pain	1-10	-
Eye pain	1-10	-
Flu syndrome	1-10	-
Impotence	1-10	-
Infection	1-10	-
Libido decreased	1-10	-
Priapism	<1	<1
Serotonin syndrome	<1	-
Taste perversion	1-10	-
Thirst	1-10	-
Tinnitus	1-10	-
Visual field defect	1-10	-
Weight gain	-	1-10
Weight loss	-	1-10

✔ =Percent not specified
- Event not reported or incidence <1%
* With lovastatin/simvastatin

Table 6e. Adverse Drug Events (%) Reported with the Antidepressants—Tricyclics and Other Norepinephrine-reuptake Inhibitors[75-86]

Adverse Event	Amitrip-tyline	Amitrip-tyline and chlor-diaze-poxide	Amitrip-tyline and perphen-azine	Amox-apine	Clomip-ramine	Desip-ramine	Dox-epin	Imip-ramine	Mapro-tiline	Nortrip-tyline	Protrip-tyline	Trimip-ramine
Cardiovascular												
Arrhythmia	✔	✔	✔	-	-	✔	-	✔	<1	✔	✔	✔
AV conduction changes	✔	✔	✔	-	-	-	-	-	-	-	-	-
Bradycardia	-	-	✔	-	-	-	-	-	-	-	-	-
Cardiac arrest	-	-	✔	-	-	-	-	-	-	-	-	-
Cardiomyopathy	✔	✔	✔	-	-	-	-	-	-	-	-	-
Congestive heart failure (CHF)	-	-	-	-	-	-	-	✔	-	-	-	-
ECG changes (nonspecific)	✔	✔	✔	-	-	-	-	✔	-	-	-	-
Edema	-	-	-	1-10	-	✔	-	-	-	-	-	-
Heart block	✔	✔	✔	-	-	-	-	✔	<1	✔	✔	✔
Hypertension	✔	✔	✔	<1	-	✔	✔	✔	<1	✔	✔	✔
Hypotension	-	1-10	✔	-	1-10	✔	✔	-	<1	-	✔	✔
Myocardial infarction (MI)	✔	✔	✔	-	-	✔	-	✔	-	✔	✔	✔
Orthostatic hypotension	✔	✔	✔	-	-	-	-	✔	-	✔	-	-
Palpitations	✔	✔	✔	-	1-10	✔	-	✔	-	✔	✔	✔
Stroke	✔	✔	✔	-	-	✔	-	✔	-	-	✔	✔
Syncope	✔	✔	✔	-	-	-	-	-	-	-	-	-
Tachycardia	✔	✔	✔	-	1-10	✔	✔	✔	-	✔	✔	✔
Central Nervous System												
Abnormal dreaming	-	-	-	-	1-10	-	-	-	-	-	-	-
Agitation	-	-	-	-	1-10	✔	-	✔	1-10	✔	✔	✔
Akathisia	-	1-10	-	-	-	-	-	-	<1	-	-	-
Anxiety	✔	✔	✔	1-10	1-10	✔	-	✔	1-10	✔	✔	✔
Ataxia	✔	>10	✔	1-10	-	✔	✔	-	<1	✔	✔	-
Confusion	-	1-10	-	-	1-10	-	-	-	-	✔	✔	-
Cerebral edema	-	-	✔	-	-	-	-	-	-	-	-	-
Cognitive function (impaired)	✔	✔	✔	-	-	-	-	-	-	-	-	-
Coma	✔	✔	✔	-	-	-	-	-	-	-	-	-
Confusion	✔	1-10	✔	1-10	-	✔	✔	✔	<1	-	-	✔
Coordination impairment	✔	✔	✔	<1	1-10	✔	-	✔	-	✔	✔	✔
Delirium	-	-	-	-	-	✔	-	-	-	✔	✔	✔
Delusions	-	-	-	-	-	-	-	✔	<1	✔	✔	✔
Depersonalization	-	-	-	-	1-10	-	-	-	-	-	-	-
Disinhibition	-	1-10	-	-	-	-	-	-	-	-	-	-

Adverse Event	Amitrip-tyline	Amitrip-tyline and chlor-diaze-poxide	Amitrip-tyline and perphen-azine	Amox-apine	Clomip-ramine	Desip-ramine	Dox-epin	Imip-ramine	Mapro-tiline	Nortrip-tyline	Protrip-tyline	Trimip-ramine
Disorientation	✔	✔	✔	-	-	✔	✔	✔	<1	✔	-	-
Dizziness	✔	1-10	✔	1-10	>10	✔	✔	✔	1-10	-	✔	-
Drowsiness	-	>10	✔	>10	>10	✔	✔	✔	>10	-	✔	✔
Dysarthria	-	>10	-	-	-	-	-	-	<1	-	-	-
Dysphagia	-	-	-	-	-	-	-	-	<1	-	-	-
Emotional lability	-	-	-	-	1-10	-	-	-	-	-	-	-
Excitement	-	-	-	1-10	-	-	-	-	-	-	-	-
Fatigue	✔	>10	✔	-	>10	✔	-	✔	1-10	-	✔	-
Fever	✔	✔	✔	-	1-10	✔	-	-	-	-	-	-
Flushing	-	-	-	-	1-10	✔	-	-	-	-	-	-
Hallucinations	✔	✔	✔	-	-	✔	-	✔	<1	✔	✔	✔
Hangover effect	-	-	-	-	-	-	-	-	-	-	✔	-
Headache	✔	✔	✔	1-10	>10	✔	✔	✔	1-10	-	-	✔
Heart block	-	-	-	-	-	✔	-	-	-	-	-	-
Hyperactivity	-	-	✔	-	-	-	-	-	-	-	-	-
Hypertonia	-	-	-	-	1-10	-	-	-	-	-	-	-
Hypomania	-	-	-	-	-	✔	-	-	-	✔	✔	-
Insomnia	✔	✔	✔	1-10	>10	✔	-	✔	1-10	✔	✔	✔
Irritability	-	>10	-	-	-	-	-	-	-	-	-	-
Lightheadedness	-	>10	-	-	-	-	-	-	-	-	-	-
Mania	-	-	-	-	-	-	-	-	<1	-	-	-
Memory impairment	-	>10	-	-	1-10	-	-	-	-	-	-	-
Migraine	-	-	-	-	1-10	-	-	-	-	-	-	-
Nervousness	-	-	-	1-10	>10	✔	-	-	1-10	-	-	✔
Nightmares	✔	✔	✔	-	-	-	-	✔	-	✔	✔	✔
Panic	-	-	-	-	-	-	-	-	-	✔	✔	-
Paradoxical excitement	-	-	✔	-	-	-	-	-	-	-	-	-
Parkinsonian syndrome	-	-	-	-	-	✔	-	-	-	-	-	-
Psychosis exacerbation	-	-	-	-	-	✔	-	✔	-	✔	✔	✔
Restlessness	✔	✔	✔	1-10	-	✔	-	✔	-	✔	✔	✔
Sedation	✔	✔	✔	-	-	-	-	-	-	-	-	-
Seizure	✔	✔	✔	<1	<1	✔	✔	✔	<1	✔	✔	✔
Sleep disorder	-	-	-	-	1-10	-	-	-	-	-	-	-
Somnolence	✔	✔	✔	-	-	-	-	-	-	-	-	-
Speech disorder	-	-	-	-	1-10	-	-	-	-	-	-	-
Syncope	-	-	-	<1	-	-	-	-	<1	-	-	-

Adverse Event	Amitrip-tyline	Amitrip-tyline and chlor-diaze-poxide	Amitrip-tyline and perphen-azine	Amox-apine	Clomip-ramine	Desip-ramine	Dox-epin	Imip-ramine	Mapro-tiline	Nortrip-tyline	Protrip-tyline	Trimip-ramine
Temperature regulation impaired	-	-	✔	-	-	-	-	-	-	-	-	-
Twitching	-	-	-	-	1-10	-	-	-	-	-	-	-
Yawning	-	-	-	-	1-10	-	-	-	-	-	-	-
Dermatological												
Alopecia	✔	✔	✔	-	<1	✔	✔	<1	-	✔	✔	-
Dermatitis	-	1-10	-	-	1-10	-	-	-	-	-	-	-
Petechiae	-	-	-	-	-	✔	-	<1	-	✔	✔	✔
Photosensitivity	✔	<1	✔	<1	<1	✔	✔	<1	<1	✔	✔	✔
Pruritus	-	-	-	-	1-10	✔	✔	<1	-	✔	✔	✔
Rash	✔	>10	✔	1-10	1-10	✔	✔	<1	<1	✔	✔	✔
Skin discoloration	-	-	✔	-	-	-	-	-	-	-	-	-
Urticaria	✔	✔	✔	-	-	✔	-	<1	-	✔	✔	-
Endocrine and Metabolic												
Amenorrhea	-	-	✔	-	-	-	-	-	-	-	-	-
Breast enlargement	-	-	✔	-	-	✔	✔	✔	-	✔	✔	✔
Galactorrhea	-	-	✔	<1	<1	✔	✔	✔	-	✔	✔	✔
Gynecomastia	-	-	✔	-	-	-	-	✔	-	✔	✔	-
Hyperglycemia	-	-	✔	-	-	✔	✔	✔	-	✔	-	-
Hypoglycemia	-	-	✔	-	-	✔	✔	✔	-	-	-	-
Lactation	-	-	✔	-	-	-	-	-	-	-	-	-
Libido changes	-	-	✔	-	>10	✔	-	-	-	-	-	-
Libido decreased	-	>10	-	-	-	-	✔	✔	-	✔	✔	-
Libido increased	-	1-10	-	-	-	-	✔	✔	-	✔	✔	-
Menstrual disorders	-	>10	✔	<1	-	-	-	-	-	-	-	-
Prolactin levels increased	-	-	-	1-10	-	-	-	-	-	-	-	-
Sexual dysfunction	-	1-10	-	-	-	✔	-	-	-	✔	-	✔
Syndrome of inappropriate antidiuretic hormone (SIADH)	✔	✔	✔	<1	<1	✔	✔	✔	-	✔	✔	✔
Gastrointestinal												
Abdominal pain/cramps	-	-	✔	-	>10	✔	-	✔	-	✔	-	-
Anorexia	✔	✔	✔	-	>10	✔	✔	✔	-	✔	✔	✔
Appetite decreased	-	>10	-	-	-	-	-	-	-	-	-	-
Appetite increased	-	>10	-	-	>10	-	-	-	-	-	✔	✔
Black tongue	✔	✔	✔	-	-	✔	-	✔	-	✔	-	-
Constipation	✔	✔	✔	>10	>10	✔	✔	✔	1-10	✔	✔	✔

Adverse Event	Amitrip-tyline	Amitrip-tyline and chlor-diaze-poxide	Amitrip-tyline and perphen-azine	Amox-apine	Clomip-ramine	Desip-ramine	Dox-epin	Imip-ramine	Mapro-tiline	Nortrip-tyline	Protrip-tyline	Trimip-ramine
Diarrhea	✔	✔	✔	<1	1-10	✔	✔	✔	-	✔	✔	✔
Dyspepsia	-	-	-	-	>10	✔	-	-	-	-	-	-
Esophageal sphincter tone decrease	-	-	-	-	-	✔	✔	-	-	-	✔	✔
Indigestion	-	-	-	-	-	-	✔	-	-	-	✔	✔
Nausea	✔	✔	✔	1-10	>10	✔	✔	✔	1-10	✔	✔	✔
Paralytic ileus	✔	✔	✔	-	-	✔	-	✔	-	-	-	-
Reflux	-	-	-	-	<1	-	-	-	-	-	-	-
Salivation decreased	-	>10	-	-	-	-	-	-	-	-	-	-
Salivation increased	-	1-10	✔	-	-	-	-	-	-	-	-	-
Stomatitis	✔	✔	✔	-	-	✔	✔	✔	-	-	-	-
Taste changes (peculiar/unpleasant)	✔	✔	✔	-	-	✔	✔	✔	-	✔	✔	✔
Vomiting	✔	✔	✔	<1	1-10	✔	✔	✔	<1	✔	✔	✔
Weight gain	✔	>10	✔	-	>10	✔	✔	✔	-	✔	✔	✔
Weight loss	-	>10	-	-	-	✔	-	✔	-	✔	✔	-
Xerostomia	✔	>10	✔	>10	>10	✔	✔	✔	>10	✔	✔	✔
Genitourinary												
Ejaculatory dysfunction	-	-	✔	-	-	-	-	-	-	-	-	-
Impotence	-	-	-	<1	-	✔	-	✔	<1	✔	✔	-
Incontinence	-	1-10	-	-	-	-	-	-	-	-	-	-
Micturation difficulties	-	>10	-	-	-	-	-	-	-	✔	-	-
Polyuria	-	-	✔	-	-	✔	-	-	-	-	-	-
Testicular edema	-	-	-	<1	-	✔	✔	-	-	✔	✔	✔
Urinary retention	✔	✔	✔	<1	1-10	✔	✔	✔	<1	✔	✔	✔
Hematologic												
Agranulocytosis	-	-	✔	<1	-	✔	✔	<1	-	✔	✔	✔
Bone marrow depression	✔	✔	✔	-	<1	-	-	-	-	-	-	-
Eosinophilia	✔	✔	✔	-	-	✔	✔	<1	-	✔	✔	✔
Hemolytic anemia	-	-	✔	-	-	-	-	-	-	-	-	-
Leukopenia	-	-	✔	<1	-	-	✔	-	-	-	✔	-
Pancytopenia	-	-	✔	-	-	-	-	-	-	-	-	-
Purpura	✔	✔	✔	-	-	✔	✔	<1	-	✔	✔	✔
Thrombocytopenia	-	-	-	-	-	✔	✔	<1	-	✔	✔	✔
Hepatic												
Cholestatic jaundice	-	-	✔	-	-	✔	-	<1	-	✔	✔	✔

Adverse Event	Amitrip-tyline	Amitrip-tyline and chlor-diaze-poxide	Amitrip-tyline and perphen-azine	Amox-apine	Clomip-ramine	Desip-ramine	Dox-epin	Imip-ramine	Mapro-tiline	Nortrip-tyline	Protrip-tyline	Trimip-ramine
Hepatitis	-	-	-	-	-	✔	-	-	-	-	-	-
Liver enzymes increased	-	-	-	-	-	✔	-	<1	-	✔	✔	✔
Neuromuscular and skeletal												
Extrapyramidal symptoms (EPS)	✔	✔	✔	<1	-	✔	✔	✔	<1	✔	✔	✔
Muscle cramps	-	1-10	-	-	-	-	-	-	-	-	-	-
Myoclonus	-	-	-	-	>10	-	-	-	-	-	-	-
Neuroleptic malignant syndrome	✔	✔	✔	<1	-	-	-	-	-	-	-	-
Numbness	✔	✔	✔	<1	-	✔	✔	✔	-	✔	✔	✔
Paresthesia	✔	✔	✔	<1	1-10	✔	✔	✔	-	✔	-	✔
Peripheral neuropathy	✔	✔	✔	-	-	✔	-	✔	-	✔	-	✔
Rigidity	-	1-10	-	-	-	-	-	-	-	-	-	-
Tardive dyskinesia	-	-	-	<1	-	-	✔	-	-	-	-	-
Tingling	-	-	-	-	-	✔	-	✔	-	✔	✔	✔
Tremor	✔	1-10	✔	1-10	>10	✔	✔	✔	1-10	✔	✔	✔
Weakness	✔	✔	✔	1-10	-	✔	✔	✔	1-10	-	✔	-
Ocular												
Accommodation disturbances	-	-	-	-	-	✔	-	✔	<1	✔	-	✔
Blurred vision	✔	✔	✔	1-10	1-10	✔	✔	✔	1-10	✔	✔	✔
Cornea and lens changes	-	-	✔	-	-	-	-	-	-	-	-	-
Eye pain	-	-	-	-	1-10	-	-	-	-	✔	✔	✔
Intraocular pressure increased	✔	✔	✔	<1	-	✔	-	-	-	-	✔	✔
Mydriasis	✔	✔	✔	<1	-	✔	-	✔	-	✔	-	✔
Otic												
Hyperacusis	-	-	-	-	<1	-	-	-	-	-	-	-
Tinnitus	✔	1-10	✔	<1	-	✔	✔	✔	<1	✔	✔	✔
Respiratory												
Nasal congestion	-	1-10	✔	-	-	-	-	-	-	-	-	-
Other												
Allergic reactions	-	-	-	<1	-	✔	✔	-	-	✔	✔	✔
Diaphoresis	✔	✔	✔	1-10	-	✔	✔	✔	-	✔	✔	-
Serotonin syndrome	✔	✔	✔	-	-	-	-	-	-	-	-	-
Withdrawal reactions	✔	✔	✔	-	-	-	-	-	-	-	-	-

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

Table 6f. Adverse Drug Events (%) Reported with the Antidepressants—Miscellaneous Antidepressants[87-88]

Adverse Event(s)	Bupropion	Mirtazapine
Cardiovascular		
Arrhythmias	5	-
Atrioventricular (AV) block	✔	-
Chest pain	3-4	-
EEG abnormality	✔	-
Extrasytoles	✔	-
Hypertension	2-4	2
Hypotension	3	-
Myocardial infarct	✔	-
Orthostatic hypotension	-	<1
Palpitation	2-6	-
Peripheral edema	-	2
Postural hypotension	✔	-
Syncope	✔	-
Tachycardia	11	-
Vasodilation	✔	2
Central Nervous System		
Abnormal dreams	3	4
Abnormal thinking	-	3
Agitation	2-9	-
Aggression	✔	-
Akathisia	2	-
Akinesia	✔	-
Amnesia	✔	-
Anxiety	5-7	-
Aphasia	✔	-
Ataxia	✔	-
Blurred vision	2-3	-
Chills	✔	-
Confusion	8	2
Central nervous system depression	-	-
Central nervous system stimulation	1-2	-
Delirium	✔	-
Delusions	✔	-
Depersonalization	✔	-
Depression	✔	-
Derealization	✔	-
Diplopia	✔	-
Dizziness	6-11	7
Drowsiness	-	-
Dyskinesia	✔	-
Dysphoria	✔	-
Emotional lability	✔	-
Euphoria	✔	-
Fever	1-2	-
Hallucinations	✔	-
Headache	25-34	-
Hostility	6	-
Hyperkinesia	✔	-
Hypoesthesia	✔	-
Hypokinesia	✔	-
Hypomania	✔	-

Adverse Event(s)	Bupropion	Mirtazapine
Incoordination	✔	-
Insomnia	11-20	-
Irritability	2-3	-
Manic reaction	✔	-
Malaise	✔	✔
Memory decreased	<3	-
Migraine	1-4	-
Nervousness	3-5	-
Neuropathy	✔	-
Pain	2-3	-
Paranoia	✔	-
Paresthesia	1-2	-
Restlessness	✔	-
Seizure	✔	-
Sensory disturbance	4	-
Sleep disturbance	4	-
Somnolence	2-3	54
Stroke	✔	-
Vertigo	✔	-
Dermatological		
Maculopapular rash	✔	-
Photosensitivity	✔	-
Pruritis	2-4	-
Rash	1-5	-
Urticaria	1-2	-
Endocrine and Metabolic		
Glycosuria	✔	-
Gynecomastia	✔	-
Hepatic damage	✔	-
Hepatitis	✔	-
Hypercholesterolemia	-	✔
Hyperglycemia	✔	-
Hypertriglyceridemia	-	✔
Hypoglycemia	✔	-
Hot flashes	1-3	-
Jaundice	✔	-
Liver function abnormal	✔	<1
Gastrointestinal		
Abdominal pain	2-9	✔
Colitis	✔	-
Constipation	5-10	13
Diarrhea	5-7	-
Dyspepsia	3	-
Flatulence	6	-
Gastric reflux	✔	-
Gastrointestinal hemorrhage	✔	-
Intestinal perforation	✔	-
Nausea	1-18	-
Pancreatitis	✔	-
Stomach ulcer	✔	-
Vomiting	2-4	✔
Xerostomia	17-26	25

Adverse Event(s)	Bupropion	Mirtazapine
Genitourinary		
Cystitis	✔	-
Prostate disorder	✔	-
Salpingitis	✔	-
Urinary frequency	2-5	2
Urinary incontinence	✔	-
Urinary retention	✔	-
Urinary tract infection (UTI)	<1	-
Urinary urgency	<2	-
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	✔	-
Rhabdomyolosis	✔	-
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	✔	-
Sinusitis	1-5	-
Upper respiratory infection	9	-
Other		
Accommodation abnormality	✔	-
Allergic reaction	✔	-
Amblyopia	2	-
Angioedema	✔	-
Anorexia	3-5	✔
Appetite increased	4	17
Auditory disturbance	5	-
Bruxism	✔	-
Coma	✔	-
Deafness	✔	-

Adverse Event(s)	Bupropion	Mirtazapine
Dehydration	-	<1
Diaphoresis	5-6	-
Dry eye	✔	-
Dyspareunia	✔	-
Dysphagia	<2	-
Dystonia	✔	-
Ecchymosis	✔	-
Edema	-	1
Ejaculation abnormality	✔	-
Esophagitis	✔	-
Facial edema	✔	-
Flu-like syndrome	-	1
Gingivitis	✔	-
Glossitis	✔	-
Gum hemorrhage	✔	-
Hirsutism	✔	-
Hypersensitivity reactions	✔	-
Hypertonia	✔	-
Impotence	✔	-
Infection	8-9	-
Intraocular pressure increased	✔	-
Leg cramps	✔	-
Libido decreased	3	-
Libido increased	✔	-
Lymphadenopathy	✔	<1
Menopause	✔	-
Menstrual complaints	2-5	-
Mouth ulcers	✔	-
Mydriasis	✔	-
Painful erection	✔	-
Phlebitis	✔	-
Salivation increased	✔	-
Sciatica	✔	-
Stomatitis	✔	-
Suicidal ideation	✔	-
Syndrome of inappropriate antidiuretic hormone (SIADH)	✔	-
Taste perversion	2-4	-
Thirst	✔	<1
Tinnitus	3-6	-
Tongue edema	✔	-
Vaginal hemorrhage	<2	-
Vaginitis	✔	-
Weight gain	-	12
Weight loss	14-23	<1

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

Table 6g. Adverse Drug Events (%) Reported with the Antidepressants—Miscellaneous Central Nervous System Agents—Monoamine Oxidase Inhibitors[89]

Adverse Event(s)	Selegiline
Cardiovascular	
Arrhythmia	<1
Atrial fibrillation	<1

Adverse Event(s)	Selegiline
Bradycardia	<1
Chest pain	≥1
Hypertension	≥1
Hypotension	3-10
Myocardial infarct	<1
Palpitation	<1
Peripheral edema	≥1
Peripheral vascular disorder	<1
Syncope	<1
Tachycardia	<1
Vasodilation	<1
Central Nervous System	
Abnormal thinking	≥1
Agitation	≥1
Amnesia	≥1
Ataxia	<1
Behavior changes	<1
Bradykinesia	<1
Delusions	<1
Depersonalization	<1
Depression	<1
Emotional lability	<1
Euphoria	<1
Fever	<1
Headache	18
Hostility	<1
Hyperesthesia	<1
Hyperkinesias	<1
Impaired judgment	
Insomnia	12
Loss of balance	<1
Manic reaction	<1
Migraine	<1
Neurosis	<1
Paranoid reaction	<1
Parasomnia	<1
Paresthesia	≥1
Vertigo	<1
Dermatological	
Acne	≥1
Application site reaction	24
Bruising	≥1
Maculopapular rash	<1
Pruritis	≥1
Rash	4
Skin benign neoplasm	<1
Skin hypertrophy	<1
Urticaria	<1
Vesiculobullous rash	<1
Endocrine and Metabolic	
Alkaline phosphatase increased	<1
Hypercholesterolemia	<1

Adverse Event(s)	Selegiline
Hyperglycemia	<1
Hypoglycemic reaction	<1
Hyponatremia	<1
Lactate dehydrogenase increased	<1
Liver function tests abnormal	<1
Gastrointestinal	
Colitis	<1
Constipation	≥1
Diarrhea	9
Dyspepsia	4
Eructation	<1
Flatulence	≥1
Gastritis	<1
Gastroenteritis	≥1
Melena	<1
Rectal hemorrhage	<1
Vomiting	≥1
Xerostomia	8
Genitourinary	
Kidney calculus	<1
Pelvic pain	<1
Polyuria	<1
Prostatic hyperplasia	<1
Urinary frequency	≥1
Urination impaired	<1
Urinary retention	<1
Urinary tract infection (UTI)	≥1
Urinary urgency	<1
Vaginal hemorrhage	<1
Vaginal moniliasis	<1
Vaginitis	<1
Hematologic	
Leukocytosis	<1
Leukopenia	<1
Musculoskeletal	
Generalized spasm	<1
Hypertonia	<1
Myalgia	≥1
Myasthenia	<1
Myoclonus	<1
Neck pain	≥1
Tenosynovitis	<1
Tremor	<1
Respiratory	
Asthma	<1
Bronchitis	≥1
Cough	≥1
Dyspnea	<1
Laryngismus	<1
Pharyngitis	3
Pneumonia	<1
Sinusitis	3

Adverse Event(s)	Selegiline
Other	
Anorexia	≥1
Appetite increased	<1
Bacterial infection	<1
Bilirubinemia	<1
Circumoral paresthesia	<1
Dehydration	<1
Dental caries	<1
Diaphoresis	≥1
Dysmenorrhea	≥1
Epistaxis	<1
Face edema	<1
Fungal infection	<1
Glossitis	<1
Heat stroke	<1
Hematuria	<1
Hernia	<1
Libido increased	<1
Lymphadenopathy	<1
Moniliasis	<1
Neoplasia	<1
Osteoporosis	<1
Otitis external	<1
Parasitic infection	<1
Periodontal abscess	<1
Salivation increased	<1
Sexual side effects	≤1
Suicide attempt	<1
Taste perversion	≥1
Tinnitus	≥1
Tongue edema	<1
Viral infection	<1
Visual field defect	<1
Weight loss	5

✓ =Percent not specified
- Event not reported or incidence <1%

Table 7. Black Box Warning for the Antidepressants[3]

Suicidality and Antidepressant Drugs
Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of [Insert established name] or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed 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. [Insert Drug Name] is not approved for use in pediatric patients. [The previous sentence would be replaced with the sentence, below, for the following drugs: Prozac: Prozac is approved for use in pediatric patients with MDD and obsessive-compulsive disorder (OCD). Zoloft: Zoloft is not approved for use in pediatric patients except for patients with obsessive-compulsive disorder (OCD). Fluvoxamine: Fluvoxamine is not approved for use in pediatric patients except for patients with obsessive-compulsive disorder (OCD).] (See Warnings: Clinical Worsening and Suicide Risk, Precautions: Information for Patients, and Precautions: Pediatric Use)

Table 8. Additional Black Box Warning For Nefazodone[23,41]

Hepatotoxicity in Elderly Patients with Dementia-Related Psychosis
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 (eg, 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 9. Additional Black Box Warning For Fluoxetine and Olanzapine[27,41]

Increased Mortality in Elderly Patients with Dementia-Related Psychosis
Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. SYMBYAX (olanzapine and fluoxetine HCl) is not approved for the treatment of patients with dementia-related psychosis.

VII. Dosing and Administration

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

Table 10. Usual Dosing for the Antidepressants[22-89]

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
Antidepressants—Monoamine Oxidase Inhibitors			
Isocarboxazid	Depression: Tablet: 10 mg two to three times 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
Phenelzine	Depression: Tablet: 15 mg three times per day; may increase to 60-90 mg/day during early phase of treatment, then reduce dose for maintenance therapy slowly after maximum benefit is obtained Elderly: Tablet: initial, 7.5 mg/day; increase by 7.5-15 mg/day every	Safety and efficacy in children have not been established.	Tablet: 15 mg

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
	three to four days as tolerated; usual therapeutic dose: 15-60 mg/day in three to four divided doses		
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
Antidepressants—Selective Serotonin- and Norepinephrine-reuptake Inhibitors			
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 Elderly: no dose adjustment is recommended on the basis of age 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 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	Safety and efficacy in children have not been established.	Capsule, delayed release: 20 mg 30 mg 60 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, sustained release: 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 Generalized Anxiety	Safety and efficacy in children have not been established.	Capsule, sustained release: 37.5 mg 75 mg 150 mg Tablet: 25 mg 37.5 mg 50 mg 75 mg 100 mg

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
	Disorder/Social Anxiety Disorder: Capsule, sustained release: 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, sustained release: 37.5 mg once daily for one week; may increase to 75 mg daily, with subsequent weekly increases of 75 mg/day; maximum: 225 mg/day		
Antidepressants—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: Oral: 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: Oral: initial, 5-10 mg/day; doses may be increased by 5-10 mg/day after at least one week	Safety and efficacy in children have not been established.	Solution: 5 mg/5 mL Tablet: 5 mg 10 mg 20 mg
Fluoxetine	Bulimia Nervosa: Oral, immediate release: 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: 60-80 mg/day; maximum: 80 mg/day; doses >20 mg may be given once daily or divided twice daily Depression: Oral, immediate release: 20 mg/day in the morning (lower doses of 5-10 mg/day have been used for initial treatment); may increase after	Depression: Children 8-18 years: Oral, immediate release: 10-20 mg/day; lower-weight children can be started on 10 mg/day, may increase to 20 mg/day after one week if needed Obsessive-Compulsive Disorder: Children 7-18 years: Oral, immediate release: 10 mg/day; in adolescents and higher-weight children, dose may be increased to 20 mg/day after two weeks; range: 10-60 mg/day	Capsule, immediate release: 10 mg 20 mg 40 mg Capsule, delayed release: 90 mg Solution: 20 mg/5 mL Tablet, immediate release: 10 mg

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
	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, delayed release: patients maintained on fluoxetine immediate release 20 mg/day may be changed to fluoxetine delayed-release capsule 90 mg/week, starting dose seven days after the last 20 mg/day dose Elderly: Oral, immediate release: 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; should not be taken at night unless patient experiences sedation <u>Obsessive-Compulsive Disorder:</u> Oral, immediate release: 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 <u>Panic Disorder:</u> Oral, immediate release: initial, 10 mg/day; after one week, increase to 20 mg/day; may increase after several weeks; doses >60 mg/day have not been evaluated <u>Premenstrual Dysphoric Disorder:</u> Oral, immediate release: 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)		20 mg
Fluoxetine and olanzapine	<u>Depression Associated with Bipolar Disorder:</u> Capsule: initial, fluoxetine 25 mg/olanzapine 6 mg once daily in the evening; dosing range: fluoxetine 25-50 mg/olanzapine 6-12 mg; safety of daily doses of fluoxetine >75 mg/olanzapine >18 mg have not been evaluated	Safety and efficacy in children have not been established.	Capsule (fluoxetine-olanzapine): 25 mg-3 mg 25 mg-6 mg 50 mg-6 mg 25 mg-12 mg 50 mg-12 mg

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
	Elderly: Capsule: initial, fluoxetine 25 mg/olanzapine 6 mg once daily in the evening; safety and efficacy have not been established in patients >65 years of age		
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 50 mg, the dose should be given in two divided doses Elderly: Tablet: reduce dose; 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, to maximum therapeutic benefit: range: 50-200 mg/day; maximum dose: children 8-11 years 200 mg/day and adolescents 300 mg/day; lower doses may be effective in female versus male patients; when total daily dose exceeds 50 mg, the dose should be given in two divided doses	Tablet: 25 mg 50 mg 100 mg
Paroxetine hydrochloride	Depression: Oral, immediate release: initial, 20 mg once daily, preferably in the morning; increase if needed by 10 mg/day increments at intervals of at least one week; maximum dose: 50 mg/day Tablet, sustained release: 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: Oral, immediate release: 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, sustained release: 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: Oral, immediate release: initial, 20 mg once daily, preferably in the morning; 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: Oral, immediate release: initial, 20	Safety and efficacy in children have not been established.	Suspension, oral: 10 mg/5 mL Tablet, immediate release: 10 mg 20 mg 30 mg 40 mg Tablet, sustained release: 12.5 mg 25 mg 37.5 mg

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
	mg once daily, preferably in the morning; 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; maximum dose: 60 mg/day <u>Panic Disorder:</u> Oral, immediate release: initial, 10 mg once daily, preferably in the morning; increase if needed by 10 mg/day increments at intervals of at least one week; recommended dose: 40 mg/day; range: 10-60 mg/day; maximum dose: 60 mg/day Tablet, sustained release: 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 <u>Premenstrual Dysphoric Disorder:</u> Tablet, sustained release: 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 <u>Posttraumatic Stress Disorder:</u> Oral, immediate release: initial, 20 mg once daily, preferably in the morning; 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 <u>Social Anxiety Disorder:</u> Oral, immediate release: 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, sustained release: initial, 12.5 mg once daily, preferably in the morning; increase if needed by 12.5 mg/day increments at intervals of at		

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
	least one week; maximum dose: 37.5 mg/day		
Paroxetine mesylate	Depression: Oral, immediate release: initial, 20 mg once daily, preferably in the morning; increase if needed by 10 mg/day increments at intervals of at least one week; maximum dose: 50 mg/day Elderly: Oral, immediate release: initial, 10 mg/day; increase if needed by 10 mg/day increments at intervals of at least one week; maximum dose: 40 mg/day Obsessive-Compulsive Disorder: Oral, immediate release: initial, 20 mg once daily, preferably in the morning; 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; maximum dose: 60 mg/day Panic Disorder: Oral, immediate release: initial, 10 mg once daily, preferably in the morning; increase if needed by 10 mg/day increments at intervals of at least one week; recommended dose: 40 mg/day; range: 10-60 mg/day; maximum dose: 60 mg/day	Safety and efficacy in children have not been established.	Tablet: 10 mg 20 mg 30 mg 40 mg
Sertraline	Depression/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 Elderly: Oral: 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: see above	Obsessive-Compulsive Disorder: Children 6-12 years: Oral: initial, 25 mg once daily Children 13-17 years: Oral: initial, 50 mg once daily May increase daily dose, at intervals of not less than one week; maximum: 200 mg/day; if somnolence is noted, give at bedtime	Concentrate, oral: 20 mg/mL Tablet: 25 mg 50 mg 100 mg

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
	Premenstrual Dysphoric Disorder: Oral: 50 mg/day either 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; if 100 mg/day has been established with luteal phase dosing, a 50 mg/day titration step for three days should be utilized at the beginning of each luteal phase dosing period		
Antidepressants—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: 25-50 mg at bedtime with 25-50 mg/day dose increase every three days for inpatients and weekly for outpatients, if tolerated; usual dose: 75-150 mg/day	Safety and efficacy in children have not been established.	Tablet: 50 mg 100 mg 150 mg 300 mg
Antidepressants—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: Adolescents: Tablet: initial, 25-50 mg/day; may administer in divided doses; increase gradually to 100 mg/day in divided doses Safety and efficacy in children <12 years of age have not been established.	Tablet: 10 mg 25 mg 50 mg 75 mg 100 mg 150 mg
Amitriptyline and chlordiazepoxide	Depression/Anxiety: Tablet: initial, three to four tablets in	Safety and efficacy in children have not been established.	Tablet (amitriptyline-chlordiazepoxide):

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
	divided doses; this 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		25 mg-10 mg 12.5 mg-5 mg
Amitriptyline and perphenazine	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 (amitriptyline-perphenazine): 10-2 mg 10-4 mg 25-2 mg 25-4 mg 50-4 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: Adolescents: Tablet: initial, 25-50 mg/day; increase gradually to 100 mg/day; may administer as divided doses or as a single dose at bedtime Safety and efficacy in children <16 years of age have not been established.	Tablet: 25 mg 50 mg 100 mg 150 mg
Clomipramine	Obsessive-Compulsive Disorder: Capsule: initial, 25 mg/day and gradually increase, as tolerated, to 100 mg/day the first two weeks; may then be increased to a total of 250 mg/day maximum	Obsessive-Compulsive Disorder: Children >10 years: Capsule: initial, 25 mg/day and gradually increase, as tolerated, to a maximum of 3 mg/kg/day or 200 mg/day, whichever is smaller Safety and efficacy in children <10 years of age have not been established.	Capsule: 25 mg 50 mg 75 mg
Desipramine	Depression: Tablet: initial, 75 mg/day in divided does; increase gradually to 150-200 mg/day 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	Depression: Adolescents: Tablet: initial, 25-50 mg/day; gradually increase to 100 mg/day in single or divided doses; maximum: 150 mg/day Safety and efficacy in children have not been established.	Tablet: 10 mg 25 mg 50 mg 75 mg 100 mg 150 mg
Doxepin	Depression/Anxiety: Oral: initial, 25-150 mg/day at	Depression/Anxiety: Adolescents: Oral: initial, 25-50	Capsule: 10 mg

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
	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: Oral: 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	mg/day in single or divided doses; gradually increase to 100 mg/day Safety and efficacy in children <12 years of age have not been established.	25 mg 50 mg 75 mg 100 mg 150 mg Concentrate, oral: 10 mg/mL
Imipramine	Depression: Capsule (outpatients): initial, 75 mg/day; dosage may be increased to 150 mg/day; if necessary, dosage may be increased to 200 mg/day; dosages higher than 75 mg/day may also be administered on a once-a day basis after optimum dosage and tolerance have been determined; the daily dosage may be given at bedtime; in some patients, it may be necessary to employ a divided-dose schedule; the usual maintenance dosage is 75 to 150 mg/day; total daily dosage can be administered on a once-a-day basis, preferably at bedtime; in some patient 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 when total daily dosage is established at 75 mg or higher	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 still seen 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 Safety and efficacy of Tofranil-PM® in children have not been established. In adolescents, Tofranil-PM® may be used when total daily dosage is established at 75 mg or higher.	Capsule (pamoate): 75 mg 100 mg 125 mg 150 mg Tablet (hydrochloride): 10 mg 25 mg 50 mg
Maprotiline	Depression/Anxiety: Tablet: initial, 75 mg/day; increase by 25 mg every two weeks up to 150-225 mg/day; given in three divided doses or in a single daily dose	Safety and efficacy in children <18 years of age have not been established.	Tablet: 25 mg 50 mg 75 mg

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
	Elderly: Tablet: 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		
Nortriptyline	Depression: Oral: 25 mg three to four times/day up to 150 mg/day Elderly: Oral: initial, 10-25 mg at bedtime; dosage can be increased by 25 mg every three days for inpatients and weekly for outpatients if tolerated; usual maintenance dose: 75 mg as a single bedtime dose or two divided doses; however, lower or higher doses may be required to stay within the therapeutic window	Safety and efficacy in children have not been established.	Capsule: 10 mg 25 mg 50 mg 75 mg Solution: 10 mg/5 mL
Protriptyline	Depression: 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	Safety and efficacy in children have not been established.	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: Capsule: 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: Capsule: initial, 50 mg/day with gradual increments up to 100 mg/day Safety and efficacy in children have not been established.	Capsule: 25 mg 50 mg 100 mg
Miscellaneous Antidepressants			
Bupropion	Depression: Tablet, immediate release: initial, 100 mg twice daily; maximum: 450 mg/day Tablet, sustained release: initial, 150 mg/day in the morning; may increase to 150 mg twice 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, sustained release 24 hours: initial, 150 mg/day in the morning; may increase as early as day four of dosing to 300 mg/day; maximum	Safety and efficacy in children have not been established.	Tablet, immediate release: 75 mg 100 mg Tablet, sustained release: 100 mg 150 mg 200 mg Tablet, sustained release 24 hours:

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
	dose: 450 mg/day Elderly: Tablet: initial, immediate release 37.5 mg twice daily or sustained release 100 mg/day; increase by 37.5-100 mg every three to four days as tolerated <u>Seasonal Affective Disorder:</u> Tablet, sustained release 24 hours: initial, 150 mg/day in the morning; if tolerated, may increase after one week to 300 mg/day <u>Smoking Cessation:</u> Tablet, immediate release: 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		150 mg 300 mg
Mirtazapine	<u>Depression:</u> Oral: initial, 15 mg nightly; titrate up to 15-45 mg/day with dose increases made no more frequently than every one to two weeks Elderly: Oral: initial, 7.5 mg/day as a single bedtime dose; increase by 7.5-15 mg/day every one to two weeks; usual dose: 15-30 mg/day; maximum dose: 45 mg/day	Safety and efficacy in children have not been established.	Tablet: 7.5 mg 15 mg 30 mg 45 mg Tablet, orally disintegrating: 15 mg 30 mg 45 mg
Miscellaneous Central Nervous System Agents—Monoamine Oxidase Inhibitors			
Selegiline	<u>Depression:</u> Patch: initial, 6 mg/24 hours once daily; may titrate based on clinical response in increments of 3 mg/day every two weeks up to a maximum of 12 mg/24 hours	Safety and efficacy in children have not been established.	Patch, transdermal: 6 mg/24 hours 9 mg/24 hours 12 mg/24 hours

VIII. Effectiveness

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

Table 11. Comparative Clinical Trials Using the Antidepressants

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Depression/Major Depressive Disorder (MDD)				
Moncrieff et al[90] Antidepressants vs active placebo	MA Patients with depression	N=751 9 studies Duration varied	Primary: Efficacy Secondary: Not reported	Primary: TCAs were statistically better than active placebo in the pooled analysis (0.39, 95% CI: 0.24 to 0.54). Secondary: Not reported
Walsh et al[91] Antidepressants vs placebo	MA Adult outpatients with MDD	N=not specified 75 trials Duration not specified	Primary: HAM-D, CGI Secondary: Not reported	Primary: The mean proportion of patients in the placebo group who responded was 29.7% (range, 12.5%-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. Secondary: Not reported
Geddes et al[92] Antidepressants vs placebo	MA 31 trials of which 15 compared TCAs with placebo for relapse prevention of depression	N=4,410 31 trials Trials ranged in length from 6-36 months	Primary: Proportion of patients relapsing; withdrawal from the trial Secondary: Not reported	Primary: Continuing treatment with antidepressants reduced the odds of relapse by 70% (95% CI: 62 to 78; $P<0.00001$) compared 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				from the trials than did those allocated to placebo (18% vs 15%, respectively; OR 1.30, 95% CI: 1.07 to 1.59). The two-thirds reduction in risk of depressive relapse seemed to be largely independent of the underlying risk of relapse, the duration of treatment before randomization, or the duration of the randomly allocated therapy. Secondary: Not reported
Archarya et al[93] Duloxetine 40-120 mg daily vs placebo	MA Patients taking duloxetine for major depressive disorder	N=2,996 (12 trials) Duration varied	Primary: Incidence of suicide-related events with duloxetine (MHID, MHRD, HAM-D Item-3) Secondary: Not reported	Primary: There were no significant differences in the incidence of suicide-related events with duloxetine 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 ($P<0.001$). Secondary: Not reported
Feighner et al[94] Nefazodone 200 mg twice daily vs placebo	DB, PC, PG Patients that were hospitalized due to depression	N=120 6 weeks	Primary: HAM-D-17, CGI-I, MADRS Secondary: Not reported	Primary: Nefazodone treatment resulted in a significant reduction ($P<0.01$) of the HAM-D-17 total score compared with placebo from the end of the first treatment week through the end of the study (–12.2 nefazodone vs –7.7 placebo). At the end of the trial, significantly more nefazodone-treated patients (50%) than placebo-treated patients (29%) had responded, as indicated by their CGI-I score ($P=0.021$) or by a $\geq$50% reduction in their HAM-D-17 scores ($P=0.017$). Significantly more patients treated with nefazodone (36%) than placebo-treated patients (14%) had a HAM-D-17 score $\leq$10 at the end of treatment ($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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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. Secondary: Not reported
Dunner DL et al[95] Paroxetine CR 12.5-62.5 mg vs placebo	Pooled analysis, DB, PC, RCT Adults with DSM-IV diagnosed MDD and nonsevere major depressive disorder	N=303 (4 studies) 8-12 weeks	Primary: Changes in depressive symptoms according to HAMD-17 and CGI-I, patients achieving remission Secondary: Not reported	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]). Secondary: Not reported
Weihs et al[96] Bupropion sustained-release 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, HAM-A, 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] Bupropion sustained-release (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, HAM-A, CGI-I, CGI-S Secondary: Adverse effects	Primary: Mean HAM-D, HAM-A, 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				patients. The adverse events of nausea, diarrhea, somnolence, and sweating were also experienced more frequently (*P*<0.05) in sertraline-treated patients. No differences were noted between the two treatments for vital signs and weight.
Rocca et al[98] Citalopram 20 mg daily vs sertraline 50 mg daily	DB, RCT Patients who were non-demented outpatients, age >65 years, with minor depressive disorder or subsyndromal depressive symptomatology	N=138 8 weeks	Primary: Change in depressive symptoms and remission rates (HAM-D) Secondary: Not reported	Primary: Both treatments induced notable improvement of depressive symptoms. No statistically significant differences were found between the 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 (*P* value not reported). 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. Secondary: Not reported:
Van Baardewijk et al[99] Duloxetine 40-120 mg daily for at least 8 weeks vs venlafaxine XR 75-225 mg daily for at least 8 weeks	MA Data derived from a Canadian meta-analysis of randomized placebo-controlled studies of adult patients with moderate-to-severe MDD according to DSM-IV and a score ≥ 15 on the HAM-D or ≥ 18 on the MADRS scale	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) Secondary: Not reported	Primary: Patients receiving duloxetine and venlafaxine XR experienced similar success rates after 6 months of treatment, 53% and 57%, respectively (*P* value not reported). Patients receiving duloxetine and venlafaxine XR experienced similar number of SFDs after 6 months of treatment, 52.72% and 57.03%, respectively (*P* value not reported). Duloxetine therapy was associated with a greater hospitalization rate compared to venlafaxine XR therapy, 47% and 43%, respectively (*P* value not reported). Secondary: Not reported
Moore et al[100] Escitalopram 20 mg daily	DB, MC, RCT Outpatients with	N=280 8 weeks	Primary: Change from baseline in the	Primary: Escitalopram group exhibited a greater improvement in the MADRS score compared to the citalopram arm (–22.4 vs –20.3, *P*<0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs citalopram 40 mg daily	major depressive disorder having an MADRS score of ≥30 at baseline		MADRS total score, adverse events, response to treatment, remission rate Secondary: Not reported	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 (*P* value not reported). Secondary: Not reported
Lam et al[101] Escitalopram 10-20 mg daily vs citalopram 20-40 mg daily	MA 3 DB, MC, R trials consisting of outpatients with major depressive disorder	N=1,321 3 trials 8 weeks	Primary: MADRS, response rate Secondary: CGI-I, CGI-S, HAMD	Primary: The analysis of pooled data demonstrated that the difference between citalopram and placebo was approximately constant; however, the difference between escitalopram and placebo (*P*=0.0010) and escitalopram and citalopram (*P*=0.0012) became greater the more severely depressed the patient was at baseline. No significant difference in response rate between the 2 treatment groups was seen at week 8. Secondary: Similar results were seen in the secondary outcomes.
Colonna et al[102] 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 (*P* value not reported). Secondary: Escitalopram patients had significantly better scores on the CGI-S at week 24 compared to citalopram patients (*P* value not reported).
Gorman et al[103] Escitalopram 10-20 mg daily vs citalopram 20-40 mg daily	MA 3 MC, R trials consisting of outpatients with major depressive disorder	N=1,321 3 trials 8 weeks	Primary: MADRS, CGI-I Secondary: Not reported	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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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). Secondary: Not reported
Wade et al[104] Escitalopram 20 mg daily vs duloxetine 60 mg daily	DB, RCT Patients diagnosed with major depressive disorder	N=294 24 weeks	Primary: Change from base-line in MADRS scores at week 24 Secondary: Not reported	Primary: At week 24, no significant difference was observed in MADRS (*P*=0.055). Secondary: Not reported
Khan et al[105] Escitalopram 10-20 mg daily (fixed at 10 mg daily for the first 4 weeks) vs duloxetine 60 mg daily	DB, MC, PG, RCT Patients diagnosed 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) Secondary: Not reported	Primary: At week 8, a significantly greater decrease in MADRS scores was observed in the escitalopram group compared to the duloxetine group using the LOCF approach (*P*<0.05). No significant differences in MADRS scores were observed between groups in the observed case (OC) analysis (*P*=0.79). Secondary: Not reported
Boulenger et al[106] Escitalopram 20 mg daily vs paroxetine 40 mg daily	DB, MC, R Patients with major depressive disorder and a baseline MADRS≥30	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	Sample 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).
Ventura et al[107] Escitalopram 10 mg daily vs sertraline 50-200 mg daily	MC, RCT Patients 18-80 years of age with a diagnosis of depression	N=212 8 weeks	Primary: Change from base-line in MADRS scores using the LOCF method Secondary: Not reported	Primary: No significant differences were observed between groups in the change from baseline in MADRS scores at week 8 (*P* value not reported). Secondary: Not reported
Montgomery, Huusom et al[108] Escitalopram 10-20 mg daily vs venlafaxine XR 75-150 mg daily	DB, RCT Patients with major depressive disorder	N=293 8 weeks	Primary: Change from baseline in MADRS scores Secondary: Not reported	Primary: No significant difference between groups was observed at week 8 in MADRS scores (*P* value not reported). Escitalopram-treated patients achieved remission significantly faster compared to venlafaxine patients in an ad hoc analysis (*P* value not reported). Secondary: Not reported
Thase et al[109] Imipramine (IMI) (mean dosage, 221 mg/day) vs sertraline (mean dosage, 163 mg/day)	DB, SS Patients with chronic major depression who failed to respond to 12 weeks of treatment with either imipramine or sertraline	N=168 12 weeks	Primary: HAM-D, CGI Secondary: Not reported	Primary: Response was defined as a 50% decrease in the 24 item HAM-D. The 2 groups were equal in response rates for completers, 63% and 55% for the sertraline and IMI groups, respectively (*P*=0.16). However, in the ITT analysis there was a statistically better outcome for the sertraline group (*P*=0.03). Those patients going from sertraline to IMI experienced significant increases in 8 adverse events and significant reductions in 3 adverse events while those patients going from IMI to sertraline experienced a significant reduction in 7 adverse events and no increase in any adverse event.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
Versiani et al[110] Mirtazapine 15-60 mg daily vs fluoxetine 20-40 mg daily	DB, RCT Adult patients 18-65 years old with DSM-IV diagnosis for major depressive episode	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] Mirtazapine 15-60 mg/day vs fluoxetine 20-40 mg/day	DB, MC, RCT Patients with major depressive disorder aged 18 to 75 years	N=123 6 weeks	Primary: HAM-D Secondary: Not reported	Primary: The mean HAM-D-17 scores were no different at week 6 for the two groups; although at week 3 (the estimated treatment difference was -3.4 in favor of mirtazapine; 95% CI: –6.1 to –0.76; *P*=0.006) and week 4 (the estimated treatment difference was -3.8 in favor of mirtazapine: 95% CI: –6.61 to –1.02, *P*=0.009), statistical significance was reported for mirtazapine. No other assessment endpoints were statistically different between the two groups at week 6. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Behke et al[112] 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] 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: A statistically significant difference favoring mirtazapine was found on the HAM-D Sleep Disturbance factor at all assessment points ($P\leq0.03$). Secondary: A statistically significantly higher percentage of patients treated with venlafaxine (15.3%) than mirtazapine (5.1%) dropped out because of adverse events ($P=0.037$).
Birkenhager et al[114] Phenelzine 10 mg twice a day vs tranylcypromine 10 mg twice a day	DB, RCT Patients with depression aged 18 to 65 years	N=77 5 weeks	Primary: HAM-D Secondary: Side effects	Primary: Seventeen (44%) of 39 patients responded to tranylcypromine and 18 (47%) of 38 patients responded to phenelzine (≥50% reduction in HAM-D; $P=0.82$). The mean reduction in HAM-D score was 10.4 ±8.3 for the tranylcypromine sample versus 8.3±8.4 for the phenelzine-treated patients ($P=0.23$). No significant differences in response between both drugs were observed ($P=0.97$). 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] Sertraline 150 mg daily vs fluvoxamine 200 mg daily	DB, RCT Patients >59 years of age with DSM-IV MDD	N=88 7 weeks	Primary: Response rate (HAM-D) Secondary: Not reported	Primary: Response rates were 55.6% for sertraline and 71.8% for fluvoxamine. No significant difference in final response rates were observed between treatment groups ($P=0.12$). Secondary: Not reported
Bielski, Ventura et al[116]	DB, RCT	N=195	Primary: MADRS	Primary: There were no significant differences in efficacy, remission rates, or

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Venlafaxine extended-release 225 mg/day vs escitalopram 20 mg/day	Patients with major depressive disorder	8 weeks	Secondary: Adverse effects	response rates between venlafaxine ER and escitalopram. Mean changes from baseline to endpoint in MADRS total score for escitalopram and venlafaxine XR were –15.9 and –13.6, respectively. Remission (MADRS score of ≤10) rates at endpoint were 41.2% for escitalopram and 36.7% for venlafaxine XR. Response (≥50% reduction from baseline MADRS score) rates for the escitalopram and venlafaxine XR groups were 58.8% and 48.0%, respectively. Secondary: More patients in venlafaxine ER group had treatment-emergent adverse effects compared to escitalopram (85.0% vs 68.4%) but this was not statistically significant and may have been due to rapid titration of the venlafaxine dose. Venlafaxine ER had a higher incidence of discontinuation due to adverse events (16% vs 4.1%; $P<0.01$).
Benkert et al[117] Venlafaxine 150-375 mg/day vs imipramine 200 mg/day	DB, PG, RCT Hospitalized patients with major depression and melancholia	N=167 6 weeks	Primary: HAM-D, MADRS Secondary: Not reported	Primary: No differences in the response rates on the HAM-D or MADRS were observed between treatments. However, among patients who demonstrated a response on the HAM-D, there was a significantly faster onset of response ($P=0.036$) and sustained response ($P=0.018$) in the venlafaxine group. The median time to response on the HAM-D among responders was 14 days with venlafaxine and 21 days with imipramine. However, no differences between treatments were observed among responders on the MADRS. Secondary: Not reported
Stahl, Zivkov et al[118] Mirtazapine up to 35 mg daily vs amitriptyline up to 280 mg daily	MA Randomized, double-blind, single-center, 6-week clinical trials of patients with major depressive episode who received	N=580 (4 trials) 6 weeks	Primary: HAM-D, HDRS, responder rate (percentages of patients with ≥50% decrease in baseline 17-item HDRS score),	Primary: Compared to placebo, both mirtazapine and amitriptyline therapy significantly improved patient HDRS, MADRS, and CGI scores from baseline ($P\leq0.05$). Significantly greater percentages of patients responded to mirtazapine or amitriptyline therapy, assessed with the HDRS criteria, compared to placebo ($P\leq0.05$).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo up to 7 capsules daily	mirtazapine, amitriptyline, or placebo after a 7-day washout period		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 randomized to mirtazapine or amitriptyline therapy exhibited remission compared to placebo ($P \leq 0.05$). There were no statistically significant differences between mirtazapine and amitriptyline in any of the primary endpoints (*P* value not reported). Secondary: Significantly greater improvement from baseline in the "depressed mood" item was seen in the mirtazapine and amitriptyline groups compared to placebo ($P \leq 0.05$). Significantly greater improvement from baseline in the anxiety/somatization, sleep disturbance, and melancholia factors was seen in the mirtazapine and amitriptyline groups compared to placebo ($P \leq 0.05$). 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 (*P* value not reported). 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 ($P \leq 0.05$). Patients on mirtazapine therapy experienced a significantly higher incidence of weight gain compared to the amitriptyline group (14.4% vs 6.7%; $P \leq 0.05$). Drowsiness and sedation were more common in the active groups compared to the placebo group ($P \leq 0.05$). Hypotension was more common in the amitriptyline group compared to the placebo (3.6% vs 0.5%; $P \leq 0.05$).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Increased appetite was more common in the mirtazapine group compared to the placebo group (3.6% vs 0; $P \leq 0.05$).
Clayton et al[119] Bupropion XL 300-450 mg daily vs escitalopram 10-20 mg daily vs placebo	DB, PC, RCT Adult outpatient with moderate-to-severe DSM-IV defined MDD with normal sexual function	N=830 8 weeks	Primary: Orgasm dysfunction at 8 weeks and incidence of worsened sexual functioning; CSFQ, HAM-D-17 Secondary: Not reported	Primary: The incidence of worsened sexual functioning at the end of the treatment period was statically significantly lower with bupropion XL than with escitalopram ($P<0.05$), not statistically different between bupropion XL and placebo ($P \geq 0.067$), 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 XL, 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 XL ($P<0.05$). Bupropion did not statistically differ from escitalopram with respect to mean change in HAM-D-17 total score, response or remission rates. Secondary: Not reported
Llorca et al[120] Escitalopram 10-20 mg daily vs citalopram 20-40 mg daily vs placebo	MA Patient between 18 and 80 years old with depression	N=506 (3 clinical trials) 8 weeks	Primary: MADRS Secondary: HAM-D, CGI-I, CGI-S	Primary: Mean change from baseline in MADRS total scores was significantly higher in the escitalopram-treated group compared with the citalopram-treated group ($P=0.003$). Response rates to escitalopram were 56% compared to 41% with citalopram ($P=0.007$). Secondary: The mean change in HAM-D from baseline between escitalopram and citalopram was in favor of escitalopram at endpoint ($P=0.007$). On both the CGI-I and CGI-S scales, patients showed a significant improvement at treatment endpoint in favor of escitalopram when compared with citalopram treatment ($P=0.01$ and $P=0.001$ for CGI-I and CGI-S, respectively).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Burke et al[121] Escitalopram 10 mg daily vs escitalopram 20 mg daily vs citalopram 40 mg daily vs placebo	DB, MC, RCT Outpatients between the ages of 18 and 65, meeting DSM-IV criteria for a major depressive episode of ≥4 weeks in duration, with MADRS score of >22 and a minimum score of 2 on item 1 (depressed mood) of the HAM-D score	N=491 9 weeks (1 week run-in; 8 weeks treatment phase)	Primary: Change from baseline in the MADRS total score at week 8 Secondary: Change from baseline in the MADRS total score at weeks 1,2,4, and 6, change from baseline in the HAM-D, CGI-S, CGI-I, HAM-A, QOL, and CES-D	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 ($P\leq0.05$). 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 $P\leq0.05$, respectively). Response to treatment was observed in 50% of escitalopram 10 mg, 51.2% of escitalopram 20 mg, and 45.6% of citalopram 40 mg groups; the difference in response rate was significantly greater than that of placebo group ($P<0.01$) but not statistically different among the three active groups (P value not reported). 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 ($P\leq0.01$). Patients randomized to the escitalopram 10 mg and 20 mg group exhibited significantly greater improvement in the HAM-A 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				(*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 (*P* value not reported); 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).
Nierenberg et al[122] Duloxetine 60 mg daily vs escitalopram 10 mg daily vs placebo	AC, DB, RCT, PC Patients 18 years of age or older diagnosed 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) Secondary: Not reported	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). Secondary: Not reported
Goldstein et al[123] Duloxetine 20-40 mg twice a day vs paroxetine 20 mg daily vs placebo	ACCS, DB, PC, RCT Patients with depression in the outpatient setting	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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				remission (57% for duloxetine 80 mg/day, 34% for paroxetine; *P*=0.022). Secondary: The only adverse event reported significantly more frequently for duloxetine 80 mg/day than for paroxetine was insomnia (19.8% for duloxetine 80 mg/day, 8.0% for paroxetine; *P*=0.031).
Vis et al[124] Duloxetine 40-120 mg daily vs venlafaxine XR 75-225 mg/day daily vs placebo	MA Studies include in MA were published, original, peer-reviewed papers reporting controlled, randomized, clinical trials with patients who were outpatients, >18 years of age, suffering from major depressive disorder	N=1,754 for efficacy N=1,791 for safety 8 studies 8 weeks	Primary: Remission and response (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 (all *P* values <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 (no *P* value reported). More patients in the active drug treatment groups than in the placebo groups dropped out due to adverse reactions (venlafaxine XR *P*<0.001; duloxetine *P*=0.008).
Nemeroff et al[125] Venlafaxine 75-225 mg/day vs fluoxetine 20-60 mg/day vs placebo	DB, MC, PC, RCT Outpatients that were 18 years or older with major depressive disorder	N=308 6 weeks	Primary: HAM-D Secondary: Not reported	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). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Rudolph et al[126] Venlafaxine extended-release 75-225 mg/day vs fluoxetine 20-60 mg/day vs placebo	DB, MC, PC, PG, RCT Outpatients, 18 years and older, who met DSM-IV criteria for major depressive disorder	N=301 8 weeks	Primary: HAM-D, MADRS, CGI Secondary: Not reported	Primary: The percentages of patients who achieved full remission of their depression (HAM-D total score ≤7) at the end of treatment were 37%, 22%, and 18% for the venlafaxine XR, fluoxetine and placebo groups, respectively. The differences in remission rates between venlafaxine XR and the other groups were statistically significant (*P*<0.05). Venlafaxine XR 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. Secondary: Not reported
Fava et al[127] Fluoxetine 20 mg daily vs sertraline 50 mg daily vs paroxetine 20 mg daily	DB, MC, RCT Patients with depression at least 18 years of age	N=284 10 to 16 weeks	Primary: HAM-D-17 scores Secondary: Improvement in insomnia/sleep disturbances	Primary: As indicated by baseline-to-endpoint improvement on the HAM-D-17, there were no statistically significant differences between fluoxetine, sertraline, and paroxetine on all outcome measures (*P*=0.365). Secondary: Insomnia improvement when using the sleep disturbance factor was similar in all patients with no significant difference between groups (*P*=0.868).
Perahia et al[128] Duloxetine 40 mg twice a day; dose titrated as follows: 3 days at 20 mg twice a day, then to 40 mg twice a day vs duloxetine 60 mg twice a day; dose titrated as follows: 3 days at 20 mg twice a day, 3 days at 40 mg twice a day, and then to	DB, MC, PC, RCT Patients age ≥ 18 meeting DSM-IV criteria for MDD	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%).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
60 mg twice a day vs paroxetine 20 mg daily; no titration vs placebo				
Thase et al[129] Phenelzine (PHZ) vs isocarboxazid (ISO) vs tranylcypromine (TRP) vs placebo	MA Patients with depression	Review of Medline and Psychological abstracts from 1959-1992	Primary: Efficacy Secondary: Not reported	Primary: For outpatients using ITT samples, all three agents appear to be equally effective (PHZ=57.9%±4.0%; ISO=60.1%±7.1%; TRP=52.6%±12.4%). When compared to placebo in outpatients, ISO (41.3%±18.0%) had a larger relative advantage compared to either PHZ (29.5% ±11.1%) or TRP (22.1%±25.4%) in the doses studied. For inpatients, PHZ was somewhat more effective (22.3%±30.7%) than placebo, whereas the ISO-placebo difference was smaller (15.3%±12.6%). Secondary: Not reported
Cipriani et al[130] Fluoxetine 20-80 mg daily vs sertraline 50-200 mg daily vs nortriptyline 50-175 mg daily vs	MA Study participants were diagnosed with depression	N=9,311 132 studies Duration varied	Primary: Number of patients who responded to treatment (HAM-D, MADRS) Secondary: Tolerability	Primary: On a dichotomous outcome fluoxetine was less effective than sertraline (PetoOR: 1.40, 95% CI: 1.11 to 1.76), mirtazapine (PetoOR: 1.64, 95% CI: 1.01 to 2.65) and venlafaxine (PetoOR: 1.40, 95% CI: 1.15 to 1.70; *P* value not reported). On a continuous outcome, fluoxetine was less effective than venlafaxine (SMD random effect: 0.11, 95% CI: 0.00 to 0.23; *P* value not reported). Secondary: Fluoxetine was better tolerated than tricyclic antidepressants considered as a group (PetoOR: 0.78, 95% CI: 0.68 to 0.89), and was better tolerated in comparison with individual antidepressants, in

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
amitriptyline 75 -300 mg daily vs venlafaxine 75-200 mg daily vs imipramine 75-300 mg daily vs nefazodone 200-500 mg daily vs citalopram 20-40 mg daily vs desipramine 125-250 mg daily vs paroxetine 20-60 mg daily vs placebo vs pramipexole* 5 mg daily vs fluvoxamine 100 -150 mg daily				particular than amitriptyline (PetoOR: 0.64, 95% CI: 0.47 to 0.85) and imipramine (PetoOR: 0.79, 95% CI: 0.63 to 0.99), and among newer antidepressants than pramipexole (PetoOR: 0.20, 95% CI: 0.08 to 0.47; *P* values not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs trazodone 50-400 mg daily vs bupropion 225-450 mg daily vs clomipramine 50-200 mg daily vs duloxetine 20-120 mg daily vs mirtazapine 30-60 mg daily vs doxepin 100-225 mg daily				
Bull et al[131] 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 physicians and patients, respectively ~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 (*P* value not reported). 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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Secondary: Not reported	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). Secondary: Not reported
Anderson et al[132] Tricyclic antidepressants (TCAs) vs Selective serotonin-reuptake inhibitors (SSRIs)	MA Patients with depression	N=10,706 102 studies Duration varied	Primary: HAM-D, MADRS Secondary: Adverse events	Primary: Efficacy was based on 102 studies (5,533 SSRI patients and 5,173 TCA patients). Efficacy was determined by comparing the mean reduction in depression scores based upon the HAM-D or the MADRS. There was no statistical difference in efficacy between the two groups (effect size –0.03, 95% CI: –0.09 to 0.03). TCAs did appear more effective for inpatients (–0.23, 95% CI: –0.4 to -0.05). Secondary: SSRIs were better tolerated with discontinuations due to adverse effects significantly greater in the TCA group (12.4% vs 17.3%, *P*<0.0001).
MacGillivray et al[133] Tricyclic antidepressants (TCAs) vs Selective serotonin-reuptake inhibitors (SSRIs)	MA Patients with depression in primary care	N=2,951 11 studies Duration varied	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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Steffens et al[134] Tricyclic antidepressants (TCAs) vs Selective serotonin-reuptake inhibitors (SSRIs)	MA Patients with depression	N=not specified 34 studies Duration varied	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 significantly more gastrointestinal problems and sexual dysfunction, whereas treatment with TCAs produced significantly more complaints of sedation, dizziness, and anticholinergic symptoms.
Generalized Anxiety Disorder (GAD)				
Davidson et al[135] Escitalopram 10-20 mg daily	FD, MC, OL extension study Patients who completed an 8-week, DB, PC, lead-in and were diagnosed with GAD were eligible to enter extension trial	N=526 24 week	Primary: CGI-I, HAM-A core $\leq$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] 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: HAM-A Secondary: CGI-S, CGI-I	Primary: Escitalopram significantly improved mean HAM-A total scores (the primary efficacy measure) relative to placebo with the mean change from baseline to week 8 in HAM-A total score –10.1 $\pm$ 0.3 for escitalopram and –7.6 $\pm$ 0.3 for placebo (*P*<0.001). Secondary: Escitalopram led to statistically significant improvements compared to placebo in both HAM-A subscales: psychic anxiety (–5.8+ 0.2 vs –3.9 $\pm$ 0.2; *P*<0.001; and somatic anxiety (–4.3 $\pm$ 0.2 vs –3.7 $\pm$ 0.2; *P*=0.02). At endpoint, 47.5% of escitalopram-treated patients and 28.6% of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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).
Dahl et al[137] Sertraline 50-150 mg daily vs placebo	BD, MC, RCT Patients were out-patients who met DSM-IV criteria for GAD based on clinical assessment and a structured interview	N=373 12 weeks	Primary: The change from baseline to endpoint in HAM-A 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 HAM-A 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 (*P* value not reported). 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).
Bielski, Bose et al[138] Escitalopram 10 to 20 mg daily vs paroxetine 20 to 50 mg daily	DB, RCT Patients diagnosed with GAD via the DSM-IV criteria	N=121 24 weeks	Primary: Mean change from baseline in the Hamilton Anxiety Scale (HAM-A) scores at week 24, treatment-emergent adverse effects Secondary: Not reported	Primary: After 24 weeks of treatment, patients receiving escitalopram had significantly greater improvement in the HAM-A 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%, *P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The following adverse events were noted to occur more frequently in the paroxetine group compared to the escitalopram-treated patients: insomnia (25.8% vs 14.8%), constipation (14.5% vs 1.6%), ejaculation disorder (30.0% vs 14.8%), anorgasmia (26.2% vs 5.9%), and decreased libido (22.6% vs 4.9%); (*P* value not reported). 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; *P* value not reported). Secondary: Not reported
Ball et al[139] Paroxetine 10-40 mg daily vs sertraline 25-100 mg daily	DB, FD, PG Patients with primary GAD	N=55 8 weeks	Primary: HAM-A 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 HAM-A scores from baseline to end of treatment ($P<0.001$). The mean percent reduction in HAM-A scores was 57.3% + 27.6% for the paroxetine group and 55.9% +27.6% for the sertraline group. With treatment response defined as 50% reduction in HAM-A from baseline to posttreatment, the percent of treatment responders was 68% in the paroxetine group and 61% in the sertraline group (*P* value not reported). 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 (*P* value not reported).
Schmitt et al[140] Venlafaxine 37.5 mg daily vs venlafaxine 75 mg daily	MA All randomized controlled trials assessing the use of antidepressants in GAD, non-randomized trials and	N=2,238 Duration of study varied from 8 weeks - 28 weeks	Primary: Absence of treatment response (treatment response is defined as absence of sufficient symptoms to meet	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 nontreatment response was 0.70 (95% CI: 0.62 to 0.79), favoring antidepressant treatment. The

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs venlafaxine 150 mg daily vs placebo vs paroxetine 20 mg daily vs imipramine 143 mg daily vs trazodone 225 mg daily vs diazepam 26 mg daily vs venlafaxine 225 mg daily vs imipramine 50-100 mg daily vs paroxetine 20 mg daily vs sertraline	those that included patients with both GAD and another Axis I comorbidity were excluded		diagnostic criteria for generalized anxiety disorder) Secondary: Acceptability of the treatment as measured by the number of people dropping out during the trial	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 nontreatment 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	Sample Size and Study Duration	End Points	Results
Obsessive-compulsive Disorder (OCD)				
Koran et al[141] 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 Secondary: Not reported	Primary: The mean reduction in Y-BOCS for the fluvoxamine group was 30.2% and for the clomipramine group 30.0% (*P*=NS). At the end of treatment, 56% of fluvoxamine patients were classified as responders (≥25% decrease in Y-BOCS score), compared 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. Secondary: Not reported
Denys et al[142] Paroxetine 15-60 mg daily vs venlafaxine 75-300 mg daily	DB, PG, RCT Patients with OCD	N=150 12 weeks	Primary: Y-BOCS Secondary: Not reported	Primary: Following an intent-to-treat, last-observation-carried-forward analysis, both paroxetine and venlafaxine were efficacious with a mean decrease of 7.8 ± 5.4 and 7.2 ± 7.5 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. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Mundo et al[143] Fluvoxamine 100 mg - 300 mg daily vs paroxetine 20 mg - 60 mg daily vs citalopram 20 mg - 60 mg daily	RCT Patients with OCD	N=30 10 weeks	Primary: NIMH-OC, Y-BOCS, HAM-D, CGI Secondary: Not reported	Primary: No significant differences were noted between the treatment groups (*P*=0.000). Results performed on NIMH-OC and Y-BOCS obsessions, compulsions, and total scores did not show any significant effect of the variable group (treatment) but only a significant effect of time (NIMH-OC: *P*=0.000; Y-BOCS obsessions: *P*=0.000; Y-BOCS compulsions: *P*=0.000; Y-BOCS total: *P*=0.000) and no significant effect of their interaction. Similar results were derived from the ANOVA with repeated measures performed on HAM-D total scores (time effect: *P*=0.000). Secondary: Not reported
Panic Disorder				
Van Ameringen et al[144] Nefazodone 300-600 mg daily; started at 100 mg daily in divided doses, doses were increased to 200 mg daily by week 2, and up to 300 mg daily by week 4 with a maximum dose of 600 mg daily vs placebo	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 Secondary: Not reported	Primary: 31.4% of nefazodone-treated patients and 23.5% of placebo-treated patients were considered responders at study endpoint (*P*=0.38). Secondary: Not reported
Sheehan et al[145] 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, HAM-A	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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Paroxetine CR was statistically more effective compared to placebo in alleviating general anxiety symptoms as measured by HAM-A; *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.
Stahl, Gergel et al[146] 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 Secondary: Not reported	Primary: A significant decrease in the frequency of panic attacks was observed in both the escitalopram and citalopram groups compared to placebo ($P \leq 0.05$). Secondary: Not reported
Rampello et al[147] 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 (*P* value not reported). Secondary: No significant differences were observed at 8 weeks in the Hamilton scales for anxiety and depression and in the Cooper Disability Scale scores (*P* value not reported). 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).
Bandelow et al[148] 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 nonagoraphobia subtypes.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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] Paroxetine 10 mg daily vs paroxetine 20 mg daily vs paroxetine 40 mg daily	DB, PG, PC, RCT Patients with panic disorder 18 years of age or older	N=278 10 weeks	Primary: Change in panic attacks from baseline, CGI-S Secondary: Marks-Sheehan Phobia Scale, Hamilton Anxiety Rating Scale, Montgomery-Asberg Depression Rating Scale	Primary: The percent of 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 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 nonsignificantly in all groups. 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 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.
Posttraumatic Stress Disorder (PTSD)				
Davidson et al[150] Fluoxetine 10-60 mg daily vs placebo	OL, RCT Patients diagnosed with PTSD, between ages of 18 and 70; patients were exclu-ded if history of	N=123 6 months	Primary: Rate of relapse defined by a change in CGI-I score that reverted back to no improvement rela-tive to baseline or	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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	bipolar, schizophre-nia, organic brain disease, alcohol or drug abuse, or mental retardation were present		worse, CGI-I score which increased by at least 2 points Secondary: CGI-S, SPRINT	meet significance for the SPRINT and CGI-S (*P*=0.08).
Friedman et al[151] Sertraline 250-200 mg daily vs placebo	DB, PC, RCT Patients had DSM-III-R diagnosis of combat-related PTSD and scored 50 or higher on CAPS-2 at the end of a 1 week placebo run in period	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[152] Paroxetine CR 12.5 mg daily or 25 mg daily vs placebo	DB, MC, PC, RCT Patients with PMDD aged 18-45 years with regular menstrual cycles	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 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[153] Paroxetine CR 12.5 mg daily vs	DB, MC, PC, RCT Female patients aged 18-45 years who had regular menstrual cycles and who met	N=373 3 menstrual cycles	Primary: VAS-Mood Secondary: Change form baseline to	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,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
paroxetine CR 25 mg daily vs placebo	the criteria for PMDD as outlined in DSM-IV		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	*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 Disease				
Wernicke et al[154] Duloxetine vs placebo	MA Randomized, double-blind, placebo-controlled clinical trials of patients diagnosed with either an MDD, diabetic peripheral neuropathy, fibromyalgia, generalized anxiety disorder, or lower urinary tract infection	N=8,504 (42 trials) 4-12 weeks	Primary: Vital signs, ECG findings, cardiovascular side effects of the study drug Secondary: Not reported	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 (*P* value not reported). 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.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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. Secondary: Not reported
Mullins et al[155] 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 Secondary: Not reported	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). Secondary : Not reported
Stein et al[156] Cochrane Review, including 17 SSRI trials, 3 MAOI (phenelzine) trials, 9 trials with reversible monoamine oxidase inhibitors (RIMAs including moclobemide*, brofaromine*), 9 trials with "other medications" including benzodiazepines, beta blocker, buspirone, gabapentin, and olanzapine in social anxiety disorder	MA 36 randomized controlled trials for social anxiety disorders 25 trials were short term (≤14 weeks or less); 7 trials had maintenance component; 8 trials had a relapse component; trials were completed prior to 2003	N=5,264 36 trials Duration varied	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). 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.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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).

*Product not available in the United States
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, HAM-A=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:
The dosing schedule of antidepressants varies according to the indication and individual being treated. Many generic antidepressants, including ones from the SSRI and tricyclic antidepressant categories, are available in formulations that can be dosed once a day. A literature search revealed no peer-reviewed studies that reported a difference in clinical outcomes based on the antidepressant's dosing schedule or regimen. One randomized, nonblinded trial compared continued compliance rates with fluoxetine 90 mg once weekly to fluoxetine 20 mg once daily in patients who had previously received four weeks of fluoxetine 20 mg once daily.[157] At the end of 12 weeks, compliance rates 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:
Although the different SSRIs show similar efficacy, the differences in their adverse event profile may result in patients switching to another agent within the SSRI class, or to another antidepressant class altogether.[91] In one study which compared fluoxetine, imipramine (IMI) and desipramine (DES) for duration of initial therapy , fluoxetine was taken for a longer period of time than desipramine or imipramine ($P<0.001$ for either DES or IMI). Statistical comparisons between the two TCAs were not done but they were numerically similar. The difference in duration of therapy was due primarily to less tolerability of desipramine and imipramine. Only 9% of the patients switched from fluoxetine due to adverse events while 27% and 28% assigned to DES and IMI respectively switched due to adverse events ($P<0.001$ for both TCAs compared to fluoxetine). The overall length of antidepressant therapy (if the patient switched to another agent) was not different regardless of which agent was initiated first. In addition, response to medication as measured by the HDRS was equivalent.[158] The authors measured total health care costs and found no difference between the 3 groups.[159]

Impact on Physician Visits:
One study comparing health care costs of fluoxetine versus imipramine and fluoxetine versus desipramine compared outpatient costs to primary care and to mental health.[159] The authors found no difference in primary care visit cost in either comparison (fluoxetine versus desipramine $P=0.19$ and fluoxetine versus imipramine $P=0.98$). There was also no difference in mental health outpatient visit cost in either comparison group (fluoxetine versus desipramine, $P=0.33$ and fluoxetine versus imipramine, $P=0.73$).[159]

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 12. Relative Cost of the Antidepressants

Generic Name	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Antidepressants—Monoamine Oxidase Inhibitors				
isocarboxazid	tablet	Marplan®	$$$$	N/A
phenelzine	tablet	Nardil®	$$$	N/A
tranylcypromine	tablet	Parnate®*	$$$	$$$
Antidepressants—Selective Serotonin- and Norepinephrine-reuptake Inhibitors				
duloxetine	delayed-release capsule	Cymbalta®	$$$$	N/A
venlafaxine	sustained-release capsule, tablet	Effexor®*, Effexor XR®	$$$-$$$$	$$$
Antidepressants—Selective Serotonin-reuptake Inhibitors				
citalopram	solution, tablet	Celexa®*	$$$$	$-$$$
escitalopram	solution, tablet	Lexapro®	$$$	N/A
fluoxetine	capsule, delayed-release capsule, solution, tablet	Prozac®*, Prozac Weekly®, Sarafem®	$$$$$	$$
fluoxetine and olanzapine	capsule	Symbyax®	$$$$$	N/A
fluvoxamine	tablet	Luvox®*†	N/A	$$$
paroxetine hydrochloride	oral suspension, sustained-release tablet, tablet	Paxil®*, Paxil CR®	$$$-$$$$$	$$$
paroxetine mesylate	tablet	Pexeva®	$$$$	N/A
sertraline	oral concentrate, tablet	Zoloft®*	$$$$	$
Antidepressants—Serotonin Modulators				
nefazodone	tablet	Serzone®*†	N/A	$
trazodone	tablet	Desyrel®*	$	$
Antidepressants—Tricyclics and Other Norepinephrine-reuptake Inhibitors				
amitriptyline	tablet	Elavil®*†	N/A	$
amitriptyline and chlordiazepoxide	tablet	Limbitrol®*, Limbitrol DS®*	$$-$$$	$$
amitriptyline and perphenazine	tablet	Etrafon A 4-10®*†	N/A	$
amoxapine	tablet	Asendin®*†	N/A	$$
clomipramine	capsule	Anafranil®*	$$$$$	$
desipramine	tablet	Norpramin®*	$$$	$
doxepin	capsule, oral concentrate	Sinequan®*†	N/A	$
imipramine	capsule, tablet	Tofranil®*, Tofranil-PM®*	$$$$$	$-$$$$$
maprotiline	tablet	Ludiomil*†	N/A	$
nortriptyline	capsule, solution	Pamelor®*	$$$$$	$
protriptyline	tablet	Vivactil®	$$$$$	N/A
trimipramine	capsule	Surmontil®*	$$$$	$$$$
Miscellaneous Antidepressants				
bupropion	sustained-release tablet, sustained-release tablet 24 hours, tablet	Wellbutrin®*, Wellbutrin SR®*, Wellbutrin XL®*	$$$$	$$$-$$$$
mirtazapine	orally disintegrating tablet, tablet	Remeron®*	$$$	$$
Miscellaneous Central Nervous System Agents—Monoamine Oxidase Inhibitors				
selegiline	transdermal patch	Emsam®‡	$$$$$	N/A

*Generic is available in at least one dosage form or strength.
†Brand is no longer available.
‡Generic is available in other dosage forms, but is not indicated for the treatment of depression.
N/A=not available

X. Conclusions

The antidepressants are indicated to treat a number of psychological disease states including but not limited to depression, anxiety disorders, obsessive compulsive disorders, and eating disorders. There are many agents in this class and most of them are available generically. National and international treatment guidelines do address the use of these agents for their respective FDA-approved indications. Guidelines for the treatment of depression state that selecting an agent should be driven by anticipated side effects, tolerability, patient preference, and quantity and quality of available clinical data, and that the effectiveness of antidepressants is usually comparable within medication classes, and comparable between medication classes.[5] Guidelines also state that medications that can be considered first-line therapy for most patients include selective serotonin-reuptake inhibitors (SSRIs), desipramine, nortriptyline, bupropion, and venlafaxine, while monoamine oxidase inhibitors (MAOIs) should be reserved for patients who are unresponsive to other available medications. These guidelines do not recommend one SSRI or MAOI over another.[5,6]

For the treatment of generalized anxiety disorder, antidepressants are recommended as first-line treatment, with the following agents considered treatment options: SSRIs, serotonin- and norepinephrine-reuptake inhibitors (SNRIs), and nonsedating tricyclic antidepressants (TCAs). Benzodiazepines may be used as adjunct agents in acute exacerbations of GAD and buspirone has also demonstrated efficacy in GAD in most clinical trials, although it has not shown efficacy against comorbid conditions and therefore is not recommended as first-line treatment for GAD.[9] First-line treatments for obsessive-compulsive disorder include cognitive-behavioral therapy (CBT), SSRIs, or a combination of the two. Clomipramine, fluoxetine, fluvoxamine, paroxetine, and sertraline are also FDA approved for the treatment of OCD. Guidelines do note that all SSRIs appear to be equally effective, though patients may respond to agents differently.[13]

Although some studies have shown a benefit when one agent is compared to another, these results have not been consistantly demonstrated. The majority of clinical studies support the conclusion that antidepressants are of equivalent efficacy when administered in comparable doses. The choice of an antidepressant is influenced by the patient's diagnosis, current medical history, past history of response, the potential for drug-drug interactions, and the adverse events profile. Treatment failure to one antidepressant class or to any specific antidepressant within a class does not predict treatment failure to another antidepressant agent, either within or outside of the same drug class.

The SSRIs, almost all of which are available generically, appear to be better tolerated than the tricyclic and other norepinephrine-reuptake inhibitors but the long term risk of relapse is comparable. All are statistically better than placebo. The MAOIs are effective treatments for patients with major depressive disorder; however, drug interactions, dietary restrictions, and side effects greatly limit their use. Guidelines also state that MAOIs should be reserved for patients who are unresponsive to other available medications. Although the MAOIs have been used in clinical practice for many years, there are limited head-to-head trials comparing these agents with each other and with the newer antidepressant classes. Since the last review of the antidepressants the transdermal dosage form of selegiline has been FDA approved. It has been reported that this agent is associated with the concerns of the oral MAOIs to a lesser extent. However this agent should still be reserved for patients who have failed first-line therapies or who are unable to take medications by mouth and 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 over-the-counter products in this class and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

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

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

References

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th ed., text revision (DSM-IV-TR). Washington, DC: American Psychiatric Association; 2000:356.
2. American Psychiatric Association practice guideline for the treatment of patients with major depressive disorder. Am J Psychiatry. 2000 Apr;157 (4 Suppl):1-45.
3. Antidepressant use in children, adolescents, and adults [Internet]. Rockville (MD): Food and Drug Administration (US): 2004 Mar 22 [updated 2007 May 2; cited 2007 Sep 25]. Available from: http://www.fda.gov/cder/drug/antidepressants/default.htm
4. Central nervous system agents 28:00, Psychotherapeutic Agents 28:16, Antidepressants 28:16.04. In: McEvoy GK, editor; American Hospital Formulary Service. AHFS drug information 2007 [monograph on the Internet]. Bethesda (MD): American Society of Health-System Pharmacists; 2007 [cited 2007 Sep 24]. Available from: http://online.statref.com.
5. Practice guideline for the treatment of patients with major depressive disorder (revision). American Psychiatric Association. Am J Psychiatry. 2000 Apr;157(4 Suppl):1-45. Available from: http://www.psych.org/psych_pract/treatg/pg/MDD2e_05-15-06.pdf.
6. Fochtmann LJ, Gelenberg AJ. Guideline watch: practice guideline for the treatment of patients with major depressive disorder, 2nd edition [guideline on the Internet]. American Psychiatric Association; 2005 Sep [cited 2007 Sep 24]. Available from: http://www.psych.org/psych_pract/treatg/pg/MDD.watch.pdf.
7. Birmaher B, Brent D, Bernet W, Bukstein O, Walter H; AACAP Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with depressive disorders [guideline on the Internet]. Washington (DC): American Academy of Child and Adolescent Psychiatry, 2007 [approved 2007 Jun 1; cited 2007 Oct 10]. Available from: http://www.aacap.org/galleries/PracticeParameters/InPress_2007_DepressiveDisorders.pdf.
8. National Collaborating Centre for Mental Health, National Institute for Clinical Excellence (NICE). Depression: management of depression in primary and secondary care [guideline on the Internet]. London (UK): National Institute for Clinical Excellence (NICE); 2004 Dec [cited 2007 Oct 9]. Available from: http://guidance.nice.org.uk/CG23/guidance/pdf/English.
9. Ballenger J, et al. Consensus statement on generalized anxiety disorder from the International Consensus Group on Depression and Anxiety. J Clin Psychiatry. 2001;62 Suppl 11:53-58.
10. McIntosh A, Cohen A, Turnbull N, Esmonde L, Dennis P, Eatock J, et al. Clinical guidelines for the management of anxiety. Management of anxiety (panic disorder, with or without agoraphobia, and generalized anxiety disorder) in adults in primary, secondary and community care [guideline on the internet]. London (UK): National Institute for Clinical Excellence (NICE); 2004 Dec [cited 2007 Jul 30]. Available from: http://guidance.nice.org.uk/CG22/guidance/pdf/English.
11. Ballenger J, et al. Consensus statement on panic disorder from the International Consensus Group on Depression and Anxiety. J Clin Psychiatry. 1998;59 Suppl 8:47-54.
12. Ballenger J, Davidson J, Lecrubier Y, Nutt D, Bobes J, Beidel D, Ono Y, et al. Consensus statement on social anxiety disorder from the International Consensus Group on Depression and Anxiety. J Clin Psychiatry. 1998;59 Suppl 17:54-60.
13. Koran L, Hanna G, Hollander E, Nestadt G, Simpson H; American Psychiatric Association. Practice guideline for the treatment of patients with obsessive-compulsive disorder. Arlington (VA): American Psychiatric Association, 2007 Jul [cited 2007 Sep 24]. Available from: http://www.psych.org/psych_pract/treatg/pg/OCDPracticeGuidelineFinal05-04-07.pdf.
14. March JS, Frances A, Kahn DA, Carpenter D, editors. The expert consensus guideline series: treatment of obsessive-compulsive disorder. J Clin Psychiatry. 1997 (Suppl 4):58.
15. Grados M, Riddle M. Obsessive-compulsive disorder in children and adolescents: treatment guidelines. CNS Drugs. 1999;12(4):257-277.
16. National Collaborating Centre for Mental Health, National Institute for Clinical Excellence (NICE). Obsessive-compulsive disorder: core interventions in the treatment of obsessive-compulsive disorder and body dysmorphic disorder. London (UK): National Institute for Clinical Excellence (NICE); 2006 Jan [cited 2007 Sep 24]. Available from http://www.nice.org.uk/CG031.
17. Ursano RJ, Bell C, Eth S, Friedman M, Norwood A, Pfefferbaum B, et al; American Psychiatric Association. Practice guideline for the treatment of patients with acute stress disorder and posttraumatic stress disorder [guideline on the Internet]. Arlington (VA): American Psychiatric Association; 2004 Nov [cited 2007 Sep 24]. Available from: http://www.psych.org/psych_pract/treatg/pg/ASD_PTSD_05-15-06.pdf.

18. American College of Obstetricians and Gynecologists (ACOG). Premenstrual syndrome. Washington (DC): American College of Obstetricians and Gynecologists (ACOG); 2000:1-9.
19. Steiner M. Premenstrual syndrome and premenstrual dysphoric disorder: guidelines for management. J Psychiatry and Neuroscience. 2000;25(5):459-467.
20. Steiner M, Pearlstein T, Cohen L. et al. Expert guidelines for the treatment of severe PMS, PMDD, and co-morbidities: the role of SSRI's. Journal of Women's Health. 2006;15(1):57-69.
21. Yager J, Devlin MJ, Halmi KA, et al. American Psychiatric Association (APA). Practice guidelines for the treatment of patients with eating disorders. Arlington, VA: American Psychiatric Association; 2006 Jun:1-128: [cited 2007 October 9]. Available from: http://www.psych.org/psych_pract/treatg/pg/EatingDisorders3ePG_04-28-06.pdf.
22. Micromedex® Healthcare Series [database on the internet]. Greenwood Village (CO): Thomson Micromedex, 2007 [cited 2007 Sep 24]. Available from: http://www.thomsonhc.com/.
23. Drug Facts and Comparisons 4.0 [database on the Internet]. St. Louis (MO): Wolters Kluwer Health, Inc; 2007 [cited 2007 Sep 24]. Available from: http://online.factsandcomparisons.com.
24. Marplan® [package insert]. Parsippany (NJ): Validus Pharmaceuticals; 2007 Jun.
25. Nardil® [package insert]. New York (NY): Pfizer Inc; 2007 Jul.
26. Parnate® [package insert]. Research Triangle Parke (NC): GlaxoSmithKline; 2007 Jun.
27. Cymbalta® [package insert]. Indianapolis (IN): Eli Lilly and Company; 2007 Jun.
28. Effexor®, [package insert]. Philadelphia (PA): Wyeth Pharmaceuticals Inc; 2007 Sep.
29. Effexor XR® [package insert]. Philadelphia (PA): Wyeth Pharmaceuticals Inc; 2007 Sep.
30. Celexa® [package insert]. St. Louis (MO): Forest Pharmaceuticals; 2007 May.
31. Lexapro® [package insert]. St. Louis (MO): Forest Pharmaceuticals; 2007 May.
32. Prozac® [package insert]. Indianapolis (IN): Eli Lilly and Company; 2007 Jun.
33. Sarafem® [package insert]. Rockaway (NJ): Warner-Chilcott; 2007 Apr.
34. Symbyax® [package insert]. Indianapolis (IN): Eli Lilly and Company; 2007 Oct..
35. Zyprexa® [package insert]. Indianapolis (IN): Eli Lilly and Company; 2006 Nov.
36. Fluvoxamine maleate tablet [package insert on the Internet]. Detroit (MI): Caraco Pharmaceutical Laboratories, Ltd; 2007 Sep [cited 2007 Oct 5]. Available from: http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=5329.
37. Paxil® [package insert]. Research Triangle Parke (NC): GlaxoSmithKline; 2007 Jun.
38. Paxil CR® [package insert]. Research Triangle Parke (NC): GlaxoSmithKline; 2007 Aug.
39. Pexeva® [package insert]. New York (NY): JDS Pharmaceuticals, LLC; 2007 Jun.
40. Zoloft® [package insert]. New York (NY): Pfizer Inc; 2007 Jul.
41. Serzone® [package insert on the Internet]. Princeton (NJ): Bristol-Myers Squibb; 2007 Jun [cited 2007 Oct 5]. Available from http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=4522.
42. Trazodone hydrocloride tablets [package insert]. Weston (FL): Apotex Inc; 2006 Sep.
43. Amitriptyline hydrochloride tablets [package insert]. Princeton (NJ): Sandoz Inc; 2007 Aug.
44. Chlordiazepoxide and amitriptyline hydrochloride tablet [package insert on the Internet]. Morgantown (WV): Mylan Pharmaceuticals Inc; 2007 Aug [cited 2007 Oct 5]. Available from: http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=5172.
45. Perphenazine and amitriptyline hydrochloride tablet [package insert on the Internet]. Morgantown (WV): Mylan Pharmaceuticals Inc; 2007 Sep. Available from: http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=5154.
46. Amoxapine tablet [package insert on the Internet]. Corona (CA):Watson Laboratories, Inc; 2007 May [cited 2007 Sep 24]. Available from: http://pi.watson.com/data_stream.asp?product_group=1199&p=pi&language=E
47. Anafranil® [package insert]. Hazelwood (MO): Mallinckrodt Inc; 2007 May.
48. Desipramine hydrochloride tablets [package insert]. Princeton (NJ): Sandoz Inc; 2007 Aug.
49. Doxepin hydrochloride capsules [package insert]. Spring Valley (NY): Par Pharmaceuticals; 2007 Aug.
50. Imipramine hydrochloride tablets [package insert]. Princeton (NJ): Sandoz Inc; 2007 May.
51. Tofranil-PM® [package insert]. Hazelwood (MO): Mallinckrodt Inc; 2007 May.
52. Maprotiline hydrochloride tablet [package insert on the Internet]. Morgantown (WV): Mylan Pharmaceuticals Inc; 2007 May. Available from: http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=4636.
53. Pamelor® [package insert]. Hazelwood (MO): Mallinckrodt Inc; 2007 May.
54. Vivactil® [package insert]. West Point (PA): Merck & Co; 1996 Jan.
55. Surmontil® [package insert]. Pomona (NY): Duramed Pharmaceuticals; 2007 Jun.
56. Wellbutrin® [package insert]. Research Triangle Parke (NC): GlaxoSmithKline; 2007 Aug.
57. Wellbutrin SR®, [package insert]. Research Triangle Parke (NC): GlaxoSmithKline; 2007 Aug.
58. Wellbutrin XL® [package insert]. Research Triangle Parke (NC): GlaxoSmithKline; 2007 Aug.
59. Remeron® [package insert]. Roseland (NJ): Organon USA Inc.; 2007 Jul.
60. Emsam® [package insert]. Tampa (FL): Somerset Pharmaceuticals; 2007 Jun.

61. Isocarboxazid: drug information. In: Rose BD, editor. UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2007 [cited 2007 Sep 24]. Available from: http://www.utdol.com/utd/index.do.
62. Phenelzine: drug information. In: Rose BD, editor. UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2007 [cited 2007 Sep 24]. Available from: http://www.utdol.com/utd/index.do
63. Tranylcypromine: drug information. In: Rose BD, editor. UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2007 [cited 2007 Sep 24]. Available from: http://www.utdol.com/utd/index.do
64. Duloxetine: drug information. In: Rose BD, editor. UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2007 [cited 2007 Sep 24]. Available from: http://www.utdol.com/utd/index.do
65. Venlafaxine: drug information. In: Rose BD, editor. UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2007 [cited 2007 Sep 24]. Available from: http://www.utdol.com/utd/index.do
66. Citalopram: drug information. In: Rose BD, editor. UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2007 [cited 2007 Sep 24]. Available from: http://www.utdol.com/utd/index.do
67. Escitalopram: drug information. In: Rose BD, editor. UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2007 [cited 2007 Sep 24]. Available from: http://www.utdol.com/utd/index.do
68. Fluoxetine: drug information. In: Rose BD, editor. UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2007 [cited 2007 Sep 24]. Available from: http://www.utdol.com/utd/index.do
69. Olanzapine and fluoxetine: drug information. In: Rose BD, editor. UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2007 [cited 2007 Sep 24]. Available from: http://www.utdol.com/utd/index.do
70. Fluvoxamine: drug information. In: Rose BD, editor. UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2007 [cited 2007 Sep 24]. Available from: http://www.utdol.com/utd/index.do
71. Paroxetine: drug information. In: Rose BD, editor. UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2007 [cited 2007 Sep 24]. Available from: http://www.utdol.com/utd/index.do
72. Sertraline: drug information. In: Rose BD, editor. UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2007 [cited 2007 Sep 24]. Available from: http://www.utdol.com/utd/index.do
73. Nefazodone: drug information. In: Rose BD, editor. UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2007 [cited 2007 Sep 24]. Available from: http://www.utdol.com/utd/index.do
74. Trazodone: drug information. In: Rose BD, editor. UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2007 [cited 2007 Sep 24]. Available from: http://www.utdol.com/utd/index.do
75. Amitriptyline : drug information. In: Rose BD, editor. UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2007 [cited 2007 Sep 24]. Available from: http://www.utdol.com/utd/index.do
76. Amitriptyline and chlordiazepoxide: drug information. In: Rose BD, editor. UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2007 [cited 2007 Sep 24]. Available from: http://www.utdol.com/utd/index.do
77. Amitriptyline and perphenazine : drug information. In: Rose BD, editor. UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2007 [cited 2007 Sep 24]. Available from: http://www.utdol.com/utd/index.do
78. Amoxapine: drug information. In: Rose BD, editor. UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2007 [cited 2007 Sep 24]. Available from: http://www.utdol.com/utd/index.do
79. Clomipramine: drug information. In: Rose BD, editor. UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2007 [cited 2007 Sep 24]. Available from: http://www.utdol.com/utd/index.do
80. Desipramine: drug information. In: Rose BD, editor. UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2007 [cited 2007 Sep 24]. Available from: http://www.utdol.com/utd/index.do
81. Doxepin: drug information. In: Rose BD, editor. UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2007 [cited 2007 Sep 24]. Available from: http://www.utdol.com/utd/index.do
82. Imipramine : drug information. In: Rose BD, editor. UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2007 [cited 2007 Sep 24]. Available from: http://www.utdol.com/utd/index.do
83. Maprotiline: drug information. In: Rose BD, editor. UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2007 [cited 2007 Sep 24]. Available from: http://www.utdol.com/utd/index.do
84. Nortriptyline: drug information. In: Rose BD, editor. UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2007 [cited 2007 Sep 24]. Available from: http://www.utdol.com/utd/index.do
85. Protriptyline: drug information. In: Rose BD, editor. UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2007 [cited 2007 Sep 24]. Available from: http://www.utdol.com/utd/index.do
86. Trimipramine: drug information. In: Rose BD, editor. UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2007 [cited 2007 Sep 24]. Available from: http://www.utdol.com/utd/index.do
87. Bupropion: drug information. In: Rose BD, editor. UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2007 [cited 2007 Sep 24]. Available from: http://www.utdol.com/utd/index.do
88. Mirtazapine: drug information. In: Rose BD, editor. UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2007 [cited 2007 Sep 24]. Available from: http://www.utdol.com/utd/index.do

89. Selegiline: drug information. In: Rose BD, editor. UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2007 [cited 2007 Sep 24]. Available from: http://www.utdol.com/utd/index.do
90. Moncrieff J, Wessely S, Hardy R. Active placebos versus antidepressants for depression. Cochrane Database Syst Rev. 2004;(1):CD003012.
91. Walsh BT, Seidman SN, Sysko R, et al. Placebo response in studies of major depression: variable, substantial, and growing. JAMA. 2002;287:1840-7.
92. Geddes JR, Carney SM, Davies C, et al. Relapse prevention with antidepressant drug treatment in depressive disorders: a systematic review. Lancet. 2003;361:653-61.
93. Acharya N, Rosen AS. Polzer JP, D'Souza DN, Perahia DG, Cavazzoni PA, Baldessarini RJ. Duloxetine: meta-analyses of suicidal behaviors and ideation in clinical trials for major depressive disorder J Clin Psychopharmacol. 2006; 26(6):587-94.
94. Feighner J, Targum S, Bennet M et al. A double-blind, placebo-controlled trial of nefazodone in the treatment of patients hospitalized for major depression.. J Clin Psychiatry. 1998;59(5):246-53.
95. Dunner DL, Lipshitx A, Pitts C, Davies JT. Efficay and tolerability of controlled-release paroxetine in the treatment of severe depression; post hoc analysis of pooled data from a subset of subjects in four double-blind clinical trials. Clin Ther. 2005;27:1901-11.
96. Weihs KL, Settle EC Jr, Batey SR, et al: Bupropion sustained release versus paroxetine for the treatment of depression in the elderly. .J Clin Psychiatry. 2000 Mar;61(3):196-202.
97. Kavoussi RJ, Segraves RT, Hughes AR, et al: Double-blind comparison of bupropion sustained release and sertraline in depressed outpatients. J Clin Psychiatry. 1997;58(12):532-537.
98. Rocca P, Calvarese P, Faggiano F, Marchiaro L, Mathis F, Rivoira E, Taricco B, Bogetto F. Citalopram versus sertraline in late-lif nonmajor clinically significant depression: a 1 year follow-up clinical trial. J Clin Psychiatry 2005;66:360-9.
99. Van Baardewijk M, Vis PMJ, Einarson TR. Cost effectiveness of duloxetine compared with venlafaxine-XR in the treatment of major depressive disorder. Curr Med Res Opin. 2005;21(8):1271-79.
100. Moore N, Verdoux H, Fantino B. Prospective, multicentre, randomized, double-blind study of the efficacy of escitalopram versus citalopram in outpatient treatment of major depressive disorder. Int Clin Psychopharmacol. 2005 May;20(3):131-7.
101. Lam RW, Andersen HF. The influence of baseline severity on efficacy of escitalopram and citalopram in the treatment of major depressive disorder: an extended analysis. Pharmacopsychiatry. 2006 Sep;39(5):180-4.
102. Colonna L, Andersen HF, Reines EH. A randomized, double-blind, 24-week study of escitalopram (10 mg/day) versus citalopram (20 mg/day) in primary care patients with major depressive disorder. Curr Med Res Opin. 2005 Oct;21(10):1659-68.
103. Gorman JM, Korotzer A, Su G. Efficacy comparison of escitalopram and citalopram in the treatment of major depressive disorder: pooled analysis of placebo-controlled trials. CNS Spectr. 2002 Apr;7(4 Suppl 1):40-4.
104. Wade A, Gembert K, Florea I. A comparative study of the efficacy of acute and continuation treatment with escitalopram versus duloxetine in patients with major depressive disorder. Curr Med Res Opin. 2007 Jul;23(7):1605-14.
105. Khan A, Bose A, Alexopoulos GS, Gommoll C, Li D, Gandhi C. Double-blind comparison of escitalopram and duloxetine in the acute treatment of major depressive disorder. Clin Drug Investig. 2007;27(7):481-92.
106. Boulenger JP, Huusom AK, Florea I, Baekdal T, Sarchiapone M. A comparative study of the efficacy of long-term treatment with escitalopram and paroxetine in severely depressed patients. Curr Med Res Opin. 2006 Jul;22(7):1331-41.
107. Ventura D, Armstrong EP, Skrepnek GH, Haim Erder M. Escitalopram versus sertraline in the treatment of major depressive disorder: a randomized clinical trial. Curr Med Res Opin. 2007 Feb;23(2):245-50.
108. Montgomery SA, Huusom AK, Bothmer J. A randomised study comparing escitalopram with venlafaxine XR in primary care patients with major depressive disorder. Neuropsychobiology. 2004;50(1):57-64.
109. Thase ME, Rush AJ, Howland RH, et al. Double-blind switch study of imipramine or sertraline treatment of antidepressant-resistant chronic depression. Arch Gen Psychiatr. 2002;59:233-9.
110. Versiani M, Moreno R, Ramakers-van Moorsel CJ, Schutte AJ. Comparative Efficacy Antidepressants Study Group. Comparison of the effects of mirtazapine and fluoxetine in severely depressed patients. CNS Drugs. 2005;19(2):137-46.
111. Wheatley D, Kremer CME: A randomized, double-blind comparison of mirtazapine and fluoxetine in patients with major depression. J Clin Psychiatry. 1998 Jun;59(6):306-12.
112. Behke K, Søgaard J, Martin S, et al: Mirtazapine orally disintegrating tablet versus sertraline. J Clin Psychopharmacol. 2003 Aug;23:4.
113. Guelfi D, Ansseau M, Timmerman L, et al: Mirtazapine versus venlafaxine in hospitalized severely depressed patients with melancholic features. J Clin Psychopharmacol. 2001;21:425-31.
114. Birkenhager TK, van den Broek WW, Mulder PG, et al. Efficacy and tolerability of tranylcypromine versus phenelzine: a double-blind study in antidepressant-refractory depressed inpatients. J Clin Psychiatry. 2004;65(11):1505-10.

115. Rossini D, Serretti A, Franchini L, Mandelli L, Smeraldi E, Ronchi DD, Zanardi R. Sertraline versus fluvoxamine in the treatment of elderly patients with major depression. J Clin Psychopharmacol 2005;25:471-5.
116. Bielski RJ, Ventura D, Chang C. A double-blind comparison of escitalopram and venlafaxine extended-release in the treatment of major depressive disorder. J Clin Psychiatry. 2004;65:1190-6.
117. Benkert O, Grunder G, Wetzel H, et al: A randomized, double-blind comparison of a rapidly escalating dose of venlafaxine and imipramine in inpatients with major depression and melancholia. J Psychiatr Res. 1996:30(6):441-51.
118. Stahl S, Zivkov M, Reimitz PE, et al. Meta-analysis of randomized, double-blind, placebo-controlled, efficacy and safety studies of mirtazapine versus amitriptyline in major depression. Acta Psychiatr Scand. 1997;96(suppl 391):22-30.
119. Clayton AH, Croft HA, Horrigan JP, Wightman DS, Krishen A, Richard NE, Modell JG. Bupropion extended release compared with escitalopram: effects on sexual functioning and antidepressant efficacy in 2 randomized, double-blind, placebo-controlled studies. J Clin Psychiatry 2006;67:736-46.
120. Llorca PM, Azorin JM, Despiegel N, Verpillat P. Efficacy of escitalopram in patient with severe depression: a pooled analysis. Int J Clin Pract. 2005 Mar;59(3):268-75.
121. Burke WJ, Gergel I, Bose A. Fixed-dose trial of the single isomer SSRI escitalopram in depressed outpatients. J Clin Psychiatry. 2002;63:331-36.
122. Nierenberg AA, Greist JH, Mallinckrodt CH, Prakash A, Sambunaris A, Tollefson GD, Wohlreich MM. Duloxetine versus escitalopram and placebo in the treatment of patients with major depressive disorder: onset of antidepressant action, a non-inferiority study. Curr Med Res Opin. 2007 Feb;23(2):401-16.
123. Goldstein DJ, Lu Y, Detke MJ, et al: duloxetine in the treatment of depression a double-blind placebo-controlled comparison with paroxetine. J Clin Psychopharmacol. 2004;24:389-99.
124. Vis PM. van Baardewijk M. Einarson TR. Duloxetine and venlafaxine-XR in the treatment of major depressive disorder: a meta-analysis of randomized clinical trials. Ann Pharmacother. 2005;39(11):1798-807.
125. Nemeroff CB, Michael E: A double-blind, placebo-controlled comparison of venlafaxine and fluoxetine treatment in depressed outpatients. J Psychiatr Res. 2007;41:351-9.
126. Rudolph RL, Feiger AD: A double-blind, randomized, placebo-controlled trial of once-daily venlafaxine extended release (XR) and fluoxetine for the treatment of depression. J. Affective Disorders. 1999:56:171-81.
127. Fava M, Hoog SL, Judge RA, Kopp JB, Nilsson ME, Gonzales JS. Acute efficacy of fluoxetine versus sertraline and paroxetine in major depressive disorder including effects of baseline insomnia. J Clin Psychopharmacol. 2002;22(2):137-47.
128. Perahia DG. Wang F. Mallinckrodt CH. Walker DJ. Detke MJ**.** Duloxetine in the treatment of major depressive disorder: a placebo- and paroxetine-controlled trial. Eur Psychiatry. 2006;21(6):367-78.
129. Thase ME, Trivedi MH, Rush AJ. MAOIs in the Contemporary Treatment of Depression. Neuropsychopharmacology. 1995;12(3):185-219.
130. Cipriani A, Brambilla P, Furukawa T, Geddes J, Gregis M, Hotopf M, et al. Fluoxetine versus other types of pharmacotherapy for depression. Cochrane Database Syst Rev. 2005 Oct 19;(4):CD004185.
131. Bull SA, Hu XH, Hunkeler EM, et al. Discontinuation of use and switching of antidepressants: influence of patient-physician communication. JAMA. 2002 Sep 18;288(11):1403-09.
132. Anderson IM. Selective serotonin reuptake inhibitors versus tricyclic antidepressants: a meta-analysis of efficacy and tolerability. J Affect Disord. 2000 Apr;58(1):19-36.
133. MacGillivray S, Arroll B, Hatcher S, et al. Efficacy and tolerability of selective serotonin reuptake inhibitors compared with tricyclic antidepressants in depression treated in primary care: systematic review and meta-analysis. BMJ. 2003;326:1014-9.
134. Steffens DC, Ranga K, Krishnan MD, et al. Are SSRIs better than TCAs? Comparison of SSRIs and TCAs: a meta-analysis. Depress Anxiety. 1997;6:10-8.
135. Davidson JR, Bose A, Wang Q. Safety and efficacy of escitalopram in the long-term treatment of generalized anxiety disorder. J Clin Psychiatry 2005;66:1441-6.
136. Goodman WK, Bose A, Wang Q. Treatment of generalized anxiety disorder with escitalopram: pooled results from double-blind, placebo-controlled trials. J Affect Disord. 87;2005;161-7.
137. Dahl AA, Ravindran A, Allgulander C, Kutcher SP, Austin C, Burt T. Sertraline in generalized anxiety disorder: efficacy in treatment in psychic an somatic anxiety factors. Acta Psychiatr Sand 2005;111:429-35.
138. Bielski RJ, Bose A, Chang CC. A double-blind comparison of escitalopram and paroxetine in the long-term treatment of generalized anxiety disorder. Ann Clin Psychiatry. 2005 Apr;17(2):65-69.
139. Ball S, Kuhn A, Wall D, Shekhar A, Goddard AW. Selective serotonin reuptake inhibitor for generalized anxiety disorder: a double-blind, prospective comparision between paroxetine and sertraline. J Clin Psychiatry 2005;66:94-9.
140. Schmitt R, Gazalle FK, Lima MS, Cunha A, Souza J, Kapczinski F. The efficacy of antidepressants for generalized anxiety disorder: a systematic review and meta-analysis. Rev Bras Psiquiatr. 2005 Mar;27(1):18-24.

141. Koran LM, McElroy SL, Davidson JRT, et al. Fluvoxamine versus clomipramine for obsessive-compulsive disorder: a double-blind comparison. J Clin Psychopharmacol. 1996;16:121-9.
142. Denys D, van der Wee N, van Megen HJ, Westenberg HG. A double blind comparison of venlafaxine and paroxetine in obsessive-compulsive disorder. J Clin Psychopharmacol. 2003;23:568-75.
143. Mundo E, Bianchi L, Bellodi L. Efficacy of Fluvoxamine, paroxetine, and Citalopram in the treatment of obsessive-compulsive disorder: A single-blind study. J Clin Psychopharmacol. 1997;17(4):267-71.
144. Van Ameringen M, Mancini C, Oakman J, Walker J, Kjernisted K, Chokka P, Johnston D, Bennett M, Patterson B. Nefazodone in the treatment of generalized social phobia; a randomized, placebo-controlled trial. J Clin Psychiatry 2007;68:288-95.
145. Sheehan DV, Burnham DB, Iyengar MK, Perea P. Efficacy and tolerability of controlled-release paroxetine in the treatment of panic disorder. J Clin Psychiatry 2005;66:34-40.
146. Stahl SM, Gergel I, Li D. Escitalopram in the treatment of panic disorder: a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry. 2003 Nov;64(11):1322-7.
147. Rampello L, Alvano A, Raffaele R, Malaguarnera M, Vecchio I. New possibilities of treatment for panic attacks in elderly patients: escitalopram versus citalopram. J Clin Psychopharmacol. 2006 Feb;26(1):67-70.
148. Bandelow B, Behnke K, Lenoir S, Hendriks GJ, Alkin T, Goebel C, et al. Sertraline versus paroxetine in the treatment of panic disorder: An acute, double-blind noninferiority comparison. J Clin Psych. 2004;65(3):405-13.
149. Ballenger JC, Wheadon DE, Steiner M, Bushnell W, Gergel IP. Double-blind, fixed-dose, placebo-controlled study of paroxetine in the treatment of panic disorder. Am J Psychiatry. 1998;155:36-42.
150. Davidson JR, Connor KM, Hertzberg MA, Weisler RH, Wislon WH, Payne VM. Maintenance therapy with fluoxetine in posttraumatic stress disorder. J Clin Psychopharmacol 2005;25:166-9.
151. Friedman MJ, Marmar CR, Baker DG, Sikes CR, Farfel GM. Randomized, double-blind comparision of sertraline and placebo for posttrumatic stress disorder in a department of vererans affairs setting. J Clin Psychiatry 2007;61:711-20.
152. Pearlstein TB, Bellew KM, Endicott J, Steiner M. Paroxetine controlled release for premenstrual dysphoric disorder: Remission analysis following a randomized, double-blind, placebo-controlled trial. Prim Care Companion J Clin Psychiatry. 2005;7:53-60.
153. Steiner M, Hirschberg AL, Bergeron R, Holland F, Gee M, Van Erp E. Luteal phase dosing with paroxeting controlled release in the treatment of premenstrual dysphoric disorder. Am J Obstet Gynecol. 2005;193:352-60.
154. Wernicke J, Lledo A, Raskin J, et al. An evaluation of the cardiovascular safety profile of duloxetine. Drug Safety.2007;30(5):437-55.
155. Mullins CD, Shaya FT, Meng F, Wang J, Harrison D. Persistence, switching, and discontinuation rates among patients receiving sertraline, paroxetine, and citalopram. Pharmacotherapy. 2005;25(5):660-7.
156. Stein DJ, Ipser JC, van Balkom AJ. Pharmacotherapy for social anxiety disorder. Cochrane Database Syst Rev. 2000 (4):CD001206. doi: 10.1002/14651858.CD001206.pub2.
157. Claxton A, de Klerk E, Parry M, Robinson JM, Schmidt ME. Patient compliance to a new enteric-coated weekly formulation of fluoxetine during continuation treatment of major depressive disorder. J Clin Psychiatry. 2000 Dec;61(12):928-32.
158. Simon GE, VonKorff M, Heiligenstein JH, Revicki DA, Grothaus L, Katon W, et al. Initial antidepressant choice in primary care. Effectiveness and cost of fluoxetine vs tricyclic antidepressants. JAMA. 1996 Jun 26;275(24):1897-902.
159. Simon GE, Heiligenstein J, Revicki D, VonKorff M, Katon WJ, Ludman E, et al. Long-term outcomes of initial antidepressant drug choice in a "real world" randomized trial. Arch Fam Med. 1999 Jul-Aug;8(4):319-25.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Cerebral Stimulants/Agents Used for ADHD
Amphetamines, AHFS Class 282004
Miscellaneous Anorexigenic Agents and Respiratory and Cerebral Stimulants, AHFS Class 282092
Atomoxetine, AHFS Class 289200
November 14, 2007

I. Overview

Attention Deficit Hyperactivity Disorder (ADHD) is a severe, debilitating condition that can affect both children and adults. A recent national survey reported the prevalence of ADHD in American children between the ages of 4 and 17 years to be 7.8%,[1] but other sources report prevalence of as high as 12% in school-aged children, with 60%-85% of children continuing to experience ADHD symptoms into their adolescent[2,3] and 30%-77% into their adult years. In the United Kingdom (UK), approximately 3%-9% of school-aged children are affected with ADHD and 10%-66% will continue to have ADHD symptoms into their adult life.[10-11] The prevalence of adult ADHD is reported to be 4.4% in the United States[11] and 4% in the UK[12]. The prevalence of patients diagnosed with ADHD differs between countries due to the difference in diagnostic criteria used.

Currently, there are two main sets of criteria used for the diagnosis of ADHD: American Psychiatric Association's (APA's) *Diagnostic and Statistical Manual of Mental Disorders*, Text Revision, 4th edition (DSM-IV-TR) and the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10).[13] The DSM-IV criteria breaks down ADHD into three subtypes: a predominantly inattentive subtype in which symptoms of inattention are displayed, but symptoms of hyperactivity and/or impulsiveness are absent; a predominantly hyperactive-impulsive subtype in which symptoms of hyperactivity-impulsiveness are displayed, but symptoms of inattention are absent; and a combined subtype in which both symptoms are displayed. The ICD-10 criteria, the preferred criteria in the UK and England, does not break down ADHD into subtypes. Within the ICD-10 criteria, the diagnosis of hyperkinetic disorder (HKD), in which symptoms of hyperactivity, impulsivity and inattention are all displayed together, is equivalent to the DSM-IV ADHD combined subtype diagnosis.[10] Both of these diagnostic criteria sets were created based on the common signs and symptoms displayed by children, which may be less prominent in the adult population, thus making it difficult to apply these criteria to the diagnosis of adult ADHD. Also, adults may display different symptoms of ADHD, such as disinhibition restlessness rather than hyperactivity, as commonly displayed in children.[14] Due to the lack of clinical evidence to guide physicians in the treatment of adult ADHD, the British Association for Psychopharmacology created a guideline based on expert opinion for the management of ADHD in adolescents in transition to adult services and in adults. Other scales, including the Wender Utah, Adult Self Report, and Conners Adult ADHD rating scales have been created to assist in the diagnosis of adult ADHD.[12]

ADHD is often characterized by excessive, long-term and developmentally inappropriate impulsivity, attention deficit and in some cases hyperactivity. Untreated or undertreated ADHD is associated with adverse sequelae that include delinquent behavior, antisocial personality traits, substance abuse, and other comorbidities.[3] Suboptimal academic performance is often the impetus for initial screening, diagnosis, and subsequent drug therapy.

The stimulant medications were introduced for the treatment of children with inattention and hyperactivity around 70 years ago.[4] Historically, the most widely used medications for ADHD have been methylphenidate and amphetamines. With the exception of atomoxetine, the newer ADHD agents fall into one of these categories and are mostly distinguished from the original product by pharmacokinetic variations, new drug delivery systems, or enantiomeric differences. Atomoxetine is currently the only nonstimulant medication approved for the treatment of ADHD. In addition to ADHD, methylphenidate and amphetamines are indicated for the treatment of narcolepsy. Modafinil is a cerebral stimulant that is structurally and pharmacologically distinct from other agents in this class and is indicated for the treatment of narcolepsy, obstructive sleep apnea (OSA) and shift work sleep disorder (SWSD).[5]

The cerebral stimulants/agents used for ADHD that are included in this review are listed in Table 1. This review consists of amphetamines, miscellaneous anorexigenic agents and respiratory and cerebral stimulants (including methylphenidate derivatives and modafinil) and miscellaneous central nervous system agents (atomoxetine). This review encompasses all dosage forms and strengths.

Table 1. Cerebral Stimulants/Agents Used for ADHD Included in this Review[6-8]

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Amphetamines—Cerebral Stimulants/Agents Used for ADHD			
amphetamine salts, mixed (amphetamine - dextroamphetamine)	extended-release (XR) capsule, tablet	Adderall®*, Adderall XR®	Adderall XR®, amphetamine-dextroamphetamine
dextroamphetamine	sustained-release (SR) capsule, tablet	Dexedrine®*†, Dextrostat®*	Dexedrine®*†, dextroamphetamine
lisdexamfetamine	tablet	Vyvanse®	none
methamphetamine	tablet	Desoxyn®	Desoxyn®
Miscellaneous Anorexigenic Agents and Respiratory and Cerebral Stimulants—Cerebral Stimulants/Agents Used for ADHD			
dexmethylphenidate	extended-release (XR) capsule, tablet	Focalin®*, Focalin XR®	Focalin®*, Focalin XR®, dexmethylphenidate
methylphenidate	chewable tablet, extended-release (XR) capsule, extended-release tablet (ER) (osmotic release), oral solution, sustained-release (SR) tablet, tablet, transdermal patch	Concerta®, Daytrana®, Metadate CD®, Metadate ER®*, Methylin®*, Ritalin®*, Ritalin LA®, Ritalin-SR®*	Concerta®, Metadate CD®, Methylin®*, Ritalin®*, methylphenidate
modafinil	tablet	Provigil®	none
Miscellaneous Central Nervous System Agents—Cerebral Stimulants/Agents Used for ADHD			
Atomoxetine	capsule	Strattera®	none

*Generic is available in at least one dosage form or strength.
†Brand name Dexedrine is only available in the sustained-release capsule (SR) formulation. Named brand Dexedrine tablets have been discontinued.

The cerebral stimulants/agents used for ADHD are classified by duration of action in Table 2.

Table 2. Cerebral Stimulants/Agents Used for ADHD Classified by Duration of Action[5,6-8,18-35]

Medication(s)	Short-Acting	Intermediate-Acting	Long-Acting
Amphetamines—Cerebral Stimulants/Agents Used for ADHD			
amphetamine products [amphetamine salts, mixed (amphetamine/dextroamphetamine), dextroamphetamine, lisdexamfetamine, methamphetamine]	Dexedrine®, Dextrostat®	Adderall®, Dexedrine®*	Adderall XR®, Desoxyn®, Vyvanse®
Miscellaneous Anorexigenic Agents and Respiratory and Cerebral Stimulants—Cerebral Stimulants/Agents Used for ADHD			
methylphenidate products (dexmethylphenidate and methylphenidate)	Focalin®, Methylin®, Ritalin®	Metadate ER®, Methylin ER®, Ritalin SR®	Concerta®, Daytrana®, Focalin XR®, Metadate CD®, Ritalin LA®,
modafinil			Provigil®
Miscellaneous Central Nervous System Agents—Cerebral Stimulants/Agents Used for ADHD			
atomoxetine			Strattera®

*Sustained-release (SR) capsule formulation

II. Evidence-Based Medicine and Current Treatment Guidelines

Treatment guidelines that incorporate the cerebral stimulants/agents used for ADHD are summarized in Table 3.

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

Clinical Guideline	Recommendation(s)
American Academy of Pediatrics (AAP): **Clinical Practice Guideline: Treatment of the School-Aged Child With Attention-Deficit Hyperactivity Disorder (2001)**[2]	Upon diagnosis, the clinician should recommend stimulant medication. 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: • Improvements in relationships with parents, siblings, teachers, and peers • Decreased disruptive behaviors • Improved academic performance, in volume of work, efficiency, completion, and accuracy • Increased independence in self-care or homework • Improved self-esteem • 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: • Most children who fail to respond to one medication may respond to an alternative stimulant. • Numerous crossover trials indicate efficacy of different stimulants in the same child. • 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 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 Child And Adolescent Psychiatry (AACAP): **Practice Parameter for the Use of Stimulant Medications in the Treatment of Children, Adolescents, and Adults (2007)**[3]	• The first agent tried should have FDA approval for the treatment of ADHD; possible agents would be dextroamphetamine, methylphenidate (MPH), mixed salts of amphetamine, and atomoxetine. • Stimulants have been proven in many clinical trials to be highly effective in the treatment of ADHD. • The physician may choose either MPH or amphetamines, as data suggests equal efficacy between the two stimulant types. • Longer-acting formulations may be used as initial treatment and are associated with greater compliance. Physicians do not need to initiate treatment with the short-acting forms, or use them to titrate to the appropriate dosage of the long-acting forms. Short-acting forms may be used to initiate therapy in low-weight (<16 kg) children where long-acting forms may not be available in the necessary smaller doses. • Typical starting doses for the individual agents are listed in this guideline. Once a medication is initiated, the dose should be titrated up every 1 to 3 weeks until the maximum dose for the stimulant 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. • Patients may show an initial response rate of up to 85% when both stimulant forms are tried, vs the response rate of only 65%-75% observed in clinical trials when patients were treated with only one stimulant. Therefore, if a patient fails one stimulant, it is recommended that another be tried. • 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

Clinical Guideline	Recommendation(s)
	metabolism of MPH in preschoolers. • In studies published comparing atomoxetine to stimulants, greater efficacy was seen in those patients treated with stimulants. • Atomoxetine may be used 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.
Institute for Clinical Systems Improvement (ICSI): **Health Care Guideline: Diagnosis and Management of Attention Deficit Hyperactivity Disorder in Primary Care for School-Age Children and Adolescents (2005)**[9]	• Stimulant medications are considered first-line therapy, as they are effective in 70%-80% of children with ADHD. • Response or lack of response to one stimulant does not predict success or failure with other stimulant agents, with studies indicating that the 70%-80% response rate to one stimulant is independent of response to others. • Therefore, if a child is a nonresponder to one stimulant, it is advisable to attempt a second or third trial with other stimulants. • Children with ADHD of the predominantly inattentive type have been shown to respond well to low doses of methylphenidate. • Children with ADHD, combined type or predominantly hyperactive (excessive movement and restlessness), have shown more positive response at moderate to high doses of methylphenidate. <u>Nonstimulant Medications</u> • Atomoxetine may be considered a first-line agent in patients where stimulants may not be an option or if a nonstimulant medication is preferred by parents and/or physicians. • When a stimulant trial is unsuccessful due to either poor response or side effects, or if there is associated comorbidity, alternative medication trials may be considered. <u>Second-line Medications Include</u> • Tricyclic antidepressants (TCAs) (desipramine, imipramine) • An α-adrenergic agonist (clonidine) • A nontricyclic antidepressant (bupropion)
National Institute for Health and Clinical Excellence (NICE): **Methylphenidate, Atomoxetine and Dexamfetamine for Attention Deficit Hyperactivity Disorder (ADHD) in Children and Adolescents (2006)**[10]	• Methylphenidate and dexamfetamine, known as dextroamphetamine in the United States (US), have been used in the treatment of ADHD for many years. Atomoxetine has been introduced more recently. • Clinicians sometimes prescribe tricyclic and other antidepressant drugs. • Treatment should be initiated only by an appropriately qualified healthcare professional with expertise in ADHD, and should be based on a comprehensive assessment and diagnosis. • There are situations in which a single-dose regimen, which can be achieved with modified-release formulations, would be the preferred treatment approach. • There could be circumstances in which the limited range of dosage strengths available in the modified-release formulations would make titration difficult and an immediate-release formulation would be preferable. • The use of dexamfetamine should be limited to refractory hyperkinetic states due to the poor quality of evidence in clinical trials and greater potential for diversion and misuse than the other drugs under consideration.
British Association of Psychopharmacology: **Evidence-Based Guidelines for the Management of Attention Deficit Hyperactivity Disorder in Adolescents in Transition to Adult Services and in**	<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. <u>Treatment Recommendations for Adults</u> • 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 far better efficacy than other

Clinical Guideline	Recommendation(s)
Adults (2007)[12]	treatments for core symptoms. However, amphetamines, methylphenidate and atomoxetine are all effective but not equivalent, since they have different actions and hazards. Abuse Potential • Abuse potential is related to drug action and formulation. Abuse is generally low among patients but it can occur with stimulants. Slow-release preparations of these agents or atomoxetine are preferred for patients with a history of substance abuse, or who are at risk for substance abuse.
American Academy of Sleep Medicine (AASM): **Practice Parameters for the Treatment of Narcolepsy (2000)[15]**	• Amphetamine, methamphetamine, dextroamphetamine, and methylphenidate are effective for the treatment of daytime sleepiness due to narcolepsy. These medications are the mainstay of narcolepsy treatment. Based on a long history in clinical practice, they have a lengthy record of efficacy. However, the benefit-to-risk ratio is not well documented, because the published clinical trials include only small numbers of patients. Recommendation: Guideline† • Modafinil is effective for treatment of daytime sleepiness due to narcolepsy. This conclusion is based on the favorable benefit-to-risk ratio for modafinil established in three clinical studies with confirmation from additional studies. Recommendation: Standard‡ • Combinations of long- and short-acting forms of stimulants may be effective for some patients. Some stimulants are short acting (3 to 4 hours). Others have longer duration of activity and longer onset of action. By combining stimulants with different activity characteristics, it may be possible to achieve alertness quickly and for longer periods of time and also not produce insomnia as an unwanted side effect. Recommendation: Option^ • Combinations of stimulants and antidepressants may be beneficial for the treatment of sleepiness and rapid eye movement (REM)-related symptoms such as cataplexy. For example, modafinil appears compatible with antidepressant medications, published evidence is limited. • Of the stimulants used to treat narcolepsy, amphetamines, especially at high doses, are the most likely to result in the development of tolerance.
European Federation of Neurological Sciences (EFNS): **Guidelines on Management of Narcolepsy (2006)[16]**	• Modafinil, 100-400 mg/day is recommended as the first-line pharmacological treatment of excessive daytime sleepiness and irresistible episodes of sleep. (Level A rating*) • Methylphenidate 10-60 mg/day is recommended as the second-line pharmacological treatment of excessive daytime sleepiness and irresistible episodes of sleep. (Level rating not specified) • Nonpharmacological treatment recommendations include taking planned naps throughout the day scheduled on a patient-by-patient basis. (Level B rating**)
American Academy of Sleep Medicine (AASM): **Practice Parameters for the Medical Therapy of Obstructive Sleep Apnea (OSA) (2006)[17]**	• Modafinil is recommended for the treatment of residual excessive daytime sleepiness in OSA patients who have sleepiness despite effective positive airway pressure (PAP) treatment and whose sleepiness has not been attributed to other causes. • Modafinil should only be used when the sleepiness of the patient has been evaluated and other causes such as poor sleep hygiene, improper use of PAP, narcolepsy, and depression have been ruled out. • Other pharmacological agents including selective serotonin-reuptake inhibitors (SSRIs), protriptyline, methylxanthine derivatives, and estrogen therapies are not recommended. • Nonpharmacological recommendations for treatment of OSA include weight loss, supplemental oxygen, and positional therapies.

†Guideline=This is a patient care strategy which reflects a moderate degree of clinical certainty. The term *guideline* implies the use of Level II Evidence (randomized trials with high-beta errors), or a consensus of Level III Evidence (nonrandomized controlled or concurrent cohort studies).
‡Standard=This is a generally accepted patient care strategy which reflects a high decree of clinical certainty. The term *standard* generally implies the use of Level I Evidence (randomized well-designed trials with low-alpha and low-beta errors), which directly addresses the clinical issue, or overwhelming Level II Evidence (randomized trials with high-beta errors).
^Option=This is a patient care strategy that reflects uncertain clinical use. The term *option* implies either inconclusive or conflicting evidence, or conflicting expert opinion.
*Level A rating=(established as effective, ineffective, or harmful) requires at least one convincing class I (an adequately powered prospective, randomized, controlled clinical trial with masked outcome assessment in a representative population or an adequately powered systematic review of prospective randomized controlled clinical trials with masked outcome assessment in representative populations) study or at least two consistent, convincing class II studies (prospective matched-group cohort study in a representative population with masked outcome assessment or a randomized, controlled trial in a representative population that lacks certain criteria).
**Level B rating=(probably effective, ineffective, or harmful) requires at least one convincing class II (prospective matched-group cohort study in a representative population with masked outcome assessment or a randomized, controlled trial in a representative population that lacks certain criteria) study or overwhelming class III evidence (all other controlled trials, including well-defined natural history controls or patients serving as own controls in a representative population, where outcome assessment is independent of patient treatment).

III. Indications

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[5,6-8,18-35]

Drug	Formulation(s) †	Duration of Action	Example Brand Name(s)	ADHD in Pediatrics (Age in Years)	ADHD in Adults	Narcolepsy in Pediatrics (Age in Years)	Narco-lepsy in Adults	Exogenous Obesity (Age in Years)	Obstructive Sleep Apnea (Age in Years)	Shift Work Sleep Disorder (Age in Years)
Amphetamines—Cerebral Stimulants/Agents Used for ADHD										
Amphetamine salts, mixed	tablet	intermediate	Adderall®*	✔ (≥3)	✔	✔ (≥6)	✔			
	extended-release (XR) capsule	long	Adderall XR®	✔ (≥6)	✔					
Dextroamphetamine	tablet	short	Dexedrine®, Dextrostat®	✔ (≥3)	✔	✔ (≥6)	✔			
	sustained-release (SR) capsule	intermediate	Dexedrine®*	✔ (≥3)	✔	✔ (≥6)	✔			
Lisdexamfetamine	capsule	long	Vyvanse®	✔ (6-12)						
Methamphetamine	tablet	long	Desoxyn®	✔ (≥6)				✔ (≥12)		
Miscellaneous Anorexigenic Agents and Respiratory and Cerebral Stimulants—Cerebral Stimulants/Agents Used for ADHD										
Dexmethylphenidate	tablet	short	Focalin®*	✔ (6-17)						
	extended-release (XR) capsule	long	Focalin XR®	✔ (≥6)	✔					
Methylphenidate	chewable tablet, solution	short	Methylin®*	✔	✔	✔ (≥6)	✔			
	tablet	short	Methylin®*, Ritalin®*	✔	✔	✔ (≥6)	✔			
	extended-release (XR) capsule	long	Metadate CD®, Ritalin LA®	✔	✔					
	sustained-release (SR) tablet	intermediate	Metadate ER®*, Methylin ER®*, Ritalin-SR®*	✔	✔	✔ (≥6) (Ritalin-SR)	✔ (Ritalin SR)			
	extended-release tablet (ER) (osmotic)	long	Concerta®	✔	✔					
	transdermal patch	long	Daytrana®	✔ (6-12)						
Modafinil	tablet	long	Provigil®			✔ (≥16)	✔		✔ (≥16)	✔ (≥16)
Miscellaneous Central Nervous System Agents—Cerebral Stimulants/Agents Used for ADHD										
Atomoxetine	capsule	long	Strattera®	✔ (≥6)	✔					

*Generic is available in at least one dosage form or strength.
†If not otherwise indicated, formulation is immediate-release.

IV. Pharmacokinetics

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 late day side effects occur. Methylphenidate plasma concentrations, however, persist after patch removal and decline in a biexponential manner resulting in a mean elimination half-life between 3-4 hours.[22] This effect may be due to continued distribution of methylphenidate from the skin after patch removal. Use of the patch greater than 9 hours per day may result in an increased exposure to methylphenidate and an increased incidence of treatment emergent adverse events. The pharmacokinetic parameters for the cerebral stimulants/agents used for ADHD are summarized in Table 5.

Table 5. Pharmacokinetic Parameters of the Cerebral Stimulants/Agents Used for ADHD[5,6-8,18-35]

Drug	Protein Binding (%)	Bioavailability (%)	Onset of Action (minutes)	Duration of Action (hours)	Metabolism	Excretion	Half-Life (hours)
Amphetamines—Cerebral Stimulants/Agents Used for ADHD							
Amphetamine salts, mixed (amphetamine-dextroamphetamine)	20	Well absorbed	Immediate-release (IR): 30-60 Extended-release (XR): 60-90	IR: 4-6 XR: 10-12 Initial dose released immediately and remainder released gradually (mimics regular BID dosing)	Extensive liver metabolism	In urine as unchanged drug and inactive metabolites. Excretion is urine pH dependant; for urine pH <6.6, excretion ranges between 67%-73% and for pH ≥6.7, excretion ranges between 17%-43%.	IR: 4-6 XR: 12
Dextroamphetamine	Not reported	Well absorbed	Immediate-release (IR): 30-60 Sustained-release (SR): 60-90	IR: 4-6 SR: 6-10 Initial dose released immediately and remainder released gradually (mimics regular BID dosing)	Extensive liver metabolism	In urine as unchanged drug and inactive metabolites. Excretion is urine pH dependant; for urine pH <6.6, excretion ranges between 67%-73% and for pH ≥6.7, excretion ranges between 17%-43%.	IR: 4-6 SR: 12
Lisdexamfetamine (Prodrug of dextroamphetamine)	Not reported	Rapid absorption	Not reported	Not reported	Intestinal and/or liver via first-pass metabolism	96% renal	<1
Methamphetamine	67	Extensive	Rapidly absorbed	10-20	Primary site is in the liver At least 7 metabolites	62% of dose is eliminated in the urine, 1/3 as intact drug and the rest as metabolites	4-5

Drug	Protein Binding (%)	Bioavailability (%)	Onset of Action (minutes)	Duration of Action (hours)	Metabolism	Excretion	Half-Life (hours)
Miscellaneous Anorexigenic Agents and Respiratory and Cerebral Stimulants—Cerebral Stimulants/Agents Used for ADHD							
Dexmethylphenidate	12-15	22-25	Immediate-release (IR): 60-90 Extended-release (XR): 60-90 for initial peak, followed by a second rising portion at 390	IR: 4-5 XR: 12 Bi-modal plasma concentration-time profile (two peaks ~4 hours apart)	Liver via deesterification to an inactive metabolite	90% in urine as metabolites	IR: 2-4.5 XR: not reported
Methylphenidate	15.2	10-52 Patch: absorption is continuous for 9 hours after application	Immediate-release (IR): 30-60 Extended-release (XR): Initial peak: 30-60 followed by a second rising portion Sustained-release (SR): 240-420 Extended-release (ER) (osmotic): 60-120 Transdermal patch: 120	IR: 3-6 XR: 8-10 Initial dose released immediately and remainder released gradually (mimics regular BID dosing) SR: 6-8 Initial dose released immediately and remainder released gradually (mimics regular BID dosing) ER (osmotic): 10 to 14 Initial dose released immediately and remainder released gradually (mimics regular BID dosing) Transdermal patch: 9	Liver via deesterification to an active metabolite	IR: 78-97% in urine as metabolites SR: 67-86%	3-4 Transdermal patch: 1-3
Modafinil	60	Rapid absorption	Not reported	8-12	Extensive liver metabolism (90%)	In urine as 33% unchanged drug and inactive metabolites	2-4

Drug	Protein Binding (%)	Bioavailability (%)	Onset of Action (minutes)	Duration of Action (hours)	Metabolism	Excretion	Half-Life (hours)
Miscellaneous Central Nervous System Agents—Cerebral Stimulants/Agents Used for ADHD							
Atomoxetine	98	63 (extensive metabolizers) 94 (poor metabolizers)	A few days to one week	Not specified	Liver metabolized to active and inactive metabolites	Renal excretion (80%) as inactive metabolite	4

V. Drug Interactions

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

Table 6. Significant Drug-Drug Interactions with the Cerebral Stimulants/Agents Used for ADHD[5]

Drug(s)	Significance Level	Interaction	Mechanism
Amphetamines—Cerebral Stimulants/Agents Used for ADHD			
Amphetamines	1	Monoamine oxidase inhibitors (MAOIs)	Interaction may lead to an increase in norepinephrine availability at the synaptic cleft.
Amphetamines	2	CYP2D6 inhibitors (strong): chlorpromazine, cocaine, delavirdine, fluoxetine, miconazole; paroxetine, pergolide, quinidine, quinine, ritonavir, ropinirole, terbinafine	CYP2D6 inhibitors (strong) may decrease the metabolism of amphetamines and increase amphetamine steady-state plasma concentrations.
Amphetamines	2	Guanethidine	Interaction may lead to a decrease in guanethidine effectiveness.
Amphetamines	2	Serotonin-reuptake inhibitors	Interaction may lead to an increase in sensitivity to sympathomimetic effects and increase the risk of serotonin syndrome.
Amphetamines	2	Urinary alkalinizers: potassium citrate, sodium acetate, sodium bicarbonate, sodium citrate, sodium lactate, tromethamine	Interaction may lead to diminished urinary elimination of amphetamines and increase the risk of amphetamine toxicity.
Miscellaneous Anorexigenic Agents and Respiratory and Cerebral Stimulants—Cerebral Stimulants/Agents Used for ADHD			
Methylphenidates	1	Monoamine oxidase inhibitors (MAOIs)	Interaction may cause a hypertensive crisis (headache, hyperpyrexia, and hypertension).
Methylphenidates	2	CYP2D6 inhibitors (strong): chlorpromazine, cocaine, delavirdine, fluoxetine, miconazole; paroxetine, pergolide, quinidine, quinine, ritonavir, ropinirole, terbinafine	CYP2D6 inhibitors (strong) may decrease the metabolism of methylphenidates and increase methylphenidate steady-state plasma concentrations.
Modafinil	2	Contraceptives, oral	Modafinil may cause induction of gastrointestinal (GI) (major) and hepatic (minor) metabolism (CYP3A4/5) of oral contraceptives.
Modafinil	2	CYP2C19 inhibitors (strong): delavirdine,	CYP2C19 inhibitors (strong) may decrease the metabolism of

Drug(s)	Significance Level	Interaction	Mechanism
		fluconazole, fluvoxamine, gemfibrozil, isoniazid, miconazole, omeprazole, ticlopidine	modafinil.
Modafinil	2	CYP3A4 inhibitors (strong): amprenavir, atazanavir, clarithromycin, conivaptan, delavirdine, diclofenac, fosamprenavir, imatinib, indinavir, isoniazid, itraconazole, ketoconazole, miconazole, nefazodone, nelfinavir, nicardipine, propofol, Quinidine; ritonavir, telithromycin	CYP3A4 inhibitors (strong) may decrease the metabolism of modafinil and increase modafinil steady-state plasma concentrations.
Modafinil	2	Ethinyl estradiol	Modafinil may cause induction of GI (major) and hepatic (minor) metabolism (CYP3A4/5) of ethinyl estradiol.
Modafinil	2	Triazolam	Modafinil may cause induction of GI (major) and hepatic (minor) metabolism (CYP3A4/5) of triazolam.
Miscellaneous Central Nervous System Agents—Cerebral Stimulants/Agents Used for ADHD			
Atomoxetine	1	Monoamine oxidase inhibitors (MAOIs)	Interaction may cause altered brain monoamine concentrations.
Atomoxetine	2	CYP2D6 inhibitors (strong): chlorpromazine, cocaine, delavirdine, fluoxetine, miconazole; paroxetine, pergolide, quinidine, quinine, ritonavir, ropinirole, terbinafine	CYP2D6 inhibitors (strong) may decrease the metabolism of atomoxetine and increase atomoxetine steady state plasma-concentrations.
Atomoxetine	2	Serotonin-reuptake inhibitors: paroxetine, fluoxetine	Serotonin-reuptake inhibitors may inhibit the metabolism (CYP2D6) of atomoxetine increase atomoxetine steady state 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 Table 7. In addition to the common adverse drug events listed in Table 7, certain serious adverse drug events have also been associated with the cerebral stimulants/agents used for ADHD. These have prompted the FDA to issue alerts regarding these medications and/or to require boxed warnings in their product information.[5,6-8,18-35]

FDA Alerts and Boxed Warnings—Drug Abuse and Misuse

The misuse and abuse of amphetamines, particularly methamphetamine, has been a serious problem in recent years. Tolerance, extreme psychological dependence, and severe social disability can result. There are reports of patients who have increased their dosage many times over the recommended dosage. To counter the relative ease with which methamphetamine can be synthesized illicitly from readily available chemicals such as ephedrine, phenylpropanolamine, or pseudoephedrine, restrictions were placed upon the distribution of these compounds in the Combat Methamphetamine Epidemic Act of 2005 (CMEA), enacted on September 30, 2006.[36] The US Department of Health and Human Services *2005 National Survey on Drug Use and Health* (NSDUH) states that more than 10.4 million Americans 12 years and older (4.3%) have used methamphetamine for nonmedical reasons at least once in their lifetimes.[37]

According to evidence-based clinical practice guidelines as well as recent meta-analyses, there is no evidence to suggest that drug abuse results from prescribed stimulants if they are properly monitored.[2,3,38,39] However, according to the NSDUH survey, nearly half (47.7%) of previous-year methamphetamine users reported obtaining the drug from a friend or relative for free, indicating that a substantial portion of methamphetamine abuse and misuse may involve prescription drugs.[40]

A boxed warning regarding the possibility of drug abuse has been mandated by the FDA for all products containing amphetamine and its derivatives, and is reproduced in Table 8. However, it is important to keep in mind that the overall rate of abuse amongst individuals with ADHD is relatively low.

Methylphenidate and amphetamines increase dopamine levels in the brain similar to cocaine and methamphetamine, and both are Class II controlled drugs, indicating a significant abuse potential. Abuse is thought to be caused by a rapid extracellular increase in dopamine which is associated with reinforcing effects. In order to produce rapid dopamine release, when these medications are abused, they are usually crushed and administered intranasally or intravenously. Methylphenidate is a less potent sympathomimetic amine than mixed amphetamine salts and recent data suggests that oral methylphenidate has a lower potential for abuse.[38] One hypothesis for the limited abuse of methylphenidate is that at orally administered clinical doses for ADHD it is a "weak stimulant" and produces slower increases in extracellular dopamine compared to other commonly abused stimulants. However, studies have shown that clinical oral doses of methylphenidate produce the same peak dopamine transporter blockade as other abused stimulants, although slightly delayed; therefore, it should not be considered a "weak stimulant."[41] The osmotic-release tablet Concerta® cannot be crushed and theoretically may offer a decreased potential for abuse. It has also been proposed that transdermal methylphenidate may possess less potential for abuse compared to orally administered cerebral stimulants, but this claim has not been evaluated in clinical trials.

Although the abuse of methylphenidate is rare, caution may be indicated in the presence of conduct disorder, preexisting chemical dependency, or a chaotic family. If the risk of drug abuse by the patient or the patient's peers or family is high, a nonstimulant medication may be preferable to methylphenidate or mixed amphetamine salts.[3,38,39] FDA-approved product labeling for all methylphenidate products bears a warning concerning their potential for abuse and this warning is reproduced below in Table 9.

FDA Alerts and Boxed Warnings—Other

On February 21, 2007, the FDA directed all manufacturers of products approved for the treatment of ADHD to develop Patient Medication Guides to alert patients to possible cardiovascular risks and risks of adverse psychiatric symptoms associated with these drugs, and to advise them of precautions that can be taken.[42] The FDA's action followed an FDA review that dealt with reports of serious cardiovascular adverse events in patients taking the usual therapeutic doses of ADHD medications.[43] The review was initiated in reaction to 12 cases of sudden death in children, both with and without underlying serious heart problems or defects.[43]

Another issue addressed by the February 2007 FDA directive was prompted by an FDA Pediatric Advisory Committee review that revealed a slightly increased risk (about 1 per 1,000) of drug-related psychiatric adverse events: these adverse events included hearing voices, becoming suspicious for no reason, or becoming manic, even in patients without prior psychiatric problems.[44] The February 2007 FDA directive also required that new labeling should address an increased risk of suicidal thinking seen with atomoxetine, which was the subject of another FDA alert issued in September 2005.[45] The black box warning for atomoxetine mandated by the FDA appears in Table 10.

The FDA recommends that children, adolescents, or adults for whom pharmaceutical treatment for ADHD is being considered should work with their providers to develop treatment plans; these should include a careful health history and evaluation of current status, particularly for cardiovascular and psychiatric problems (including assessment for a family history of such problems).[42]

Another FDA alert pertains to atomoxetine. Two case reports (via the FDA MedWatch system) of hepatotoxicity in patients taking atomoxetine (one adult, one child) have resulted in the addition of a warning to the product labeling stating: "Postmarketing reports indicate that Strattera® can cause severe liver injury in rare cases. Although no evidence of liver injury was detected in clinical trials of about 6,000 patients, there have been two reported cases of markedly elevated hepatic enzymes and bilirubin, in the absence of other obvious explanatory factors, out of more than 2 million patients during the first two years of postmarketing experience."[33,45,46]

Other Warnings

The use of the methylphenidate transdermal patch may result in contact sensitization as evidenced by development of an allergic contact dermatitis. Patients who develop contact sensitization to transdermal methylphenidate and require oral treatment with methylphenidate should be monitored under close medical supervision. It is possible that patients sensitized to transdermal methylphenidate may not be able to take methylphenidate in any form.[27]

It is unknown what the true incidence of sensitization is with transdermal methylphenidate, when used as directed. However, a study was conducted to measure skin sensitization. This study involved an induction phase involving continuous exposure to the same site for 3 weeks, followed by 2 weeks of rest, then rechallenge. Transdermal methylphenidate was more irritating compared to a placebo patch control and a negative control (saline). Eighteen (13.5%) of 133 subjects were confirmed to have been sensitized.[27]

Table 7. Adverse Drug Events (%) Reported with the Cerebral Stimulants/Agents Used for ADHD[5,6-8,18-34]

Adverse Event	Amphetamine Products				Methylphenidate Products				Other Products	
	Amphetamine Salts (Mixed) IR and XR*	Dextro-amphetamine IR and XR	Lisdex-amfetamine	Meth-amphetamine	Dex-methylphenidate IR and XR	Methyl-phenidate, Short- and Intermediate-acting	Methyl-phenidate, Long-acting, Oral	Methyl-phenidate, Long-acting, Patch	Atomox-etine	Modafinil
Cardiovascular										
Angina	-	-	-	-	✔	✔	✔	✔	-	-
Cardiac arrhythmia	-	-	-	-	✔	✔	✔	✔	-	-
Cardiomyopathy	✔	✔	✔	-	-	-	-	-	-	-
Cerebral arteritis	-	-	-	-	✔	✔	✔	✔	-	-
Cerebral occlusion	-	-	-	-	✔	✔	✔	✔	-	-
Chest pain	-	-	-	-	-	-	-	-	-	3
Edema	-	-	-	-	-	-	-	-	-	1
Hyper-/ hypotension	-	-	-	-	✔	✔	✔	✔	-	-
Hypertension	✔	✔	✔	✔	-	-	-	-	1-9	3
Orthostatic hypotension	-	-	-	-	-	-	-	-	2	-
Myocardial infarction	✔	-	✔	-	-	✔	✔	✔	-	-
Palpitations	✔, 2-4*	✔	✔	✔	✔	✔	✔	✔	4	2
Pulse increase/decrease	-	-	-	-	✔	✔	✔	✔	-	-
QT prolongation	-	-	-	-	-	-	-	-	<1	-
Sudden death	✔	-	✔	-	✔	-	✔ †	-	-	-
Tachycardia	✔, 6*	✔	✔	✔	3	✔	✔	✔	2-3	2
Vasodilation	-	-	-	-	-	-	-	-	-	2
Central Nervous System										
Abnormal dreams	-	-	-	-	-	-	-	-	4	-
Abnormal behavior	-	-	-	-	-	-	✔ †	-	-	-
Aggressive behavior	-	✔	-	-	✔	✔	✔	✔	<1	-
Agitation	8*	-	-	-	-	-	-	-	<1	1
Akathisia	-	-	-	-	-	-	-	-	<1	-
Anxiety	8*	-	-	-	5-6	-	-	-	<1	5
Crying	-	-	-	-	-	-	-	-	2	-
Depression	✔	-	✔	-	✔	✔	✔	✔	-	2
Dizziness	✔, 2-7*	✔	5	✔	6	✔	✔	✔	6	5

Adverse Event	Amphetamine Products				Methylphenidate Products				Other Products	
	Amphetamine Salts (Mixed) IR and XR*	Dextro-amphetamine IR and XR	Lisdex-amfetamine	Meth-amphetamine	Dex-methylphenidate IR and XR	Methyl-phenidate, Short- and Intermediate-acting	Methyl-phenidate, Long-acting, Oral	Methyl-phenidate, Long-acting, Patch	Atomox-etine	Modafinil
Drowsiness	-	-	-	-	✔	✔	✔	✔	-	-
Dysphoria	✔	✔	✔	✔	-	-	-	-	-	-
Early morning awakening	-	-	-	-	-	-	-	-	<2	-
Euphoria	✔	✔	✔	✔	-	-	-	-	-	-
Fatigue/lethargy	-	-	-	-	-	-	-	-	7-9	-
Fever	5*	-	2	-	5	✔	✔	✔	3	-
Hyperactivity	-	-	-	-	-	-	✔ †	-	-	-
Headache	✔, 26*	✔	12	✔	25-26	✔	✔	✔	17-27	34
Hostility	-	-	-	-	-	-	-	-	<1	-
Hypomania	-	-	-	-	-	-	-	-	<1	-
Insomnia	✔, 12-27*	✔	4-19	✔	✔	✔	✔	13	16	5
Ischemic neurological deficit	-	-	-	-	-	-	✔ †	-	-	-
Irritability	-	-	10	-	-	-	-	-	8	-
Jittery feeling	-	-	-	-	12	-	-	-	-	-
Labile affect	2-9*	-	3	-	-	-	-	6	-	-
Mania	-	✔	-	-	-	-	-	-	<1	✔
Mood swings	-	-	-	-	-	-	-	-	2-5	-
Nervousness	6*	-	-	-	✔	✔	✔	✔	-	7
Neuroleptic malignant syndrome (NMS)	-	-	-	-	✔	✔	✔	✔	-	-
Overstimulation	✔	✔	✔	✔	-	-	-	-	-	1
Panic disorder	-	-	-	-	-	-	-	-	<1	-
Psychotic episodes	✔	✔	✔	✔	-	-	-	-	-	✔
Restlessness	✔	✔	✔	✔	12	-	-	-	-	-
Rigors	-	-	-	-	-	-	-	-	3	-
Seizures	✔	-	✔	-	-	-	-	-	-	-
Somnolence	2-4*	-	2	-	-	-	-	-	7	2
Speech disorder	2-4*	-	-	-	-	-	-	-	-	-
Stroke	✔	-	✔	-	-	-	-	-	-	-
Suicidal ideation	-	-	-	-	-	-	-	-	<1	-
Syncope	-	-	-	-	-	-	-	-	<1	-

Adverse Event	Amphetamine Products				Methylphenidate Products				Other Products	
	Amphetamine Salts (Mixed) IR and XR*	Dextro-amphetamine IR and XR	Lisdex-amfetamine	Meth-amphetamine	Dex-methylphenidate IR and XR	Methyl-phenidate, Short- and Intermediate-acting	Methyl-phenidate, Long-acting, Oral	Methyl-phenidate, Long-acting, Patch	Atomox-etine	Modafinil
Tourette's exacerbation	✔	✔	✔	✔	✔	✔	✔	✔	-	-
Toxic psychosis	-	-	-	-	✔	✔	✔	✔	-	-
Vertigo	-	-	-	-	-	-	-	-	-	1
Dermatological/Allergic Reactions										
Anaphylaxis	✔	-	✔	-	-	-	-	-	-	-
Angioedema	✔	-	✔	-	-	-	-	-	<1	-
Dermatitis	-	-	-	-	-	-	-	-	2-4	-
Diaphoresis	2-4*	-	-	-	-	-	-	-	2	1
Fixed drug eruption	-	-	-	-	-	-	✔ †	-	-	-
Erythema	-	-	-	-	-	-	-	✔	-	-
Erythema multiforme	-	-	-	-	✔	✔	✔	✔	-	-
Exfoliative dermatitis	-	-	-	-	✔	✔	✔	✔	-	-
Flushing	-	-	-	-	-	-	-	-	2	-
Hair loss	-	-	-	-	✔	✔	✔	✔	-	-
Herpes simplex	-	-	-	-	-	-	-	-	-	1
Hypersensitivity reactions	✔	-	✔	-	✔	✔	✔	✔	-	-
Photosensitivity	2-4*	-	-	-	-	-	-	-	-	-
Rash	✔	✔	3	✔	✔	✔	✔	✔	-	-
Stevens-Johnson syndrome	✔	-	✔	-	-	-	-	-	-	-
Toxic epidermal necrolysis	✔	-	✔	-	-	-	-	-	-	-
Urticaria	✔	✔	✔	✔	✔	✔	✔	✔	<1	-
Endocrine and Metabolic										
Changes in libido	✔	✔	✔	✔	-	-	-	-	-	-
Dysmenorrhea	2-4*	-	-	-	-	-	✔	-	7	-
Growth suppression	-	-	-	✔	-	✔	✔	✔	-	-
Hot flushes	-	-	-	-	-	-	-	-	3	-
Libido decreased	2-4*	-	-	-	-	-	-	-	6	-

Adverse Event	Amphetamine Products				Methylphenidate Products				Other Products	
	Amphetamine Salts (Mixed) IR and XR*	Dextro-amphetamine IR and XR	Lisdex-amfetamine	Meth-amphetamine	Dex-methylphenidate IR and XR	Methyl-phenidate, Short- and Intermediate-acting	Methyl-phenidate, Long-acting, Oral	Methyl-phenidate, Long-acting, Patch	Atomox-etine	Modafinil
Menstrual disturbances	-	-	-	-	-	-	-	-	2-3	-
Orgasm abnormal	-	-	-	-	-	-	-	-	2	-
Gastrointestinal (GI)										
Abdominal pain	11-14*	-	12	-	15	✔	✔	✔	20	-
Anorexia	✔	✔	-	✔	6	✔	✔	5	<2	4
Appetite decreased/loss	22-36*	-	39	-	30	✔	✔	26	10-14	-
Constipation	✔, 2-4*	✔	✔	✔	-	-	-	-	3-10	2
Diarrhea	✔, 2-6*	✔	✔	✔	-	✔	✔	✔	4	6
Dry mouth	✔, 2-35*	✔	5	✔	7	-	-	-	4-21	4
Dyspepsia	2-4*	-	-	-	5-8	-	-	-	4-6	5
Flatulence	-	-	-	-	-	-	-	-	2	1
Other GI disturbances	✔	✔	-	✔	-	-	-	-	-	-
Mouth ulceration	-	-	-	-	-	-	-	-	-	1
Nausea	2-8*	-	6	✔	9	✔	✔	12	12	11
Stomach cramps	-	-	-	-	✔	-	-	-	-	-
Thirst	-	-	-	-	-	-	-	-	-	1
Tooth disorder	2-4*	-	-	-	-	-	-	-	-	-
Unpleasant taste	✔	✔	✔	✔	-	-	-	-	-	1
Vomiting	2-7*	-	9	✔	-	✔	✔	10	11-15	-
Weight loss	✔, 4-11*	✔	9	✔	✔	✔	✔	9	2	-
Genitourinary										
Abnormal urine	-	-	-	-	-	-	-	-	-	1
Ejaculatory disturbance	-	-	-	-	-	-	-	-	5	-
Erectile disturbance	-	-	-	-	-	-	-	-	7	-
Hematuria	-	-	-	-	-	-	-	-	-	1
Impotence	✔, 2-4*	✔	✔	✔	-	-	-	-	3	-
Prostatitis	-	-	-	-	-	-	-	-	3	-
Pyuria	-	-	-	-	-	-	-	-	-	1
Urinary retention/	-	-	-	-	-	-	-	-	8	-

Adverse Event	Amphetamine Products				Methylphenidate Products				Other Products	
	Amphetamine Salts (Mixed) IR and XR*	Dextro-amphetamine IR and XR	Lisdex-amfetamine	Meth-amphetamine	Dex-methylphenidate IR and XR	Methyl-phenidate, Short- and Intermediate-acting	Methyl-phenidate, Long-acting, Oral	Methyl-phenidate, Long-acting, Patch	Atomox-etine	Modafinil
hesitation										
Urinary tract infection	5*	-	-	-	-	-	-	-	-	-
Hematologic										
Agranulocytosis	-	-	-	-	-	-	-	-	-	✔
Anemia	-	-	-	-	✔	✔	✔	✔	-	-
Eosinophilia	-	-	-	-	-	-	-	-	-	1
Leukopenia	-	-	-	-	✔	✔	✔	✔	-	-
Thrombocytopenic purpura	-	-	-	-	✔	✔	✔	✔	-	-
Hepatic										
Hepatic coma	-	-	-	-	✔	✔	✔	✔	-	-
Hepatotoxicity	-	-	-	-	-	-	-	-	<1	-
Jaundice	-	-	-	-	-	-	-		<1	-
Abnormal liver function tests	-	-	-	-	✔	✔	✔	✔	-	2
Infections										
Ear infection	-	-	-	-	-	-	-	-	3	-
Flu-like syndrome	-	-	-	-	-	-	-	-	<1	4
Infection	2-4*	-	-	-	-	-	-	-	-	-
Influenza	-	-	-	-	-	-	-	-	3	-
Necrotizing vasculitis	-	-	-	-	✔	✔	✔	✔	-	-
Viral infection	2*	-	-	-	-	-	-	-	-	-
Neuromuscular and Skeletal										
Arthralgia	-	-	-	-	✔	✔	✔	✔	-	-
Back pain	-	-	-	-	-	-	-	-	-	6
Dyskinesia	✔	✔	✔	-	✔	✔	✔	✔	-	1
Hyperkinesia	-	-	-	-	-	-	-	-	-	1
Hypertonia	-	-	-	-	-	-	-	-	-	1
Paresthesia	-	-	-	-	-	-	-	-	4	2
Tic (exacerbation)	✔	✔	2	✔	-	-	-	7	-	-
Tremor	✔	✔	✔	✔	-	-	-	-	-	1
Twitching	2-4*	-	-	-	-	-	-	-	-	-
Weakness	2-6*	-	-	-	-	-	-	-	-	-

Adverse Event	Amphetamine Products				Methylphenidate Products				Other Products	
	Amphetamine Salts (Mixed) IR and XR*	Dextro-amphetamine IR and XR	Lisdex-amfetamine	Meth-amphetamine	Dex-methylphenidate IR and XR	Methyl-phenidate, Short- and Intermediate-acting	Methyl-phenidate, Long-acting, Oral	Methyl-phenidate, Long-acting, Patch	Atomox-etine	Modafinil
Ocular										
Abnormal vision	-	-	-	-	-	-	-	-	-	1
Accommodation difficulties	-	-	-	-	✔	✔	✔	✔	-	1
Amblyopia	-	-	-	-	-	-	-	-	-	1
Blurred vision	-	-	-	-	✔	✔	✔	✔	-	1
Eye pain	-	-	-	-	-	-	-	-	-	1
Mydriasis	-	-	-	-	-	-	-	-	<2	-
Respiratory										
Cough	-	-	-	-	-	✔	✔	✔	11	-
Dyspnea	2-4*	-	-	-	-	-	-	-	-	-
Epistaxis	-	-	-	-	-	-	-	-	-	1
Lung disorder	-	-	-	-	-	-	-	-	-	2
Nasal congestion	-	-	-	-	-	-	-	6	-	-
Nasopharyngitis	-	-	-	-	-	-	-	5	-	-
Pharyngitis	-	-	-	-	-	✔	✔	✔	-	4
Pharyngolaryngeal pain	-	-	-	-	4	-	-	-	-	-
Rhinitis	-	-	-	-	-	-	✔	-	-	7
Rhinorrhea	-	-	-	-	-	-	-	-	4	-
Sinus headache	-	-	-	-	-	-	-	-	3	-
Sinusitis	-	-	-	-	-	✔	✔	✔	6	-
Upper respiratory tract infection	-	-	-	-	-	✔	✔	✔	-	-

IR=immediate release, XR=extended release
✔ Percent not specified
-Event not reported or incidence <1%
*Extended release
†Metadate CD®

Table 8. Black Box Warning for Amphetamines and Methamphetamine[5,6,18-21]

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

Table 9. Black Box Warning for Methylphenidate and Dexmethylphenidate[5,7,22-32]

WARNING
ORAL Methylphenidate hydrochloride and dexmethylpenidate should be given cautiously to emotionally unstable patients, such as those with a history of drug dependence or alcoholism, because such patients may increase dosage on their own initiative. Chronically abusive use can lead to marked tolerance and psychic dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during drug withdrawal, since severe depression as well as the effects of chronic overactivity can be unmasked. Long term follow-up may be required because of the patient's basic personality disturbances.
TRANSDERMAL Methylphenidate patch should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during withdrawal from abusive use, since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow-up.

Table 10. Black Box Warning for Atomoxetine[5,8,33]

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. Patients who are started on therapy should be monitored closely for suicidality (suicidal thinking and behavior), clinical worsening, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Atomoxetine is approved for ADHD in pediatric and adult patients. Atomoxetine is not approved for major depressive disorder.
Pooled analyses of short-term (6 to 18 weeks) placebo-controlled trials of atomoxetine in children and adolescents (a total of 12 trials involving over 2,200 patients, including 11 trials in ADHD and 1 trial in enuresis) have revealed a greater risk of suicidal ideation early during treatment in those receiving atomoxetine compared to placebo. The average risk of suicidal ideation in patients receiving atomoxetine was 0.4% (5/1,357 patients), compared to none in placebo-treated patients (851 patients). No suicides occurred in these trials.

VII. Dosing and Administration

The usual dosing regimens for the cerebral stimulants/agents are summarized in Table 11.

Table 11. Usual Dosing for the Cerebral Stimulants/Agents Used for ADHD[5,6-8,18-34]

Drug	Usual Adult Dose†	Usual Pediatric Dose†	Availability†
Amphetamines—Cerebral Stimulants/Agents Used for ADHD			
Amphetamine salts, mixed (amphetamine-dextro-amphetamine)	ADHD: Tablet: 5 mg once or twice daily in the morning; may increase daily dose in 5 mg increments at weekly intervals until optimal response	ADHD: Tablet: Children 3-5 years: 2.5 mg once daily; may increase dose by 2.5 mg daily at weekly intervals until optimal response	Tablet: 5 mg 7.5 mg 10 mg 12.5 mg

Drug	Usual Adult Dose†	Usual Pediatric Dose†	Availability†
	obtained; maximum dose: 40 mg daily Patients taking the immediate-release product twice daily can be switched to an equivalent dose of the sustained-release form given once daily. Capsule, extended-release (XR): 20 mg daily; may titrate at weekly intervals to appropriate efficacy and tolerability as indicated; maximum dose: not specified <u>Narcolepsy:</u> Tablet: 5-60 mg daily in divided doses, depending on individual response	obtained; maximum dose: 40 mg daily Children ≥6 years: 5 mg once or twice daily in the morning; may increase dose by 5 mg daily at weekly intervals; maximum dose: 40 mg daily Give first dose upon awakening and additional doses at 4 to 6 hour intervals Capsule, extended-release (XR): Children ≥6 years: 5-10 mg once daily; may increase dose by 5-10 mg daily at weekly intervals; maximum dose: 30 mg daily Adolescents 13-17 years: 10 mg once daily; may increase to 20 mg daily after one week if ADHD symptoms not adequately controlled; maximum dose: not specified Should be given upon awakening <u>Narcolepsy:</u> Tablet: Children 6-12 years: 5 mg once daily; may increase dose daily dose in 5 mg increments at weekly intervals until optimal response is obtained Children ≥12 years: 10 mg once daily; may increase daily dose in 10 mg increments at weekly intervals until optimal dose obtained Give first dose upon awakening and additional doses at 4 to 6 hour intervals	15 mg 20 mg 30 mg Capsule, extended-release (XR): 5 mg 10 mg 15 mg 20 mg 25 mg 30 mg
Dextro-amphetamine	<u>ADHD:</u> Tablet: Recommended dosing not specified Capsule, sustained-release (SR): Recommended dosing not specified <u>Narcolepsy:</u> Tablet: 5-60 mg daily in divided doses, depending on individual response Capsule, sustained-release (SR): Sustained-release capsules may be used for a once-a-day dosage wherever appropriate	<u>ADHD:</u> Tablet: Children 3-5 years: 2.5 mg once daily; may increase by 2.5 mg daily at weekly intervals until optimal response is obtained; maximum dose: 40 mg daily Children ≥6 years: Initial 5 mg once or twice daily; increase dose in increments of 5 mg/day at weekly intervals until optimal response is reached; maximum dose: 40 mg daily Give first dose upon awakening and additional doses at 4 to 6 hour intervals Capsule, sustained-release (SR):	Tablet: 5 mg 10 mg Capsule, sustained-release (SR): 5 mg 10 mg 15 mg

Drug	Usual Adult Dose†	Usual Pediatric Dose†	Availability†
		Children 3-5 years: 2.5 mg once daily; may increase daily dose in 2.5 mg increments at weekly intervals until optimal response is obtained; maximum dose: 40 mg daily Children ≥6 years: 5 mg once or twice daily; may increase daily dose in 5 mg increments at weekly intervals until optimal response is reached; maximum dose: 40 mg daily <u>Narcolepsy:</u> Tablet: Children 6-12 years: 5 mg once daily; may increase dose daily dose in 5 mg increments at weekly intervals until optimal response is obtained Children ≥12 years: 10 mg once daily; may increase daily dose in 10 mg increments at weekly intervals until optimal dose obtained Give first dose upon awakening and additional doses at 4 to 6 hour intervals Capsule, sustained-release (SR): Sustained-release capsules may be used for a once-a-day dosage wherever appropriate	
Lisdex-amfetamine	<u>ADHD:</u> Safety and efficacy has not been established in persons >12 years old.	<u>ADHD:</u> Children 6-12 years: 30 mg once in the morning; may increase dose in 20 mg increments at weekly intervals; maximum dose: 70 mg daily Lisdexamfetamine (Vyvanse®) should be taken in the morning to avoid potential for insomnia.	Capsule: 30 mg 50 mg 70 mg
Meth-amphetamine	<u>ADHD:</u> Safety and efficacy have not been established in adults. <u>Exogenous Obesity:</u> 5 mg taken one-half hour before each meal; treatment should not exceed a few weeks in duration	<u>ADHD:</u> Children ≥6 years: 5 mg once or twice daily; may increase in 5 mg increments at weekly intervals until optimum response is achieved; usual effective dose is 20-25 mg daily; maximum dose: not specified <u>Exogenous Obesity:</u> Children ≥12 years: 5 mg taken one-half hour before each meal Treatment should not exceed a few weeks	Tablet: 5 mg

Drug	Usual Adult Dose†	Usual Pediatric Dose†	Availability†
Miscellaneous Anorexigenic Agents and Respiratory and Cerebral Stimulants—Cerebral Stimulants/Agents Used for ADHD			
Dexmethyl-phenidate	ADHD: Tablet: Safety and efficacy have not been established in persons >17 years old. Capsule, extended-release (XR): Methylphenidate naïve: 10 mg daily; may increase dose in 10 mg increments at weekly intervals; maximum dose: 20 mg daily The effectiveness of dexmethylphenidate extended-release capsules (Focalin XR®) for long-term use (ie, for more than 7 weeks) has not been systematically evaluated in controlled trials with adult subjects.	ADHD: Tablet, immediate release: Children ≥6 years: Methylphenidate naïve: 2.5 mg twice daily; may increase dose in 2.5-5 mg increments at weekly intervals; maximum dose: 20 mg daily (10 mg twice daily) Methylphenidate experienced: One-half of the dose of dexmethylphenidate; maximum dose: 20 mg daily (10 mg twice daily) Doses should be taken at least 4 hours apart. When switching from methylphenidate to dexmethylphenidate, the starting dose of dexmethylphenidate should be half that of methylphenidate. Capsule, extended-release (XR): Children ≥6 years: Methylphenidate naïve 5 mg daily; may increase dose in 5 mg increments at weekly intervals; maximum dose: 20mg daily Dexmethylphenidate extended-release capsules (Focalin XR®) are for oral administration once daily in the morning.	Tablet: 2.5 mg 5 mg 10 mg Capsule, extended-release (XR): 5 mg 10 mg 15 mg 20 mg
Methylphenidate	ADHD: Tablet, chewable (Methylin®): 20-60 mg daily in 2 to 3 divided doses; maximum dose: 60 mg daily Administer 30-45 minutes before meals and the last dose should be taken before 6 PM to avoid insomnia Tablet, (Ritalin®, Methylin®): 20-60 mg daily in 2 to 3 divided doses; maximum dose: 60 mg daily Administer 30-45 minutes before meals and the last dose should be taken before 6 PM to avoid insomnia Tablets, extended-release (ER) (osmotic) (Concerta®): Methylphenidate naive: 18 mg once daily; may increase dose in 18 mg increments at weekly intervals; maximum dose: 54 mg once daily Tablet, sustained-release (SR) (Metadate ER®, Methylin ER®, Ritalin-SR®): Methylphenidate sustained-release tablets	ADHD: Tablet, chewable (Methylin®): Children ≥6 years: 5 mg twice daily (before breakfast and lunch); may increase dose in 5-10 mg increments at weekly intervals; maximum dose: 60 mg daily Administer 30-45 minutes before meals and the last dose should be taken before 6 PM to avoid insomnia. Tablet, (Ritalin®, Methylin®): Children ≥6 years: 5 mg twice daily (before breakfast and lunch); may increase dose in 5-10 mg increments at weekly intervals; maximum dose: 60 mg daily Administer 30-45 minutes before meals and the last dose should be taken before 6 PM to avoid insomnia Tablets, extended-release (ER) (osmotic) (Concerta®) Children 6-12 years: Methylphenidate naive: 18 mg once daily; maximum dose: 54 mg once daily	Tablet, chewable: 2.5 mg 5 mg 10 mg Tablet: 5 mg 10 mg 20 mg Tablet, extended-release (ER) (osmotic): 18 mg 27 mg 36 mg 54 mg Tablet, sustained-release(SR): 10 mg 20 mg Capsule,

Drug	Usual Adult Dose†	Usual Pediatric Dose†	Availability†
	have a duration of action of approximately 8 hours. Therefore, methylphenidate sustained-release tablets may be used in place of the immediate-release tablets when the 8-hour dosage of methylphenidate sustained release corresponds to the titrated 8-hour dose of methylphenidate immediate release. Patients converting from immediate-release or sustained-release methylphenidate may follow the dosage conversion chart included in the official labeling. Should be given orally once daily in the morning Tablet, sustained-release (SR) (Metadate ER®, Methylin ER®, Ritalin-SR®): Methylphenidate sustained-release tablets have a duration of action of approximately 8 hours. Therefore, methylphenidate sustained-release tablets may be used in place of the immediate-release tablets when the 8-hour dosage of methylphenidate sustained release corresponds to the titrated 8-hour dose of methylphenidate immediate release. Capsule, extended-release (XR) (Metadate CD®): 20 mg once daily; may increase dose in 10-20 mg increments at weekly intervals; maximum dose: 60 mg daily Capsule, extended-release (XR) (Ritalin LA®): 20 mg once daily; may increase dose in 10 mg increments at weekly intervals; maximum dose: 60 mg daily Dose conversions from immediate- release or other extended-release products are included in the package insert. Oral solution, (Methylin®): 20-60 mg daily in 2 to 3 divided doses; maximum dose: 60 mg daily Administer 30-45 minutes before meals and the last dose should be taken before 6 PM to avoid insomnia Transdermal patch: Safety and efficacy have not been	Adolescents 13-17 years: Methylphenidate naive: 18 mg once daily; maximum dose: 72 mg once daily or 2 mg/kg/day Patients converting from immediate-release or sustained-release methylphenidate may follow the dosage conversion chart included in the official labeling. Should be given orally once daily in the morning Tablet, sustained-release (SR) (Metadate ER®, Methylin ER®, Ritalin-SR®): Children ≥6 years: Methylphenidate sustained-release tablets have a duration of action of approximately 8 hours. Therefore, methylphenidate sustained-release tablets may be used in place of the immediate-release tablets when the 8-hour dosage of methylphenidate sustained release corresponds to the titrated 8-hour dose of methylphenidate immediate release. Capsule, extended-release (XR) (Metadate CD®): Age ≥6 years: 20 mg once daily; may increase dose in 10-20 mg increments at weekly intervals; maximum dose: 60 mg daily Capsule, extended-release (XR) (Ritalin LA®): 20 mg once daily; may increase dose in 10 mg increments at weekly intervals; maximum dose: 60 mg daily Dose conversions from immediate-release or other extended-release products are included in the package insert. Oral solution, (Methylin®): Children ≥6 years: 5 mg twice daily (before breakfast and lunch); may increase dose in 5-10 mg increments at weekly intervals; maximum dose: 60 mg daily Administer 30-45 minutes before meals and the last dose should be taken before 6 PM to avoid insomnia. Transdermal patch: Children 6-12 years: Week 1: 10 mg patch Week 2: 15 mg patch Week 3: 20 mg patch Week 4: 30 mg patch	extended-release (XR): 10 mg 20 mg 30 mg 40 mg 50 mg 60 mg Oral solution: 5 mg/5 mL 10 mg/5 mL Transdermal patch: 10 mg 15 mg 20 mg 30 mg

Drug	Usual Adult Dose†	Usual Pediatric Dose†	Availability†
	established in persons >12 years old. Narcolepsy: Tablet: 10-60 mg daily in 2 to 3 divided doses; administer 30 to 45 minutes before meals Tablet, sustained-release (SR) (Ritalin SR® only): Methylphenidate sustained-release tablets have a duration of action of approximately 8 hours. Therefore, methylphenidate sustained-release tablets may be used in place of methylphenidate immediate-release tablets when the 8-hour dosage of methylphenidate sustained release corresponds to the titrated 8-hour dose of methylphenidate immediate release.	Patch should be applied to hip area 2 hours before an effect is needed and removed 9 hours after application. Dose titration, final dosage and wear time should be individualized according to the needs and response of the patient. Narcolepsy: Tablet: Children ≥6 years: 5 mg twice daily (before breakfast and lunch); may increase dose in 5-10 mg increments at weekly intervals Tablet, sustained-release (SR) (Ritalin SR® only): Children ≥6 years: Methylphenidate sustained-release tablets have a duration of action of approximately 8 hours. Therefore, methylphenidate sustained-release tablets may be used in place of the immediate-release tablets when the 8-hour dosage of methylphenidate sustained release corresponds to the titrated 8-hour dose of methylphenidate immediate release.	
Modafinil	Narcolepsy: Adults and adolescents ≥16 years: 200 mg as a single daily dose in the morning Obstructive Sleep Apnea: Adults and adolescents ≥16 years: 200 mg as a single daily dose in the morning Shift Work Sleep Disorder: Adults and adolescents ≥16 years: 200 mg as a single dose taken approximately 1 hour prior to start of work shift Doses up to 400 mg as a single daily dose have been well tolerated, but there is no consistent evidence that this dose confers additional benefit beyond that of the 200 mg dose	Safety and effectiveness in children <16 years of age have not been established for any indication.	Tablets: 100 mg 200 mg
Miscellaneous Central Nervous System Agents—Cerebral Stimulants/Agents Used for ADHD			
Atomoxetine	ADHD: 40 mg daily; may increase dose after a minimum of 3 days to a target total daily dose of approximately 80 mg administered either as a single daily dose in the morning or as evenly divided doses in the morning and late afternoon/early evening; maximum dose: 100 mg daily	ADHD: Children and adolescents ≤70 kg body weight: 0.5 mg/kg per day; may increase dose after a minimum of 3 days to a target total daily dose of approximately 1.2 mg/kg administered as a single morning dose or as evenly divided doses in the morning and late afternoon/early evening; maximum dose: 100 mg daily or 1.4 mg/kg, whichever is less Children and adolescents over 70 kg body weight: Use adult dose.	Capsules: 10 mg 18 mg 25 mg 40 mg 60 mg 80 mg 100 mg

†If not otherwise indicated, formulation is immediate-release

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the cerebral stimulants/agents used for ADHD are summarized in Table 12.

Table 12. Comparative Clinical Trials Using the Cerebral Stimulants/Agents[16-28]

Study and Drug Regiment	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Attention Deficit Hyperactivity Disorder (ADHD)				
Biederman, Lopez et al[47] AMP-XR (Adderall XR®) 10, 20, or 30 mg QD vs placebo	DB, MC, PC, PG, RCT Children between 6 to 12 years who were diagnosed with ADHD (hyperactive-impulsive or combined subtypes) and responded to stimulants or were naive to stimulant treatment	N=584 3 weeks	Primary: CGIS (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 CGIS teacher and parent scales (*P*<0.001). Secondary: The CGIS 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 CGIS teacher scores in the AMP-XR group were statistically significantly improved at all time points compared to those in the placebo group (*P*<0.001).
Goodman et al[48] AMP-XR (Adderall XR®) 10-60 mg QD (There was not a control arm in the study.)	MC, OL, PRO Adults ≥18 years diagnosed with ADHD (any subtype) and who were willing and able to comply with study requirements	N=725 10-week interim analysis of the QU.E.S.T. trial	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%; *P* value not reported). 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.
Greenhill et al[49] DXM-XR (Focalin XR®) 5-30 mg QD	DB, MC, PC, PG, RCT Children and adolescents aged 6-17 years diagnosed with	N=97 7 weeks	Primary: CADS-T Secondary: CADS-P	Primary: DXM-XR significantly increased CADS-T scores from baseline compared to placebo (16.3 vs 5.7, *P*<0.001). Secondary:

Study and Drug Regiment	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo (Dose began at 5 mg QD and was titrated over 5 weeks)	ADHD (any subtype), a minimum baseline CADS-T score based on age as defined by investigators, were attending school and had the same teacher for the duration of the study, were functioning at age-appropriate levels, and females who had reached menarche, had a negative pregnancy test and were using a reliable contraception throughout the study.		CGI-I CGI-S CHQ (physical and psychosocial)	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 (*P* value not reported). DXM-XR did significantly improve mean CHQ psychosocial scores compared to placebo (11.9 vs 4.3, *P*<0.001).
Spencer et al[50] DXM-XR (Focalin XR®) 20, 30, 40 mg QD vs placebo	DB, FXD, MC, PG, PC, RCT Adults aged 18-60 years 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 significant"), 40 mg= 64.8% (*P*=0.031), and placebo= 41.5%.

Study and Drug Regiment	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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 (*P* values not reported).
Biederman, Krishnan et al[51] LDX 30, 50 or 70 mg QD with a forced dose titration vs placebo	DB, FD, MC, PC, PG, RCT Children between 6 and 12 years 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, Boellner et al[52] LDX 30, 50 or 70 mg QD vs placebo AMP-XR 10, 20, or 30 mg (reference arm)	DB, MC, PC, RCT, XO Children between 6 and 12 years diagnosed with ADHD in an analog classroom setting	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).
Wilens et al[53] MPH-ER (Concerta®) 18-54 mg QD	MC, OS, PRO Children between 6 to 13 years diagnosed with	N=432 1 year	Primary: Heart rate (HR) and blood pressure after 1	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

Study and Drug Regiment	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(There was not a control arm in the study.)	ADHD, with normal hematology, blood chemistry and urinalysis values, and those who agreed to take only the study drug for treatment of ADHD		year Secondary: Not reported	elevations (3.3 mm Hg, *P*<0.001) and HR (3.9 bpm, *P*<0.0001) at the 12-month end point. Secondary: Not reported
Greenhill et al[54] MPH-XR (Metadate CD®) 20-60 mg QD vs placebo	DB, MC, PC, PG, RCT Children between 6 to 16 years diagnosed with ADHD and who had not failed a previous trial of stimulant medications	N=321 3 weeks	Primary: CGIS (teacher) Secondary: CGIS (parents), CGI-I scores, adverse events	Primary: CGIS 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: CGIS 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] Methylphenidate transdermal system (MTS) 10-27 mg QD delivered over a 9-hour wear time vs placebo transdermal system (PTS) Dose optimization over 5 weeks then randomized to 1	RCT, OL (first 5 weeks) then DB, PC Children 6-12 years old with ADHD Patients were excluded if they had a comorbid psychiatric diagnosis, history of seizures or tic disorders, mental retardation, or any illness or skin disorder that might jeopardize	N=80 7 weeks	Primary: Evaluate time 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	Primary: Mean SKAMP-D scores were improved with MTS vs placebo (mean score 3.2 vs 8.0) and at all time points assessed including 12 hours postapplication (*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-

Study and Drug Regiment	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
week active therapy then 1 week placebo. Dose optimization could occur after a minimum of 1 week.	safety or compromise study assessments.		MTS	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). *P* value was not reported. 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, Manos et al[56] Three doses of MTS: 6.25 cm^2 (0.45 mg/hour), 12.5 cm^2 (0.9 mg/hour), and 25 cm^2 (1.8 mg/hour), 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).	DB, DR, MC, RCT Children aged 7–12 years with ADHD Before the study, 11 children were receiving amphetamine compounds, 10 were receiving MPH, and 15 were not medicated.	N=36 8 days	Primary: MTS efficacy and influence of exposure time on morning effects Secondary: Not reported	Primary: All doses of MTS were significantly improved vs placebo on measures of social behavior in recreational settings, classroom functioning, and parent ratings of evening behavior (*P*<0.05). Beneficial effects of MTS patches were observed at all time points after application of the patch and were still seen for 3 hours after the patch had been removed (ie, throughout the 12-hour assessment). Incidence of skin rash was reported as 40%-50%. Secondary: Not reported
Pelham, Burrows-McLean et al[57] Three doses of MTS 12.5 cm^2, 25 cm^2, and 37.5 cm^2 ±	DR, RCT Children aged 6-12 years with ADHD	N=27 6 weeks	Primary: Proportion that reached individual target goals in Daily Report Card	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

Study and Drug Regiment	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
behavior modification (BMOD) Each participant had 2 days on each treatment without concomitant BMOD and 4 days on each treatment with concomitant BMOD.	All participants were enrolled in a summer treatment program, 25 had combined type ADHD and 2 had hyperactive/impulsive type.		(DRC) scores Secondary: Not reported	(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. Secondary: Not reported
Biederman, Heiligenstein et al[58] Atomoxetine 1.2-1.8 mg/kg/day vs placebo	DB, MC, PC, RCT (two studies) Girls aged 7 to 13 years diagnosed with ADHD	N=51 9 weeks	Primary: ADHD-RS Secondary: CPRS-R, CGIS (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 CGIS scores compared to placebo (1.5 vs 0.6, $P<0.001$).
Michelson et al[59] Atomoxetine 1.2-1.8 mg/kg/day vs placebo	MC, OL, PC, RCT Children between 8 to 18 years diagnosed with ADHD and with a symptom severity score at least 1.5 standard deviations above age and gender norms on the ADHD-RS or subscales	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 (P value not reported). Secondary: Atomoxetine 1.2 mg/kg showed significant decreases in all scales of CPRS-R ($P<0.05$). Atomoxetine 1.8 mg/kg showed significant increase in all scales of CHQ ($P<0.05$).
Spencer et al[60] Atomoxetine up to 90 mg daily vs	DB, MC, PC, RCT (pooled data from 2 trials) Children between 7 and 13 years diagnosed with ADHD and who were	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

Study and Drug Regiment	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo	determined to be of normal intelligence			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] Atomoxetine vs placebo	MA All 9 studies (1) were PC, RCT; (2) treated any subtype of ADHD (3) compared atomoxetine (single or multiple doses) to placebo; (4) conducted in children and adolescents; (5) evaluated ADHD-RS; (6) reported adverse events, dropouts and withdrawals	N=1,828 Not reported	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] Atomoxetine 0.5 mg/kg/day-1.8 mg/kg/day (titrated based on judgment of investigator) vs standard current therapy (SCT); patients in this group received any medication the clinician deemed to be appropriate (agents included MPH and clonidine)	MC, OL, PRO, RCT Children 7-15 years old diagnosed with ADHD and had a symptom severity score ≥1.5 standard deviations above the ADHD-RS age norm for their ADHD subtype	N=201 10 weeks	Primary: CHIP-CE Secondary: ADHD-RS, CGI-S, CGI-I, HSPP, FBIM	Primary: Quality of life greatly improved over the 10 weeks in the atomoxetine group vs the SCT group as demonstrated by the significant increase in CHIP-CE (*P*<0.001). Secondary: ADHD-RS, CGI-S, and CGI-I scores were significantly improved in the atomoxetine group over the SCT group (all *P*<0.001). The atomoxetine group was significantly better in improving the HSPP Social Acceptance domain over the SCT group (*P*=0.03), but the groups were not significantly different in the other five HSPP domains (*P*>0.05). There was not a statistically significant difference between groups in reduction in FBIM scores (*P*>0.05).
Faraone et al[63]	MA	N=2,988	Primary: Effect sizes	Primary: All of the drugs groups produced a significant measure of effect

Study and Drug Regiment	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
A total of 14 drugs were evaluated: AMP-IR, AMP-XR, atomoxetine, bupropion, DEX-IR, DEX-ER, DEXM-IR, modafinil, MPH-ER, MPH-IR, MPH-XR, MTS, pemoline*	Meta-analysis of 29 studies	Duration was different among studies	Secondary: Not reported	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). The 2 classes of stimulant medications (short acting and long acting) did not differ significantly from one another (*P*=0.14). Secondary: Not reported
Pliszka et al[64] AMP-IR (Adderall®) 12.5 mg ±4 mg daily vs MPH-IR 25 ±13 mg daily vs placebo	DB, PC, PG, RCT Children in grades 1 through 5 with the diagnosis of ADHD who had no other medical illnesses and were not currently being treated with any other nonstimulant psychotropic medication	N=58 3 weeks	Primary: CGIS (parent and teacher) Secondary: Not reported	Primary: More responders on both CGIS scores were reported with AMP-IR versus MPH-IR or placebo (*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). Secondary: Not reported
McCracken et al[65] AMP-IR (Adderall®) 10 mg QD vs AMP-XR (Adderall XR®) 10, 20, or 30 mg QD vs placebo	DB, PC, RCT, XO Children aged 6 to 12 years diagnosed with ADHD (combined or hyperactive-impulsive subtype) with no evidence of mental retardation, no history of positive response to psychostimulant medication, or no prior stimulant treatments	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 (*P*<0.0001) on attention and deportment SKAMP scales. Secondary: The AMP-XR group displayed continued efficacy (in SKAMP score improvements) at time points beyond that of the AMP-IR group (ie, 12 hours post dose) (*P* value not reported).
Pelham, Aronof et al[66] AMP-IR (Adderall®) 7.5 or	DB, PC, RCT, XO Children between 5.8 to	N=25 6 weeks	Primary: Time course and dose-dependant	Primary: Both doses of AMP-IR were generally more efficacious in reducing negative behaviors and improving academic productivity

Study and Drug Regiment	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
12.5 mg BID vs MPH-IR (Ritalin®) 10 or 17.5 mg BID vs placebo	12.7 years with a diagnosis of ADHD enrolled in a summer treatment program		response information Secondary: Not reported	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 (*P* value not reported). 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 (*P* values not reported). Secondary: Not reported
Wigal et al[67] DXM (Focalin®) 2.5-10 mg BID vs MPH-IR 5-20 mg BID vs placebo BID (doses were titrated until a therapeutic response was obtained)	DB, MC, PC, RCT Children ages 6-17 years diagnosed with ADHD (any subtype), enrolled in elementary school, were within 30% of normal body weight, were anticipated to be available for the entire study and females were premenarche	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 significantly 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

Study and Drug Regiment	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				compared to placebo (*P*=0.0236). MPH-IR did not reach statistical significance compared to placebo (*P* value not reported).
Faraone et al[68] AMP-IR (Adderall®) vs MPH-IR Various doses for both	MA Meta-analysis of 4 studies	N=216 3 weeks up to 8 weeks	Primary: CGIS (parent, teacher and investigator) Secondary: Not reported	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 CGIS scores with teacher ratings (*P*≥0.26). Secondary: Not reported
Efron et al[69] MPH-IR 0.3 mg/kg/dose BID vs DEX-IR 0.15 mg/kg/dose BID Patients received 1 drug for 2 weeks then crossed over to the other stimulant for 2 weeks.	DB, RCT, XO Children between 5 and 15 years who were diagnosed with ADHD, with no history of intellectual disability, gross neurologic abnormality, or Tourette's syndrome; and for whom a trial of stimulant medication was judged clinically appropriate	N=125 4 weeks	Primary: SERS Secondary: Not reported	Primary: There was a statistically significant decrease in the mean number of side effects in the MPH-IR group vs the DEX-IR group (8.19 vs 7.19, *P*=0.03) based on the results of the SERS questionnaire which assess the 17 most common side effects of stimulants including trouble sleeping, decreased appetite and anxiousness. Mean severity of side effects statistically significantly improved in the MPH-IR group compared to the DEX-IR group (3.24 vs 3.73, *P*<0.01). A majority of parents rated their children as improved compared to their "usual selves" in both of the treatment groups (68.8% in the DEX-IR groups and 72% in the MPH-IR) (*P* value not reported). Secondary: Not reported
Gau et al[70] MPH-XR (Concerta®) 18 mg or 36 mg QD vs MPH-IR 5 mg or 10 mg TID	OL, RCT Children ages 6-15 years diagnosed with ADHD (any subtype) and were taking MPH (on a total daily dose MPH 10 mg but not more than 40 mg	N=64 28 days	Primary: CTRS-RS CPRS-RS SKAMP-A SKAMP-D Secondary: SAICA CGI	Primary: Each of the 4 treatment groups displayed a significant decrease in all measures of CTRS-RS, CPRS-RS, SKAMP-A, SKAMP-D at each of the follow-up visits (all *P*<0.001) compared to baseline, but there were no significant differences between the treatment groups (all *P*>0.05). Secondary: Patients in both the MPH-XR and MPH-IR groups experienced significant improvements from baseline in academic performance

Study and Drug Regiment	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	for past 3 months)			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.
Biederman, Wigal et al[71] Atomoxetine 0.5 mg/kg/day x 3 days, then 1.2 mg/kg/day x 14 days vs AMP-XR (Adderall XR®)10 mg QD x 3 days, then 20 mg QD x 7 days, then 30 mg QD x 7days	DB, FD, MC, PG, RCT Girls aged 6-12 years diagnosed with ADHD (combined subtype) and were capable of understanding and following classroom instruction and functioning academically at age appropriate levels.	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 (50 vs 44; *P* not reported). Most adverse events reported were of mild or moderate severity.
Wang et al[72] 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 ages 6 to 16 years diagnosed with ADHD	N=330 ~8 weeks	Primary: ADHD-RS Secondary: CPRS-RS, CGI-S TEAEs, weight	Primary: Atomoxetine was not significantly different than methylphenidate in improving ADHD symptoms based on ADHD-RS scores (atomoxetine, 77.4%; methylphenidate, 81.5%; *P*=0.404). Secondary: Both atomoxetine and MPH-IR treatment groups significantly improved CPRS-RS and CGI-S scores from baseline (all *P*<0.001), the groups were not statistically significant from each other in both measures (*P*>0.05).

Study and Drug Regiment	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				TEAEs that occurred significantly more frequently in the atomoxetine group, compared with the methylphenidate group, included anorexia (37.2% vs 25.3%; *P*=0.024), nausea (20.1% vs 10.2%; *P*=0.014), somnolence (26.2% vs 3.6%; *P*<0.001), dizziness (15.2% vs 7.2%; *P*=0.024) and vomiting (11.6% vs 3.6%; *P*=0.007), most of which were of mild or moderate severity. Patients in the atomoxetine group experienced a small but significantly greater mean weight loss at the end of 8 weeks compared to those in the methylphenidate group (-1.2 kg vs -0.4 kg; *P*<0.001).
Wolraich et al[73] MPH-ER (Concerta®) 18-54 mg QD vs MPH-IR 5-15 mg TID vs placebo	DB, PC, PG, RCT Children between 6 and 12 years diagnosed with ADHD (any subtype) Patients who were taking MPH or had taken it in the past, had to have been on a total daily MPH dose (IR or IR/SR combination) of at least 10 mg (maximum of 60 mg).	N=282 28 days	Primary: Iowa Conners I/O and O/D rating scale (parents and teachers) Secondary: SNAP-IV scores (teachers and parents), CGI-I scores (investigators), global assessment of efficacy (parents and teachers)	Primary: Both MPH-ER and MPH-IR demonstrated a statistically significant improvement in the Iowa Conners I/O and O/D rating scale scores compared to placebo at week 1 and at the end of the study (*P*<0.001). There was no significant difference in the mean Iowa Conners scale scores between the MPH-ER and MPH-IR treatment groups at week 1 (*P*=0.838) or at the end of the study (*P*=0.539). Secondary: Teacher and parent SNAP-IV scores were significantly better for patients in the MPH-ER and MPH-IR groups than for those in the placebo group (*P*<0.001). There was not a significant difference in SNAP-IV scores between the MPH-ER and MPH-IR groups (*P* values not reported). 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).
Cox et al[74] MPH-ER (Concerta®) 36 mg	DB, PC, RCT, XO Adolescents aged 16-19	N=35 21-38 days	Primary: Impaired Driving Score (IDS),	Primary: Overall IDS values were significantly better than with placebo

Study and Drug Regiment	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
once daily, days 1-5, and 72 mg once daily, days 6-17 vs AMP-XR (Adderall XR®) 15 mg once daily, days 1-5, and 30 mg once daily, days 6-17 vs placebo (substituted for active treatment once for each subject, on one of the two assessment days, ie, days 10 or 17)	years diagnosed with ADHD and licensed to drive; subjects with tics or subtance abusers were excluded	(17 days of treatment with 4-21 days between treatments 5 and 6)	assessed using an Atari Research Driving Simulator on days 10 and 17; subjective ratings of driving performance by participants and investigators Secondary: Not reported	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). Secondary: Not reported
Pelham, Gnagy et al[75] MPH-ER (Concerta®) 18-54 mg QD vs MPH-IR 5-15 mg TID vs placebo	DB, PC, RCT, XO Children between 6 and 12 years diagnosed with ADHD (any subtype) and were taking MPH on entry to the study or must have been receiving a stable dose for at least 4 weeks before the beginning of the study	N=68 1 week	Primary: Iowa Conners I/O and O/D rating scales (teacher and parents), SKAMP scale (teacher) Secondary: Not reported	Primary: MPH-ER and MPH-IR were better than placebo in the Iowa Conners I/O and O/D rating scale scores from teachers and parents (*P*<0.05). MPH-ER scored significantly better than MPH-IR in the parent Iowa Conners I/O rating scales (*P*<0.05). In the SKAMP scales, MPH-ER and MPH-IR were similar in efficacy (*P* value not reported), but both were significantly better than placebo (*P* value not reported). Secondary: Not reported
Lopez et al[76] MPH-ER (Concerta®) 18 mg or 36 mg QD vs	DB, PC, RCT Children between 6 and 12 years who were diagnosed with ADHD, and who were previously stabilized on	N=36 28 days	Primary: SKAMP scales Secondary: Not reported	Primary: Both MPH-ER and MPH-XR statistically improved SKAMP scale scores compared to placebo (*P*<0.001). Secondary: Not reported

Study and Drug Regiment	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
MPH-XR (Ritalin LA®) 20 mg QD vs placebo	equivalent dose of 10 mg twice daily of MPH prior to the study			
Swanson et al[77] MPH-ER (Concerta®) 18-54 mg QD vs MPH-XR (Metadate CD®) 20-60 mg QD vs placebo	DB, MC, PC, RCT, XO Children between 6 to 12 years diagnosed with ADHD (inattentive type, hyperactive-impulsive type, or combined type) being treated with MPH in doses of 10-60 mg daily (5-20 mg per dose, 1-3 times a day)	N=184 7 weeks	Primary: SKAMP scales, PERMP Secondary: Not reported	Primary: MPH-ER and MPH-XR demonstrated similar efficacy, and both were better than placebo in SKAMP and PERMP scores ($P<0.016$). Secondary: Not reported
Pelham, Greenslade et al[78] MPH-IR 10 mg BID vs MPH-SR (Ritalin SR®) 20 mg QD vs DEX-SR (Dexedrine Spansule®) 10 mg QD vs pemoline* 56.25 mg QD vs	DB, PC, RCT, XO Boys between 8 and 13 years diagnosed with ADHD	N=22 8 weeks	Primary: Evaluated social behavior during activities, classroom performance, and performance on a continuous performance task Secondary: Not reported	Primary: Each of the active treatment groups were more effective than placebo on most measures of social behavior from the medication assessment ($P<0.05$). DEX-SR and pemoline* tended to produce the most consistent effects. The continuous performance task results showed that all four medications had an effect within 2 hours, and the effects lasted for 9 hours vs placebo ($P<0.025$). Secondary: Not reported

Study and Drug Regiment	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo BID				
Silva et al[79] Methylphenidate ER, osmotic-release (Concerta®) 18 mg vs methylphenidate ER, osmotic-release (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 consecutive Saturdays). Subjects continued their regular ADHD medications on Sunday through Thursday of the study weeks, with no medications allowed on Friday	MC, RCT, SB, XO Children 6-12 years of age diagnosed with ADHD and stabilized on MPH (20-40 mg/day); study conducted in a classroom setting; subjects with IQ≤80, Tourette's syndrome or tic disorder, seizure disorder, significant medical or psychiatric illness, or substance abuse disorder were excluded	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 (P values not reported), 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 (P values not reported).
Kratochvil et al[80] Atomoxetine titrated up to 2 mg/kg/day	HTH, MC, OL Boys 7-15 years old and girls 7-9 years old diagnosed with ADHD	N=228 10 weeks	Primary: ADHD-RS Secondary: CPRS-R, CGI-S,	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).

Study and Drug Regiment	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs MPH-IR up to 60 mg daily			side effects	Secondary: There were no statistically significant differences between treatment groups on all of the CPRS-R and CGI-S outcome measures (*P*<0.001). Tolerability was also similar between the two drugs with no statistical differences in discontinuations (*P*=0.18). Statistically significant increases in pulse and blood pressure were seen with both atomoxetine and MPH-IR (*P*<0.05). The authors state that these changes were incremental and unlikely to be clinically important.
Kemner et al[81] Atomoxetine 0.5 mg/kg once daily vs methylphenidate ER (Concerta®), 18 mg once daily Doses were adjusted during weeks 1 and 2 based on clinical response.	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) Secondary: Not reported	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 (ie, ≥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 (*P* value not reported). Secondary: Not reported
Starr et al[82] Atomoxetine 0.5 mg/kg once daily	OL, R African-American children ages 6-12	N=183 3 weeks	Primary: Investigator-related ADHD-RS and CGI-I,	Primary: For the ADHD-RS scores, toth treatment groups achieved significant improvements from baseline at all time points (*P*<0.001).

Study and Drug Regiment	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs methylphenidate ER, osmotic-release (Concerta®), 18 mg once daily Doses were adjusted during weeks 1 and 2 based on clinical response.	diagnosed with ADHD; subgroup of Kemner et al (above)		performed at weeks 1, 2, and 3; parental satisfaction questionnaire (PSQ) Secondary: Not reported	Improvements from baseline, defined as ADHD-RS score reductions of ≥30% or ≥50%, were significantly greater in the methylphenidate ER group starting at week 3 ($P<0.03$ for ≥30% reduction, $P<0.006$ for ≥50% reduction). Significantly more children treated with methylphenidate ER than atomoxetine achieved a CGI-I score of ≤2 after week 3 ($P<0.01$). Parent-rated PSQ scores revealed statistically significantly greater improvements with methylphenidate ER than with atomoxetine (*P* value not reported). Secondary: Not reported
Narcolepsy				
U.S. Modafinil in Narcolepsy Group[83] Modafinil 200 mg or 400 mg QD vs placebo	DB, MC, PC, PG, RCT Adults between 18 and 68 years 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 (*P* value not reported). Secondary: Mean sleep latency for MSLT significantly increased in both modafinil treatment groups compared to placebo ($P<0.001$). Modafinil groups did not differ from each other (*P* value not reported). 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 (*P* value not reported). 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 (*P* value not reported).
U.S. Modafinil in Narcolepsy Group[84]	DB, MC, PC, RCT	N=271	Primary: MWT, CGI-C	Primary: MWT improved for both modafinil groups versus placebo

Study and Drug Regiment	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Modafinil 200 mg or 400 mg QD vs placebo	Adults between 17 and 67 years diagnosed with narcolepsy who had a MSLT	9 weeks	Secondary: MSLT, ESS	(*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] Modafinil 200 mg or 400 mg QD vs placebo	MC, PC, RCT, XO Patients between 27 and 59 years 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 (*P* value not reported). Both modafinil treatment groups significantly decreased the patient assessed mean number of involuntary sleep and somnolence episodes by 24% in the 200 mg group and 26% in the 400 mg group as compared to placebo (*P*<0.013 and *P*<0.007). Secondary: ESS was significantly decreased in modafinil 200 mg (*P*<0.018) and modafinil 400 mg (*P*<0.0009) groups compared to placebo.
Billiard et al[86] Modafinil 300 mg (100 mg AM and 200 mg at noon or vice versa) vs placebo	DB, MC, PC, RCT, XO Patients between 27 and 54 years 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).

Study and Drug Regiment	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Boivin et al[87] Modafinil 300 mg (200 mg in AM and 100 mg at noon) vs placebo	DB, PC, RCT, XO Patients between 31 and 61 years 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 Secondary: Not reported	Primary: Subjective sleepiness was significantly reduced in the modafinil group compared to the placebo group ($P<0.05$) based on home questionnaires. Modafinil significantly reduced the number of gaps and % of error at the FCRTT ($P\leq0.05$), 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* values stated as "not significant," actual values are not reported). Secondary: Not reported
Thorpy et al[88] Modafinil 200 mg daily then 400 mg daily without a washout period between treatments, with a 2-day washout period between treatments, or by using a taper-down/titrate-up protocol	OL, RCT Adults between 17 and 65 years diagnosed with narcolepsy who had been receiving MPH for EDS for a month	N=40 5 weeks	Primary: ESS, tolerability Secondary: Not reported	Primary: Mean ESS scores were <12 for all groups at the end of the study: 11.3 in the no-washout group, 8.2 for in the washout group, and 10.1 in the taper-down/titrate-up group (*P* values not reported). 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 (*P* values not reported). Secondary: Not reported
Obstructive Sleep Apnea (OSA)				
Black et al[89] Modafinil 200 or 400 mg QD vs placebo	DB, MC, PC, PG, RCT Adults 18-70 years old diagnosed with obstructive sleep apnea/hypopnea syndrome and having residual excessive	N=305 12 weeks	Primary: MWT, ESS Secondary: CGI-C, Functional Outcomes of Sleep	Primary: Both modafinil treatment groups significantly improved mean sleep latency on the MWT compared to placebo ($P<0.001$). Both modafinil treatment groups 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 $P>0.15$).

Study and Drug Regiment	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	sleepiness during continuous positive airway pressure therapy			Secondary: At the end of the study, both modafinil treatment groups had significant improvements in CGI-C compared to placebo (*P*<0.001). Both modafinil treatment groups 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[90] Modafinil 200 mg QD vs placebo Medications given 30-60 minutes before the start of work shift.	DB, MC, PC, RCT Adults 18 to 60 years old diagnosed with SWSD and worked each month at least five night shifts for ≤12 hours, with ≥6 hours or worked between 10 PM and 8 AM and at least three shifts occurring consecutively	N=204 3 months	Primary: MSLT, CGI-C, Psychomotor Vigilance Test Secondary: Not reported	Primary: The modafinil treatment group produced a significant increase in overall mean MSLT from 2.1 minutes at baseline to 3.8 minutes at endpoint compared to the placebo change of 2.04 to 2.37 minutes (*P*=0.002). The modafinil treatment group significantly improved the CGI-C test scores with 74% of the patients rated as at least minimally improved compared with 36% in the placebo group (*P*<0.001). The modafinil treatment group produced a significant decrease in mean number of lapses of attention during the Psychomotor Vigilance Test from baseline versus placebo (*P*=0.005). Secondary: Not reported

*Agent no longer available in the US
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, CAARS=Conner's adult ADHD rating scale, CADS-T=Conners ADHD/DSM IV scale-teacher version, CADS-P=Conners ADHD/DSM IV scale-parent version, 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, CGIS=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, 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, HR=heart rate, HSPP=Harter Self-Perception Profile, I/O=inattention/overactivity, 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

Additional Evidence

Dose Simplification:
Once-daily formulations increase patient compliance, and eliminate the need for medication dosing in schools. 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 compare immediate-release stimulants with extended-release, once-daily products. A study by Lage et al drew upon a pharmacy claims database to analyze medication compliance among patients who took methylphenidate immediate-release (IR) three times daily vs those taking methylphenidate extended-release (XR, Concerta®) once daily.[91] They found better compliance with the XR patients, less likelihood of switching medications, and a lower probability of discontinuing the medication (all results were statistically significant). XR usage was also associated with significantly fewer emergency-room visits and fewer general-practitioner visits.

Stable Therapy:
Cerebral stimulants should not be discontinued abruptly as this may potentiate ADHD symptoms. However, atomoxetine may be discontinued without tapering.[5]

Impact on Physician Visits:
An evidence-based medicine literature search 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 Cerebral Stimulants/Agents Used for ADD/ADHD

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Amphetamines—Cerebral Stimulants/Agents used for ADHD				
amphetamine salts, mixed (amphetamine-dextroamphetamine)	sustained-release capsule, tablet	Adderall®*, Adderall XR®	$$$$	$$
dextroamphetamine	sustained-release capsule, tablet	Dexedrine®*, Dextrostat®*	$-$$$	$$
lisdexamfetamine	tablet	Vyvanse®	$$$$	N/A
methamphetamine	tablet	Desoxyn®	$$$$$	N/A
Miscellaneous Anorexigenic Agents and Respiratory and Cerebral				

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Stimulants—Cerebral Stimulants/Agents used for ADHD				
dexmethylphenidate	extended-release capsule, tablet	Focalin®*, Focalin XR®	$$-$$$$	$$
methylphenidate	chewable tablet, extended-release capsule, extended-release tablet (osmotic release), solution, sustained-release tablet, tablet, transdermal patch	Concerta®, Daytrana®, Metadate CD®, Metadate ER®*, Methylin®*, Ritalin®*, Ritalin LA®, Ritalin-SR®*	$$-$$$$	$-$$
modafinil	tablet	Provigil®	$$$$$	N/A
Miscellaneous Central Nervous System Agents—Cerebral Stimulants/Agents used for ADHD				
atomoxetine	capsule	Strattera®	$$$$	N/A

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

X. Conclusions

The two major types of cerebral stimulants, amphetamines and methylphenidate-based products, have clearly demonstrated efficacy for improving ADHD symptom scores versus placebo. When it comes to a comparison of the two, a few clinical trials demonstrate a slight statistically significant advantage with amphetamines versus methylphenidate; however, these studies were small and of short duration.[54,56,57] The overall body of evidence clearly indicates no significant differences in efficacy. Studies cited in the AAP Clinical Practice Guideline did not detect an efficacy difference between amphetamines and methylphenidate when dosed equipotently[2] and the current AACAP Practice Parameters, published in 2007, state that the physician may choose either methylphenidate or amphetamines, as data suggests equal efficacy between the two stimulant types.[3]

There are several generic formulations of the short- and intermediate-acting cerebral stimulants. All brand short- and intermediate-acting cerebral stimulants within this class review are comparable to each other and to the generics and over-the-counter (OTC) products in the class and offer no significant clinical advantage over other alternatives in general use.

Even though there are pharmacokinetic differences between the extended-release long-acting cerebral stimulants, no differences in efficacy have been reported.[64-66] For children with ADHD, the advantage of the once-daily dosage forms over the immediate-release forms is that medication need not be taken during school hours. Since both methylphenidate and mixed amphetamine salts are class II controlled substances, and drug diversion as well as school policies and procedures remain paramount issues, this is an important consideration. Administration of medications during school hours, especially C-II medications, can be difficult since the medication must be administered by a licensed school nurse. In addition, because of the HIPAA mandates concerning patient confidentiality, ADHD treatment requires added security. Since the therapeutic effects of cerebral stimulants are dose-dependent, and control of hyperactivity and inattention during school hours is necessary for the child's continued academic and social success, it is important to maintain medication efficacy throughout the school day.[88] Also, long-acting formulations taken with breakfast have a pharmacokinetic advantage over short- and intermediate-acting formulations; depending upon circumstances and the age of the patient, this may or may not translate into a therapeutic advantage.[65,75,77,91,92]

There are no long-acting cerebral stimulants that are available generically. The clinical data reports that the immediate-release and extended-release products possess comparable safety and efficacy. Methylphenidate has been the most extensively studied and prescribed cerebral stimulant for ADHD, and data suggests that it may possess a lower degree of abuse potential,[2,38] but addiction to methylphenidate can and does occur. However, little is known about the actual prevalence of methylphenidate abuse. In a recent review of evidence on the abuse potential of methylphenidate, the author states that there is little evidence that methylphenidate possesses

significant abuse potential in those taking it for clinical purposes.[93] The majority of stimulant abuse tends to occur when used for nonmedical purposes, and with the immediate-release products. Therefore, the long-acting cerebral stimulants reviewed in this class may offer significant clinical advantage in general use over the other brands, generics, and over-the-counter products in the same class, but are comparable to each other.

The use of the methylphenidate transdermal patch has been associated with dermatological adverse effects including contact sensitization. Notably, patients who develop contact sensitization to transdermal methylphenidate may not be able to take methylphenidate in any form.[27] Although methylphenidate transdermal patch has been shown to be efficatious against placebo it has not been evaluated against other long acting methylphenidate formulations and is not specifically addressed in treatment guidelines. For these reasons this agent should be reserved for patients who are unable to take medications by mouth and should be managed through the medical justification portion of the prior authorization process.

Although guidelines state that proven first-line treatments for ADHD include psychostimulants and atomoxetine, there is a lack of evidence to support the long-term safety of atomoxetine and it is typically recommended as a first-line agent in patients with an active substance abuse problem, comorbid anxiety, tics, in those who experience severe side effects while taking stimulants, in other situations where stimulants may not be an option or if a nonstimulant medication is preferred by parents and/or physicians.[3,9,15] Although atomoxetine has demonstrated efficacy in reduction of ADHD symptoms compared to placebo, there is limited comparative data versus methylphenidate or amphetamines at this time.[51-53,68]

According to the American Academy of Sleep Medicine (AASM) Practice Parameters for the Treatment of Narcolepsy, amphetamines, methylphenidate, and modafinil are all recommended treatment options for narcolepsy.[15] The European Federation of Neurological Sciences distinguish modafinil as the first line pharmacological treatment of excessive daytime sleepiness and irresistible episodes of sleep.[16] It is important to note that epidemiological studies indicate a prevalence of 0.02%-0.16% for narcolepsy, indicating that this agent would not be used for general use.[13] Currently, there are no head-to-head trials comparing modafinil to conventional therapies. Currently Alabama Medicaid recipients are able to obtain modafinil through the electronic prior authorization process as well as the medical justification potion of the manual prior authorization process when a diagnosis of narcolepsy is noted.

Therefore, with the exception of the long-acting cerebral stimulants that are FDA approved for the treatment of ADHD, all brand products within the class reviewed are comparable to each other and to the generics and over-the-counter products in this class and offer no significant clinical advantage over other alternatives in general use. Since transdermal methylphenidate has not been evaluated against other long acting methylphenidate formulations, is not specifically addressed in treatment guidelines, and is associated with an increased incidence of treatment emergent-adverse events and contact sensitization that has not been reported with oral stimulants, it is advisable that these agents be managed through the existing medical justification portion of the prior-authorization process.

XI. Recommendations

No brand short- or intermediate-acting cerebral stimulant is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

Alabama Medicaid should work with manufacturers on cost proposals so that at least one oral brand long-acting cerebral stimulant that is FDA approved for the treatment of ADHD is selected for preferred status.

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

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

References

1. Visser SN, Lesesne CA, Perou R. National estimates and factors associated with medication treatment for childhood attention deficit/hyperactivity disorder. Pediatrics. 2007;119(1):s99-106.
2. Subcommittee on Attention-Deficit Hyperactivity Disorder, Committee on Quality Improvement. Clinical practice guideline: treatment of school aged children with attention deficit hyperactivity disorder [guideline on the internet]. Pediatrics. 2001 [cited 2007 Sep 10];108:1033-44. Available from: http://aappolicy.aappublications.org/cgi/content/full/pediatrics;108/4/1033.
3. American Academy of Child and Adolescent Psychiatry. Practice parameters for the assessment and treatment of children, adolescents, and adults with attention-deficit/hyperactivity disorder [guideline on the internet]. J Am Acad Child Adolesc Psychiatry. 2007 Jul [cited 2007 Sep 10];46(7):894-921. Available from: http://www.aacap.org/galleries/PracticeParameters/JAACAP_ADHD_2007.pdf.
4. Gillberg C, reviewer. ADHD: a stimulating account. Lancet. 2001 Nov 17;358(9294):1739. Review of: Solanto MV, Arnsten AFT, Castellanos FX, editors. Stimulant drugs and ADHD: basic and clinical neuroscience.
5. Drug Facts and Comparisons 4.0 [database on the internet]. St. Louis: Wolters Kluwer Health, Inc.; 2007 [cited 2007 Aug 31]. Available from: http://online.factsandcomparisons.com.
6. Central nervous system agents 28:00, Anorexigenic agents and respiratory and cerebral stimulants 28:20, Amphetamines 28:20.04. In: McEvoy GK, editor; American Hospital Formulary Service. AHFS drug information 2007 [monograph on the Internet]. Bethesda (MD): American Society of Health-System Pharmacists; 2007 [cited 2007 Sep 10]. Available from: http://online.statref.com.
7. Central nervous system agents 28:00, Anorexigenic agents and respiratory and cerebral stimulants 28:20, Miscellaneous anorexigenic agents and respiratory and cerebral stimulants 28:20.92. In: McEvoy GK, editor; American Hospital Formulary Service. AHFS drug information 2007 [monograph on the Internet]. Bethesda (MD): American Society of Health-System Pharmacists; 2007 [cited 2007 Sep 10]. Available from: http://online.statref.com.
8. Central nervous system agents 28:00, Central nervous system agents, miscellaneous 28:92. In: McEvoy GK, editor; American Hospital Formulary Service. AHFS drug information 2007 [guideline on the Internet]. Bethesda (MD): American Society of Health-System Pharmacists; 2007 [cited 2007 Sep 10]. Available from: http://online.statref.com.
9. Institute for Clinical Systems Improvement. Health care guideline: diagnosis and management of attention deficit hyperactivity disorder in primary care for school-age children and adolescents [guideline on the Internet]. 7th ed. Bloomington (MN): Institute for Clinical Systems Improvement; 2007 Mar [cited 2007 Sep 12]. Available from: http://www.icsi.org/adhd/adhd_2300.html.
10. National Institute for Health and Clinical Excellence. Methylphenidate, atomoxetine and dexamfetamine for attention deficit hyperactivity disorder (ADHD) in children and adolescents [guideline on the Internet]. London (UK): National Institute for Health and Clinical Excellence, 2006 Mar [cited 2007 Sep 13]. Available from: http://guidance.nice.org.uk/TA98/guidance/pdf/English.
11. Kessler RC, Adler L, Barkley R, Biederman J, Conners CK, et al. The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication. Am J Psychiatry. 2006;163(4):716-23.
12. Nutt DJ, Fone K, Asherson P, Bramble D, Hill P, Matthews K, et al; British Association for Psychopharmacology. Evidence-based guidelines for management of attention-deficit/hyperactivity disorder in adolescents in transition to adult services and in adults: recommendations from the British Association for Psychopharmacology [guideline on the internet]. J Psychopharmacol. 2006 Jan [cited 2007 Sep 14];21(1):10-41. Available from: http://www.bap.org.uk/consensus/adult_ADHD.html.
13. American Psychiatric Association: diagnostic and statistical manual of mental disorders, 4th ed, text revision. [monograph on the internet]. Washington: American Psychiatric Association, 2000 [cited 2007 Jul 16]. Available from: http://online.statref.com/Document/Document.aspx?DocID=1&StartDoc=1&EndDoc=1&FxID=37&offset=151&level=2&State=False&SessionId=9FD39DGSXWDOTZNU.
14. Searight HR, Burke JM, Rottneck F. Adult ADHD: Evaluation and treatment in family medicine. Am Fam Physician 2000;62:2077-86,2091-2.
15. Littner M, Johnson SF, McCall WV, Anderson WM, Davila D, Hartse SK, et al; Standards of Practice Committee. Practice parameters for the treatment of narcolepsy: an update for 2000 [guideline on the internet] Sleep. 2001 Jun 15 [cited 2007 Sep 14];24(4):451-66. Available from: http://www.aasmnet.org/Resources/PracticeParameters/PP_Narcolepsy_Update.pdf.
16. Billiard M, Bassetti C, Dauvilliers Y, Dolenc-Groselj L, Lammers GJ, et al. EFNS guidelines on management of narcolepsy. Eur J Neurol 2006;13:1035-48.
17. Morgenthaler TI, Kapen S, Lee-Chiong T, Alessi C, Boehlecke B, Brown T, et al; Standards of Practice Committee; American Academy of Sleep Medicine. Practice parameters for the medical therapy of obstructive sleep apnea

[guideline on the internet]. Sleep. 2006 Aug 1 [cited 2007 Sep 14];29(8):1031-5. Available from: http://www.aasmnet.org/Resources/PracticeParameters/PP_MedicalTherapyOSA.pdf.
18. Adderall® [package insert]. Pomona (NY): Barr Laboratories; March 2007.
19. Adderall XR® [package insert]. Wayne (PA): Shire US; March 2007.
20. Dexedrine Spansule® [package insert]. Research Triangle Park (NC): GlaxoSmithKline, March 2007.
21. Dextroamphetamine sulfate [package insert]. St. Louis (MO): Mallinckrodt; February 2007.
22. Focalin® [package insert]. East Hanover (NJ): Novartis Pharmaceuticals; April 2007.
23. Focalin XR® [package insert]. East Hanover (NJ): Novartis Pharmaceuticals; April 2007.
24. Vyvanse® [package insert]. Wayne (PA): Shire US; February 2007.
25. Desoxyn® [package insert]. Deerfield (IL): Ovation Pharmaceuticals; May 2007.
26. Concerta® [package insert]. Fort Washington (PA): McNeil Pediatrics; March 2007.
27. Daytrana® [package insert]. Wayne (PA): Shire US; March 2007.
28. Metadate CD® [package insert]. Smyrna (GA): UCB; February 2007.
29. Metadate ER® [package insert]. Smyrna (GA): UCB; February 2007.
30. Methylin® [package insert]. St. Louis (MO): Mallinckrodt; March 2007.
31. Ritalin®, Ritalin-SR® [package insert]. East Hanover (NJ): Novartis Pharmaceuticals; April 2007.
32. Ritalin LA® [package insert]. East Hanover (NJ): Novartis Pharmaceuticals; April 2007.
33. Strattera [package insert]. Indianapolis (IN): Eli Lilly & Co.; August 2007.
34. Provigil® [package insert]. West Chester (PA): Cephalon; December 2004.
35. Micromedex® Healthcare Series [database on the internet]. Greenwood Village (CO): Thomson Micromedex; c2007 [cited 2007 Jun 14]. Available from: http://www.thomsonhc.com/.
36. Office of National Drug Control Policy (US). Pushing back against meth: a progress report on the fight against methamphetamine in the United States [monograph on the Internet]. Rockville (MD): Office of National Drug Control Policy, 2006 Nov 30 [cited 2007 Sep 14], Available from: http://www.whitehousedrugpolicy.gov/publications/pdf/pushingback_against_meth.pdf.
37. Drug facts: Office of National Drug Control Policy—methamphetamine [Internet]. Rockville (MD): Office of National Drug Control Policy, 2006 Jun 6 [cited 2006 Sep 14]. Available from:: http://www.whitehousedrugpolicy.gov/drugfact/methamphetamine/index.html.
38. Huss M, Lehmkuhl U. Methylphenidate and substance abuse: a review of the pharmacology, animal, and clinical studies. J Atten Disord. 2002;6(1):S65-71.
39. Barkley RA, Fisher M, Smallish L et al. Does the treatment of attention deficit/hyperactivity disorder with stimulants contribute to drug use/abuse? A 13-year prospective study. Pediatrics. 2003;111:97-109.
40. Department of Health And Human Services (US), Substance Abuse and Mental Health Services Administration, Office of Applied Studies. Results from the 2005 National Survey on Drug Use and Health: National Findings (NSDUH Series H-30, DHHS Publication No. SMA 06-4194). Rockville (MD): Substance Abuse and Mental Health Services Administration, 2006 [cited 2007 Sep 14]. Available from: http://www.oas.samhsa.gov/NSDUH/2k5NSDUH/2k5results.htm.
41. Volkow N, Swanson JM. Variables that affect the clinical use and abuse of methylphenidate in the treatment of ADHD. Am J Psychiatry. 2003;160:1909-18.
42. FDA directs ADHD drug manufacturers to notify patients about cardiovascular adverse events and psychiatric adverse events [press release on the Internet]. Rockville (MD): Food and Drug Administration (US): 2007 Feb 21 [cited 2007 Sep 14]. Available from: http://www.fda.gov/bbs/topics/NEWS/2007/NEW01568.html.
43. Alert for healthcare professionals: Adderall and Adderall XR (amphetamine) [press release on the Internet]. Rockville (MD): Food and Drug Administration (US): 2005 Feb 9 [updated 2005 Sep 23;cited 2007 Sep 14]. Available from: http://www.fda.gov/Cder/drug/InfoSheets/HCP/adderalHCP.htm.
44. Food and Drug Administration (US), Pediatric Advisory Committee. Minutes of the Pediatric Advisory Committee, March 22, 2006 [Internet]. Rockville (MD): Food and Drug Administration (US): 2006 Mar 22 [cited 2007 Sep 14]. Available from: http://www.fda.gov/ohrms/dockets/ac/06/minutes/2006-4210m_Minutes%20PAC%20March%2022%202006.pdf.
45. FDA issues public health advisory on Strattera (atomoxetine) for attention deficit disorder. Rockville (MD): Food and Drug Administration (US): 2005 Sep 29 [cited 2007 Sep 14]. Available from: http://www.fda.gov/bbs/topics/NEWS/2005/NEW01237.html.
46. FDA talk paper: new warning for Strattera [press release on the Internet]. Rockville (MD): Food and Drug Administration (US): 2004 Dec 17 [cited 2007 Sep 14]. Available from: http://www.fda.gov/bbs/topics/ANSWERS/2004/ANS01335.html.

47. Biederman J, Lopez FA, Boellner SW, et al. A randomized, double blind, placebo controlled parallel group study of SLI381 (Adderall XR) in children with attention-deficit/hyperactivity disorder. Pediatrics. 2002;110:258-66.
48. Goodman DW, Ginsberg L, Weisler, RH, Cutler AJ, Hodgkins P. An Interim Analysis of the Quality of Life, Effectiveness, Safety, and Tolerability (QU.E.S.T.) Evaluation of Mixed Amphetamine Salts Extended Release in Adults With ADHD. CNS Spectr. 2005;10(Suppl 20):26-34.
49. Greenhill LL, Muniz R, Ball RR, Levine A, Pestreich L, et al. Efficacy and safety of dexmethylphenidate extended-release capsules in children with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 2006;45(7):817-23.
50. Spencer TJ, Adler LA, McGough JJ, Muniz R, Jiang H, et al. Efficacy and safety of dexmethylphenidate extended-release capsules in adults with attention-deficit/hyperactivity disorder. Biol Psychiatry 2007;61:1380-7.
51. Biederman J, Krishnan S, Zhang Y, et al. Efficacy and tolerability of lisdexamfetamine dimesylate (NRP-104) in children with attention-deficit/hyperactivity disorder: A phase III, randomized, multicenter, double-blind, parallel-group study. Clin Ther. 2007;29:450–63.
52. Biederman J, Boellner SW, Childress A, et al. Lisdexamfetamine dimesylate and mixed amphetamine salts extended-release in children with ADHD: A double-blind, placebo-controlled, crossover analog classroom study. Biol Psychiatry. 2007 Jul 11. (Epub ahead of print). Available from: http://dx.doi.org/10.1016/j.biopsych.2007.04.015.
53. Wilens TE. Biederman J. Lerner M. Concerta Study Group. Effects of once-daily osmotic-release methylphenidate on blood pressure and heart rate in children with attention-deficit/hyperactivity disorder: results from a one-year follow-up study. Journal of Clinical Psychopharmacology. 2004; 24(1):36-41.
54. Greenhill LL, Findling RL, Swanson JM et al. A double-blind, placebo-controlled study of modified-release methylphenidate in children with attention-deficit/hyperactivity disorder. Pediatrics. 2002;109:e39.
55. McGough JJ, Wigal SB, Abikoff H, Turnbow JM, et al. A randomized, double-blind, placebo-controlled, laboratory classroom assessment of methylphenidate transdermal system. J of Att Dis. 2006;9(3):476-85.
56. Pelham WE, Manos MJ, Ezzell CE, Tresco KE, et al. A dose-ranging study of methylphenidate transdermal system in children with ADHD. J Am Acad Adolesc. 2005;44(6):522-9.
57. Pelham WE, Burrows-MacLean L, Gnagy EM, Fabiano GA, et al. Transdermal methylphenidate, behavioral, and combined treatment for children with ADHD. Exp Clin Psychopharmacology. 2005;13:111-26.
58. Biederman J, Heiligenstein JH, Faries DE et al. Atomoxetine ADHD Study Group. Efficacy of atomoxetine versus placebo in school-age girls with attention-deficit/hyperactivity disorder. Pediatrics. 2002;110(6):e75.
59. Michelson D, Adler L, Spencer T et al. Atomoxetine in the treatment of children and adolescents with attention deficit, hyperactivity disorder: A randomized, placebo controlled, dose response study. Pediatrics. 2001;108(5):e83.
60. Spencer T, Heiligenstein JH, Biederman J et al. Results from 2 proof-of-concept, placebo-controlled studies of atomoxetine in children with attention-deficit/hyperactivity disorder. J Clin Psychiatry. 2002;63(12):1140-7.
61. Cheng JYW, Chen RYL, Ko JSN, Ng EML. Efficacy and safety of atomoxetine fir attention-deficit/hyperactivity disorder in children and adolescents-meta-analysis and meta-regression analysis. Psychopharmacology 2007;194:197-209.
62. Prasad S, Harpin V, Poole L, Zeitlin H, Jamdar S, Puvanendran K; The SUNBEAM Study Group. A multi-centre, randomised, open-label study of atomoxetine compared with standard current therapy in UK children and adolescents with attention-deficit/hyperactivity disorder (ADHD). Curr Med Res Opin. 2007 Feb;23(2):379-94.
63. Faraone SV, Bierderman J, Spencer TJ, Aleardi M. Comparing the Efficacy of Medications for ADHD Using Meta-analysis. MedGenMed. 2006;8(4):4.
64. Pliszka SR, Browne RG, Olvera RL et al. A double-blind, placebo controlled study of Adderall and methylphenidate in the treatment of attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2000; 39(5):619-26.
65. McCracken JT, Biederman J, Greenhill LL et al. Analog classroom assessment of a once-daily mixed amphetamine formulation, SLL381 (Adderall XR) in children with ADHD. J Am Acad Child Adolesc Psychology. 2003;426(6):673-83.
66. Pelham WE, Aronof HR, Midlam JL et al. A comparison of Ritalin and Adderall; efficacy and time course in children with attention hyperactivity deficit disorder. Pediatrics. 1999;103:e43.
67. Wigal S, Swanson JM, Feifel D, Sangal RB, Elia J, et al. A double-blind, placebo-controlled trial of dexmethylphenidate hydrochloride and d,l-threo-methylphenidate hydrochloride in children with attention-deficit/hyperactivity disorder. J Am Acad Adolesc Psychiatry 2004;43(11):1406-14
68. Faraone SV, Biederman J, Roe C. Comparative efficacy of Adderall and methylphenidate in attention-deficit/hyperactivity disorder: a meta-analysis. J Clin Psychopharmacol. 2002;22(5):468-73.
69. Efron D, Jarman F, Barker M. Efficacy of methylphenidate and dextroamphetamine in children with attention hyperactivity disorder: a double blind crossover trial. Pediatrics. 1997;100:662-8.

70. Gau SS, Shen HY, Soong WT, Gau CS. An open-label, randomized, active-controlled equivalent trial of osmotic release oral system methylphenidate in children with attention-deficit/hyperactivity disorder in Taiwan. J Child Adolesc Psychopharmacol. 2006 Aug;16(4):441-55.
71. Biederman J, Wigal SB, Spencer TJ, McGough JJ, Mays DA. A post hoc subgroup analysis of an 18-day randomized controlled trial comparing the tolerability and efficacy of mixed amphetamine salts extended release and atomoxetine in school-age girls with attention-deficit/hyperactivity disorder. Clin Ther 28(2):280–293.
72. Wang Y, Zheng Y, Du Y, Song DH, Shin YJ, Cho SC, et al. Atomoxetine versus methylphenidate in paediatric outpatients with attention deficit hyperactivity disorder: a randomized, double-blind comparison trial. Aust N Z J Psychiatry. 2007 Mar;41(3):222-30.Clin Ther. 2006 Feb;28(2):280-93.
73. Wolraich ML, Greenhill LL, Pelham W et al. Randomized, controlled trial of OROS methylphenidate once a day in children with attention-deficit/hyperactivity disorder. Pediatrics. 2001;108:883-92.
74. Cox DJ, Merkel RL, Moore M, Thorndike F, Muller C, Kovatchev B. Relative benefits of stimulant therapy with OROS methylphenidate versus mixed amphetamine salts extended release in improving the driving performance of adolescent drivers with attention-deficit/hyperactivity disorder. Pediatrics. 2006 Sep;118(3):e704-10.
75. Pelham WE, Gnagy EM, Burrows-Maclean L et al. Once-a-day Concerta - methylphenidate versus three times daily methylphenidate in laboratory and natural settings. Pediatrics. 2001;107:e105.
76. Lopez F, Silva R, Pestreich L et al. Comparative efficacy of two once daily methylphenidate formulations (Ritalin LA and Concerta) and placebo in children with attention deficit hyperactivity disorder across the school day. Paediatr Drugs. 2003;5(8):545-55.
77. Swanson JM, Wigal SB, Wigal T et al. A comparison of one-daily extended-release methylphenidate formulations in children with attention-deficit/hyperactivity disorder in the laboratory school (the Comacs study). Pediatrics. 2004;113:e206-16.
78. Pelham WE, Greenslade KE, Vodde-Hamilton M, et al. Relative efficacy of long-acting stimulants on children with attention deficit-hyperactivity disorder: a comparison of standard methylphenidate, sustained-release methylphenidate, sustained-release dextroamphetamine, and pemoline. Pediatrics. 1990; 86:226-37.
79. Silva R, Muniz R, Pestreich LK, Brams M, Childress A, Lopez FA. Efficacy of two long-acting methylphenidate formulations in children with attention- deficit/hyperactivity disorder in a laboratory classroom setting. J Child Adolesc Psychopharmacol. 2005 Aug;15(4):637-54.
80. Kratochvil CJ, Heiligenstein JH, Dittmann R. et al. Atomoxetine and methylphenidate treatment in children with ADHD: a prospective, randomized, open-label trial. J Am Acad Child Adolesc Psychiatry. 2002;41(7):776-84.
81. Kemner JE, Starr HL, Ciccone PE, Hooper-Wood CG, Crockett RS. Outcomes of OROS methylphenidate compared with atomoxetine in children with ADHD: a multicenter, randomized prospective study. Adv Ther. 2005 Sep-Oct;22(5):498-512.
82. Starr HL, Kemner J. Multicenter, randomized, open-label study of OROS methylphenidate versus atomoxetine: treatment outcomes in African-American children with ADHD. J Natl Med Assoc. 2005 Oct;97(10 Suppl):11S-16S.
83. Randomized trial of modafinil for the treatment of pathological somnolence in narcolepsy. US Modafinil in Narcolepsy Multicenter Study Group. Ann Neurol. 1998 Jan;43(1):88-97.
84. Randomized trial of modafinil as a treatment for the excessive daytime somnolence of narcolepsy: US Modafinil in Narcolepsy Multicenter Study Group. Neurology. 2000 Mar 14;54(5):1166-75.
85. Broughton RJ, Felming JAE, George CFP, et al. Randomized, double blind, placebo controlled crossover trial of modafinil in the treatment of excessive daytime sleepiness in narcolepsy. Neurology. 1997;49:444-51.
86. Billiard M, Besset A, Montplaisir J, et al. Modafinil: A double-blind multicenter study. Sleep. 1994;17(8):S107-112.
87. Boivin DB, Montplasir J, Petit D, et al. Effects of modafinil on symptomatology of human narcolepsy. Clin Neuropharmaco. 1993;16:46-53.
88. Thorpy MJ, Schwartz JR, Kovacevic-Ristanovic R, Hayduk R. Initiating treatment with modafinil for control of excessive daytime sleepiness in patients switching from methylphenidate: an open label safety study. Psychopharmacology. 2003;167:380-5.
89. Black JE, Hirshkowitz M. Modafinil for treatment of residual excessive sleepiness in nasal continuous positive airway pressure-treated obstructive sleep apnea/hypopnea syndrome. SLEEP 2005;28(4):464-71.
90. Czeisler CA, Walsh JK, Roth T, Hughes RJ, Wright KP, et al. Modafinil for excessive sleepiness associated with Shift-Work Sleep disorder. N Engl J Med 2005;353:476-86.
91. Lage M, Hwang P. Effect of methylphenidate formulation for attention deficit hyperactivity disorder on patterns and outcomes of treatment. J Child Adol Psychopharmacol. 2004;14(4):575-81.
92. Sallee FR, Ambrosini PJ, Lopez FA, et al. Health-related quality of life and treatment satisfaction and preference in a community assessment study of extended-release mixed amphetamine salts for children with attention-deficit/hyperactivity disorder. J Outcomes Res. 2004;8:27-49.

93. Kollins SH. Comparing the abuse potential of methylphenidate versus other stimulants: A review of available evidence and relevance to the ADHD patient. J Clin Psychiatry 2003;64 (Suppl 11):14-18.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Anxiolytics, Sedatives, and Hypnotics
Barbiturates AHFS Class 282404
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I. Overview

The first barbiturates were discovered in the early 1900s and were among the first synthetic agents developed for their anesthetic, hypnotic, and sedative properties. They were widely used for these purposes throughout the first half of the 20th century. Though their exact mechanism of action is not fully understood, the pharmacologic properties of barbiturates appear to be related to the activation of γ-aminobutyric acid (GABA) and inhibition of excitatory glutamate receptors.[1,2]

In recent decades, the barbiturates have been employed primarily as sedative-hypnotics for the short-term treatment of insomnia and for induction of daytime sedation.[1-4] Barbiturates have also served as adjuncts to anesthesia and as agents for the treatment of seizure disorders.[1-4] Despite their extensive usage in the past, the barbiturates have been associated with a potential for abuse and addiction. In addition, they have many unfavorable side effects and a narrow therapeutic range with a low therapeutic index.[1] Due to these safety issues, at the present time barbiturates have been largely replaced by newer and safer agents, most notably the benzodiazepines. Recent concerns regarding the potential risk for severe allergic reaction and complex sleep-related behaviors with all sedative-hypnotic drugs also apply to the barbiturates class and potentially have limited their use as a hypnotic.[5] Today, barbiturates are used occasionally, for anesthesia, for the treatment of seizure disorders, and for alcohol detoxification.[1-4]

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

Table 1. Barbiturates Included in this Review

Generic Name	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
amobarbital	injection	Amytal®	none
butabarbital	elixir, tablet	Butisol®*	butabarbital
methohexital	injection	Brevital®	none
pentobarbital	injection	Nembutal®	none
phenobarbital	elixir, injection, tablet	Luminal®*	phenobarbital
secobarbital	capsule	Seconal®	none

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

II. Evidence-Based Medicine and Current Treatment Guidelines

Treatment guidelines that incorporate the barbiturates are summarized in Table 2.

Table 2. Treatment Guidelines Using the Barbiturates

Clinical Guideline	Recommendations
American Academy of Sleep Medicine (AASM), Standards of Practice Committee: **Practice Parameters for the Psychological and Behavioral Treatment of Insomnia: An Update (2006)[6]**	• Insomnia as a primary disorder is known as "primary insomnia," as opposed to insomnia due to or associated with another condition such as medical or psychiatric illness, substance abuse disorder, or another sleep disorder. The latter is referred to in the guideline as "secondary insomnia." • Psychological and behavioral interventions are effective and recommended in the treatment of both chronic primary insomnia and secondary insomnia. • Stimulus control is effective in the treatment of chronic insomnia and involves training that reassociates the bed and bedroom with sleep and promotes a consistent sleep-wake schedule.

Clinical Guideline	Recommendations
	• Chronic insomnia is effectively treated with relaxation training (progressive muscle relaxation) and autogenic training to reduce tension, as well as reduce disruptive thoughts at bedtime. • Sleep restrictions, such as limiting time in bed to actual time asleep, are useful in chronic insomnia. • Cognitive behavior therapy, with or without relaxation therapy, is recommended in the treatment of chronic insomnia. This form of therapy focuses on changing patient beliefs and attitudes about insomnia. Stimulus control therapy, sleep restriction, relaxation training and sleep hygiene education may also be involved. • Paradoxical intention, where the patient attempts to stay awake, is effective in sleep initiation insomnia. • The use of visual or auditory biofeedback to reduce somatic arousal is useful in chronic insomnia. • There is insufficient evidence that sleep hygiene monotherapy is effective. • Imagery training has not been proven effective as monotherapy or in combination with other approaches. • There is limited evidence that cognitive therapy alone is effective in treating insomnia. • Insufficient evidence was available to recommend one single therapy over another, or to recommend single therapy versus a combination of psychological and behavioral interventions. • Psychological and behavioral interventions are effective and recommended in treating insomnia in older adults. • Psychological and behavioral interventions are effective in treating insomnia in chronic hypnotic users.
National Institutes of Health (NIH), State-of-the-Science Conference Statement: **Manifestations and Management of Chronic Insomnia in Adults (2005)**[7]	<u>Conference Statement</u> • "Evidence supports the efficacy of cognitive-behavioral therapy and benzodiazepine receptor agonists in the treatment of this disorder [chronic insomnia], at least in the short term. Very little evidence supports the efficacy of other treatments, despite their widespread use." <u>General Considerations</u> • The most common treatments used by individuals with chronic insomnia are prescription medications, over-the-counter antihistamines, and alcohol. • The major forms of psychological treatments are cognitive and behavioral therapies. <u>Prescription Medications with Food and Drug Administration (FDA) Approval for the Treatment of Insomnia</u> • Benzodiazepine receptor agonists include benzodiazepines (eg, flurazepam, temazepam, and triazolam) as well as nonbenzodiazepine-structured anxiolytic agents acting at benzodiazepine receptors (eg, 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 (eg, 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. • 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.

Clinical Guideline	Recommendations
	Data on other antidepressants (eg, 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 (eg, diphenhydramine) are the most commonly used over-the-counter agents for chronic insomnia; however, there is no systematic evidence for efficacy and there are significant concerns about the risks of these medications. <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.
Treatment Guidelines from the Medical Letter on Drugs and Therapeutics: **Treatment of Insomnia (2006)**[8]	• Short-term use of a short-acting nonbenzodiazepine benzodiazepine receptor agonist (NBRA) is generally effective and safe (minimal adverse events and drug interactions), but it is not clear that NBRAs are more effective or safer than benzodiazepines. • Short-acting benzodiazepines and NBRAs may not prevent early morning awakening; when this occurs, a drug with an intermediate duration of action may be more helpful. • Nonprescription first generation antihistamines such as diphenhydramine are not recommended for treatment of insomnia; tolerance develops quickly and they can cause next-day sedation that impairs driving skills. • Cognitive behavioral therapy is safer and in some patients may be more effective than drugs for the treatment of chronic insomnia. • Barbiturates and chloral hydrate are not recommended due to their many side effects and the possibility of physical dependence and abuse.
American Society of Addiction Medicine (ASAM), Committee on Practice Guidelines: **Pharmacological Management of Alcohol Withdrawal (1997)**[9]	• 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 oversedation. • 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 (eg, 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

Clinical Guideline	Recommendations
	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 illness(es), 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 (eg, 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 and the elderly are the same as for adults. • Risk versus benefit should be considered when administering benzodiazepines and barbiturates during pregnancy as they are both associated with adverse effects on the fetus.
The Status Epilepticus Working Party: **The Treatment of Convulsive Status Epilepticus in Children (2000)**[10]	• Give high flow oxygen, measure blood glucose and confirm epileptic seizure. <u>Immediate Intravenous (IV) Access</u> • If intravenous (IV) access is available give lorazepam 0.1 mg/kg IV. • Repeat lorazepam once if seizing at 10 minutes. • If seizing continues after an additional 10 minutes, administer phenytoin 18 mg/kg IV or phenobarbitone* (if already on phenytoin) 20 mg/kg IV and paraldehyde 0.4 mL/kg rectally (PR) mixed with an equal volume of olive oil. • Rapid sequence induction of anesthesia using thiopentone** 4 mg/kg IV is recommend if seizing continues for an additional 20 minutes. <u>No immediate IV Access</u> • Give diazepam 0.5 mg/kg PR. • Add lorazepam 0.1 mg/kg IV if still seizing at 10 minutes or paraldehyde 0.4 mL/kg PR if no IV access. • If seizure activity continues for another 10 minutes, give phenytoin 18 mg/kg IV or phenobarbitone* 20 mg/kg IV (or intraosseous if no IV access) in addition to paraldehyde 0.4 mL/kg mixed with same volume of olive oil, PR if not already given and contact anesthetist or intensive care medic. • Rapid sequence induction of anesthesia using thiopentone** 4 mg/kg IV is recommend if seizing continues for an additional 20 minutes after the initiation of paraldehyde.

Clinical Guideline	Recommendations
Journal of Child Neurology: **Treatment of Pediatric Epilepsy: Expert Opinion (2005)**[11]	• 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.
European Federation of Neurological Societies (EFNS): **Guideline on the Management of Status Epilepticus (2006)**[12]	<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> • Anaesthetic 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.

*Synonym for phenobarbital
**Synonym for thiopental

III. Indications

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[4,13-16]

Indication	Amo-barbital	Buta-barbital	Metho-hexital	Pento-barbital	Pheno-barbital	Seco-barbital
Anesthesia						
Anesthesia, induction			✔			
Anesthesia for short surgical procedures with minimal painful stimuli			✔			
For use along with other parenteral agents to supplement subpotent inhalational anesthetic agents for longer surgical procedures			✔			
Induction of a hypnotic state			✔			
Preanesthetic			✔	✔		✔
Anticonvulsant						
Acute convulsive episodes associated with status epilepticus, cholera, eclampsia, meningitis, tetanus, and toxic reactions to strychnine or local anesthetics				✔	✔ *	
Treatment of generalized and partial seizures					✔ †	
Treatment of partial and generalized tonic-clonic and cortical focal seizures					✔ *	
Sedative-Hypnotic						
Insomnia, short-term treatment (hypnotic)	✔	✔		✔	✔ *	✔
Sedation	✔	✔		✔	✔	✔

*Injection formulation only
†Tablet and elixir formulation only

IV. Pharmacokinetics

The pharmacokinetic parameters for the barbiturates are summarized in Table 4.

Table 4. Pharmacokinetic Parameters of the Barbiturates[3]

Drug	Duration of action	Bioavaila-bility (%)	Protein binding (%)	Metabolism	Active Metabolites	Elimination (%)	Half-Life (hours)
Amobarbital	Inter-mediate	Not reported	Not reported	Hepatic	Yes; 3-hydroxy-amobarbital and N-hydroxy-amobarbital	Fecal (4-5) Renal (79-92)	8-42
Butabarbital	Inter-mediate	Not reported	Not reported	Hepatic	Not reported	Renal (% not reported)	34-100
Methohexital	Short	17	Not reported	Hepatic	Not reported	Renal (<1)	3.9
Pentobarbital	Short	95	5	Hepatic	Not reported	Renal (% not reported)	15-48
Phenobarbital	Long	80-100	20-60	Hepatic	None	Renal (21)	36-117

Drug	Duration of action	Bioavaila-bility (%)	Protein binding (%)	Metabolism	Active Metabolites	Elimination (%)	Half-Life (hours)
Secobarbital	Short	90	52-57	Hepatic	Yes; methyl carboxpropyl, hydroxy methylbutyl, and dihydroxypropyl methylbutyl derivatives	Renal (% not reported)	19-34

V. Drug Interactions

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

Table 5. Significant Drug-Drug Interactions with the Barbiturates[4]

Drug(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 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	Ethanol	Acute ethanol ingestion inhibits hepatic microsomal enzymes, decreasing hepatic drug metabolism, thus decreasing clearance. Chronic ethanol ingestion may increase clearance because of hepatic enzyme induction. Impaired hand-eye coordination, additive central nervous system effects, and death have been noted upon acute ingestion.
Phenobarbital	1	Voriconazole	Certain barbiturates (long-acting) may increase the metabolism (CYP3A4) of voriconazole. Voriconazole plasma concentrations may be reduced, decreasing the therapeutic effect.
Barbiturates	2	β-Blockers (metoprolol, propranolol)	Barbiturates enhance enzyme induction and hepatic first-pass extraction that may reduce oral bioavailability of certain β-blockers. Pharmacokinetic effects of certain β-blockers may be reduced by concomitant treatment with barbiturates.
Barbiturates	2	Corticosteroids	Decreased pharmacologic effects of the corticosteroid may be observed, 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 doxycycline's half-life and serum levels, possibly resulting in a decreased therapeutic effect.
Barbiturates	2	Estrogens	Induction of hepatic microsomal enzymes by barbiturates increases elimination of estrogenic substances, decreasing plasma concentration. Oral contraceptive induced water retention may exacerbate seizures. Contraceptive failure has been reported.
Barbiturates	2	Felodipine	Mechanism is unknown; however, the metabolism of felodipine may be increased due to induction of mixed function oxidases by barbiturates, causing an increase in first-pass metabolism and decreased bioavailability. The pharmacologic effects of felodipine may be decreased.

Drug(s)	Significance Level	Interaction	Mechanism
Barbiturates	2	Griseofulvin	Serum levels of griseofulvin are decreased after pretreatment with phenobarbital. Decreased griseofulvin absorption and increased hepatic metabolism by phenobarbital have been suggested as potential mechanisms.
Barbiturates	2	Methadone	The actions of methadone may be reduced. Patients receiving chronic methadone treatment may experience opiate withdrawal symptoms. Mechanism is unknown but may involve increased hepatic metabolism of methadone by barbiturates.
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	Nifedipine	Enhanced metabolic clearance caused by enzyme induction leads to decreased serum nifedipine concentrations, possibly reducing efficacy.
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	Theophyllines	Decreased theophylline levels may possibly result in reduced therapeutic effects. Barbiturates may induce cytochrome P450, stimulating theophylline metabolism and increasing clearance.
Methohexital	2	Narcotic analgesics	Drug actions may be additive.
Phenobarbital	2	Clozapine	Clozapine plasma concentrations may be reduced through induction of hepatic metabolism of clozapine, decreasing the pharmacologic effects.
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

Barbiturates may be habit-forming. Dependence is most commonly seen with short-acting agents after chronic use (>90 days). This class should be avoided in patients with a history of substance abuse, particularly alcohol abuse, due to synergistic effects and the increased potential of overdose. Patients who abruptly discontinue barbiturates after prolonged use may experience withdrawal symptoms that commonly include: anxiety, muscle twitches, weakness, tremors, dizziness, nausea, vomiting, insomnia and orthostatic hypotension. Major withdrawal symptoms including seizure or coma may occur within 16 hours of discontinuation and can last up to 5 days. Avoidance of withdrawal symptoms is best achieved by a slow and gradual taper, individualized to the patient with consideration of duration of therapy, concomitant illness, and total daily dose. Barbiturates have a narrow therapeutic index and the risk of overdose is much greater than with newer sedative-hypnotics. The risk is also substantially increased in the presence of any other central nervous system depressant, especially alcohol. The lethal dose of barbiturates can vary; however, single doses of 2-10 grams are often fatal. Treatment of an overdose is primarily supportive and hemodialysis may be required for severely intoxicated patients. Emesis may be induced in conscious patients, or administration of activated charcoal may accelerate the elimination of barbiturates.[1-4]

In March of 2007 the FDA issued a press release regarding its request that all drug manufacturers of medications approved for the treatment of sleep disorders revise product labeling to include warnings and potential risks of adverse events. Various products containing butalbital, secobarbital, and pentobarbital were among the drugs targeted in the alert. These adverse events include severe allergic reaction and angioedema, as well as complex

sleep-related behaviors including sleep-driving, making phone calls and eating and preparing food while asleep. The FDA has also requested that consumers be informed through the development of a Patient Medication Guide.[5]

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

Table 6. Adverse Drug Events (%) Reported with Barbiturates[17-22]

Adverse Event(s)	Amo-barbital	Buta-barbital	Metho-hexital	Pento-barbital	Pheno-barbital	Seco-barbital
Cardiovascular						
Bradycardia	✔	-	-	✔	✔	-
Hypotension	✔	<1	✔	✔	✔	✔
Peripheral vascular collapse	-	-	✔	-	-	-
Syncope	✔	-	-	✔	✔	-
Central Nervous System						
Abnormal thinking	✔	-	-	-	-	-
Agitation	✔	-	-	✔	✔	-
Anxiety	✔	-	-	✔	✔	-
Ataxia	✔	-	-	✔	✔	-
Confusion	✔	1-10	-	✔	✔	✔
Central nervous system depression	✔	-	-	✔	✔	✔
Central nervous system excitation	-	-	-	✔	✔	-
Dizziness	✔	>10	-	✔	✔	✔
Drowsiness	-	>10	-	✔	✔	✔
Faint feeling	-	1-10	-	-	-	✔
Fever	✔	-	-	-	-	✔
Hallucinations	✔	<1	-	✔	✔	✔
Hangover effect	-	>10	-	✔	✔	✔
Headache	✔	1-10	✔	✔	✔	✔
Impaired judgment	-	-	-	✔	✔	-
Insomnia	✔	1-10	-	✔	✔	✔
Lethargy	-	-	-	✔	✔	-
Lightheadedness	-	>10	-	-	-	✔
Mental depression	-	1-10	-	-	-	✔
Nervousness	✔	1-10	-	✔	✔	✔
Nightmares	✔	1-10	-	✔	✔	✔
Psychiatric disturbances	✔	-	-	-	-	-
Seizure	-	-	✔	-	-	-
Somnolence	✔	-	-	✔	✔	-
Unusual excitement	-	1-10	-	-	-	✔
Dermatological						
Angioedema	-	<10	-	-	-	✔
Exfoliative dermatitis	-	<1	-	✔	✔	✔
Injection site reaction	✔	-	-	-	-	-
Pain at injection site	-	-	✔	✔	✔	✔
Rash	-	<1	-	✔	✔	✔
Stevens-Johnson syndrome	-	<1	-	✔	✔	✔
Urticaria	-	-	-	-	-	✔
Endocrine and Metabolic						
Liver damage	✔	-	-	-	-	-
Transaminase elevation	-	-	✔	-	-	-
Gastrointestinal						
Abdominal pain	-	-	✔	-	-	-
Constipation	✔	1-10	-	✔	✔	✔
Cramping	-	-	✔	-	-	-

Adverse Event(s)	Amo-barbital	Buta-barbital	Metho-hexital	Pento-barbital	Pheno-barbital	Seco-barbital
Diarrhea	-	-	✔	-	-	-
Nausea	✔	1-10	✔	✔	✔	✔
Rectal bleeding	-	-	✔	-	-	-
Vomiting	✔	1-10	✔	✔	✔	✔
Genitourinary						
Oliguria	-	-	-	✔	✔	-
Hematologic						
Agranulocytosis	-	<1	-	✔	✔	✔
Hemolytic anemia	-	-	✔	-	-	-
Megaloblastic anemia	✔	<1	-	✔	✔	✔
Thrombocytopenia	-	<1	-	✔	✔	✔
Thrombophlebitis	-	<1	✔	✔	✔	✔
Musculoskeletal						
Hyperkinesia	✔	-	-	✔	✔	-
Involuntary muscle movement	-	-	✔	-	-	-
Rigidity	-	-	✔	-	-	-
Tremor	-	-	✔	-	-	-
Respiratory						
Apnea	✔	-	✔	✔	✔	✔
Atelectasis (postoperative)	✔	-	-	-	-	-
Cough	-	-	✔	-	-	-
Hypoventilation	✔	-	-	✔	✔	-
Laryngospasm	-	-	✔	✔	✔	✔
Respiratory depression	-	<1	✔	✔	✔	✔
Other						
Anaphylaxis	-	<1	-	-	-	✔
Complex sleep-related behavior	-	<1	-	-	-	✔
Dependence	-	<1	-	-	-	-
Gangrene	-	-	-	✔	✔	-
Hypersensitivity reaction	✔	-	-	-	-	-

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

FDA-approved product information for methohexital contains the following boxed warning.[15]

Table 7. Black Box Warning for Methohexital

WARNING
Methohexital should be used only in hospital or ambulatory care settings that provide for continuous monitoring of respiratory (eg, pulse oximetry) and cardiac function. 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 assured. For deeply sedated patients, a designated individual other than the practitioner performing the procedure should be present to continuously monitor the patient.

VII. Dosing and Administration

The usual dosing regimens for the barbiturates are summarized in Table 8.

Table 8. Usual Dosing for the Barbiturates[17-22]

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
Amobarbital	Insomnia, Short-Term Therapy: 65-200 mg intramuscular (IM)/intravenous (IV) at bedtime;	Insomnia, Short-Term Therapy: 2-3 mg/kg IM/IV; maximum: 500 mg	Vial: 500 mg

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
	maximum: 500 mg Sedation: 30-50 mg IM/IV two to three times daily	Sedation (6-12 years): 30-50 mg IM/IV two to three times daily	
Butabarbital	Insomnia, Short-Term Therapy: 50-100 mg by mouth (PO) at bedtime Preoperative Sedation: 50-100 mg PO 60-90 minutes before surgery Sedation: 15-30 mg PO three to four times daily	Preoperative Sedation: 2-6 mg/kg PO 60-90 minutes before surgery; maximum: 100 mg	Elixir: 30 mg/5 mL Tablet: 30 mg 50 mg
Methohexital	Anesthesia: Induction: 50-120 mg; 20-40 mg every 4-7 minutes	Anesthesia (≥1 month old): Induction: 6.6-10 mg/kg IM	Vial: 500 mg
Pentobarbital	Insomnia, Short-Term Therapy: 150-200 mg IM at bedtime or 100 mg IV; may repeat every 1-3 minutes; maximum: 200-500 mg Preoperative Sedation: 150-200 mg IM Status Epilepticus: Loading: 2-15 mg/kg slowly over 1-2 hours; maintenance: 0.5-3 mg/kg/hour	Insomnia, Short-Term Therapy: 2-6 mg/kg IM; maximum: 100 mg/dose Preoperative Sedation (≥ 6months): 2-6 mg/kg IM; maximum: 100 mg/dose or 1-3 mg/kg IV; maximum: 100 mg Sedation (5-12 years): 2 mg/kg IV 5-10 minutes prior to procedure, may repeat one time Sedation (>12 years): 100 mg prior to procedure Status Epilepticus: 5-15 mg/kg slowly over 1-2 hours; maintenance: 0.5-5 mg /kg/hour	Vial: 50 mg/mL
Phenobarbital	Insomnia, Short-Term Therapy: 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: 300-800 mg/day IV followed by 120-240 mg/dose at 20 minute intervals until seizures controlled or a total of 1-2 g; maintenance: 1-3 mg/kg/day IV/PO in divided doses or 50-100 mg two to three times daily	Insomnia, Short-Term Therapy (Children): 3-5 mg/kg at bedtime IM/IV/ subcutaneously (SC) Preoperative Sedation (Children): 1-3 mg/kg IM/IV/PO 60-90 minutes prior to procedure Sedation (Children): 2 mg/kg three times daily Status Epilepticus (Infants and Children): Loading: 10-20 mg/kg IV in a single or divided dose, may administer additional 5 mg/kg/dose every 15-30 minutes until seizure controlled or maximum: 40 mg/kg Seizure (Infants): 5-8 mg/kg/day IV/PO in 1-2 divided doses Seizure (1-5 Years): 6-8 mg/kg/day IV/PO in 1-2 divided doses	Disposable syringe/vial: 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

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
		Seizure (5-12 Years): 4-6 mg/kg/day IV/PO in 1-2 divided doses Seizure (>12 Years): 1-3 mg/kg/day IV/PO in divided doses or 50-100 mg two to three times daily	
Secobarbital	Insomnia, Short-Term Therapy: 100-200 mg at bedtime	Preoperative Sedation (Children): 2-6 mg/kg 1-2 hours prior to procedure; maximum: 100 mg/dose Sedation (Children): 6 mg/kg/day divided every eight hours	Capsule: 100 mg

VIII. Effectiveness

Though the barbiturates as a class have been used for over a century, limited direct comparison trials are available evaluating them for the treatment of their FDA-approved indications. Table 9 below summarizes clinical studies evaluating the safety and efficacy of the barbiturates.

Table 9. Comparative Clinical Trials Using the Barbiturates

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Alcohol Detoxification				
Mariani et al[23] 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 and 60 mg PRN for breakthrough withdrawal symptoms vs gabapentin 1,200 mg initially, then 600 mg every 6 hours for a total of 2,400 mg on day 1 then 600 mg TID for 1 day, 600 mg BID for 1 day then 600 mg QD for 1 day and phenobarbital 60 mg PRN for breakthrough withdrawal symptoms	OL, RCT Patients between the ages of 18 and 60 years, admitted for inpatient alcohol detoxification	N=27 4 days	Primary: Treatment failure; severity of withdrawal symptoms as determined by the Clinical Institute Withdrawal Assessment for Alcohol (CIWA), the Profile of Mood States Scale, an Alcohol Craving Scale, an irritability subscale of the Buss-Durkee Hostility Index, the Hamilton Anxiety Scale, the Rosenthal Dysphoria Scale, and the Sleep Problems Scale; hours of sleep per night Secondary: Not reported	Primary: There was no significant difference in the number of patients completing treatment among the phenobarbital treatment group compared to the gabapentin group (62% vs 71%; $P<0.70$). Rescue medication was required in 38% of the phenobarbital group and this proportion did not differ significantly from the gabapentin group (57%; $P<0.45$). The results of each withdrawal-symptom rating scale and the number of hours of sleep per night did not differ significantly between treatment groups (*P* values not reported). No withdrawal seizures or symptoms of alcohol withdrawal delirium were demonstrated in either treatment group. Secondary: Not reported
Insomnia				
Mello de Paula et al[24] Pentobarbital 100 mg vs	DB, R Adult patients with insomnia and at least 3 of the following	N=60 16 nights	Primary: Efficacy (sleep onset, duration, frequency of awakenings, feeling of restfulness, alcohol,	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 ($P<0.001$).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
zopiclone* 7.5 mg vs placebo	occurring regularly for at least 1 month: sleep onset exceeding 30 minutes, duration of 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 nonrestful sleep		coffee and cigarette consumption, patient judgment of therapeutic effect), side effects Secondary: Not reported	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. Fewer side effects were experienced in the zopiclone group ($P<0.05$). Secondary: Not reported
Okawa et al[25] 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 Secondary: Not reported	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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				mouth. More patients on triazolam reported side effects. Nineteen patients reported drowsiness, dizziness, nausea and lightheadedness. Secondary: Not reported
Seizures				
Painter et al[26] Phenobarbital 25 mcg/mL vs phenytoin 3 mcg/mL The alternate drug was added if initial treatment failed.	R, SB Neonates with seizures	N=59 5 years	Primary: Complete seizure control determined by electroencephalography Secondary: Not reported	Primary: Phenobarbital controlled seizures completely in 43% of patients, while phenytoin controlled seizures in 45% of patients (*P*=1.00). Secondary: Not reported
Smith et al[27] Phenobarbital vs carbamazepine	MA, 4 RCT Children or adults with partial-onset seizures or generalized-onset tonic-clonic seizures	N=684 Duration not reported	Primary: Time to withdrawal, time to 12-month remission, time to first seizure Secondary: Not reported	Primary: Time to withdrawal was significantly improved with carbamazepine over phenobarbital (HR: 1.63; 95% CI: 1.23 to 2.15). There was no significant difference between treatment groups for the time to 12-month remission and time to first seizure (HR: 0.87; 95% CI: 0.65 to 1.17 and HR: 0.85; 95% CI: 0.68 to 1.05 respectively). Further analysis of each type of seizure indicated that phenobarbital provided statistical benefit over carbamazepine for time to first partial-onset seizure, whereas carbamazepine demonstrated benefit over phenobarbital in patients for time to first generalized-onset tonic-clonic seizures. Secondary: Not reported
Treiman et al[28] Phenobarbital 15 mg/kg vs	DB, MC, R Adults with overt or subtle generalized convulsive status	N=518 5 years	Primary: Success (defined as cessation of all motor and electrical seizure activity within 20	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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
diazepam 0.15 mg/kg followed by phenytoin 18 mg/kg vs lorazepam 0.1 mg/kg vs phenytoin 18 mg/kg	epilepticus		minutes of start of drug infusion and no recurrence of seizure activity within the next 40 minutes), side effects, outcomes 30 days posttreatment Secondary: Not reported	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 (*P* values not reported). There were no significant differences among any of the treatment groups with respect to adverse effects or 30-day posttreatment outcomes. Secondary: Not reported

*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:
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Stable Therapy:
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Impact on Physician Visits:
An evidence-based medicine literature search 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 Barbiturates

Generic Name	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
amobarbital	injection	Amytal®	$$$$-$$$$$	N/A
butabarbital	elixir, tablet	Butisol®*	$$$$	N/A
methohexital	injection	Brevital®	$$	N/A
pentobarbital	injection	Nembutal®	$$$$$	N/A
phenobarbital	elixir, injection, tablet	Luminal®*	$$$$$	$
secobarbital	capsule	Seconal®	$	N/A

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

X. Conclusions

Though barbiturates were widely used during the early 20th century, safety and abuse issues coupled with the availability of newer and safer agents have limited their use in the outpatient setting in recent years. Currently, no clinical guideline recommends a barbiturate as a first-line therapy option for any condition in an outpatient setting. Barbiturate use in insomnia is limited to short-term use only and the limited trials available suggest that they are not as effective as other sedative-hypnotics. All of the barbiturates are primarily metabolized via hepatic enzymes,

and elderly patients and patients with hepatic insufficiency are more susceptible to class-related adverse effects. Butabarbital and phenobarbital are all available generically in at least one dosage form.

Within the limited range of published, peer-reviewed, clinical trials for this class, there is insufficient evidence that demonstrates that one agent is more efficacious or safer than another. In general, the barbiturates should not be considered as a first-line therapy choice for any indication.

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and over-the-counter products in this class 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 cost effective products and possibly designate one or more preferred brands.

References

1. Nemeroff C, Putnam J. Barbiturates and similarly acting agents. In: Sadock B, Sadock V, editors. Kaplan & Sadock's comprehensive textbook of psychiatry [monograph on the internet]. 8th ed. Philadelphia: Lippincott Williams & Wilkins; 2005 [cited 2007 Jul 16]. Available from: http://www.r2library.com/marc_frame.aspx?ResourceID=214.
2. Central nervous system agents 28:00, Anxiolytics, sedatives, and hypnotics 28:24, Barbiturates 28:24.04. In: McEvoy GK, editor; American Hospital Formulary Service. AHFS drug information 2007 [monograph on the Internet]. Bethesda (MD): American Society of Health-System Pharmacists; 2007 [cited 2007 Aug 9]. Available from: http://online.statref.com/document.aspx?fxid=1&docid=651.
3. Micromedex® Healthcare Series [database on the internet]. Greenwood Village (CO): Thomson Micromedex, 2007 [cited 2007 Aug 13]. Available from: http://www.thomsonhc.com/.
4. Drug Facts and Comparisons 4.0 [database on the internet]. St. Louis: Wolters Kluwer Health, Inc.; 2007 [cited 2007 Aug 13]. Available from: http://online.factsandcomparisons.com.
5. FDA news. FDA requests label change for all sleep disorder drug products. Rockville, MD: US Food and Drug Administration; 2007 Mar 14 [cited 2007 Aug 14] Available from: http://www.fda.gov/bbs/topics/NEWS/2007/NEW01587.html.
6. Morgenthaler T, Kramer M, Alessi C, Friedman L, Boehlecke B, Brown T, et al; American Academy of Sleep Medicine. Practice parameters for the psychological and behavioral treatment of insomnia: an update. An American Academy of Sleep Medicine report. Sleep. 2006;29(11):1415-9. Available from: http://www.aasmnet.org/PracticeParameters.aspx?cid=109.
7. NIH State-of-the-Science Conference statement on manifestations and management of chronic insomnia in adults. NIH Consens Sci Statements [serial on the Internet]. 2005 Jun 13-15 [cited 2007 Aug 8]; 22(2) 1-30. Available from: http://consensus.nih.gov/2005/2005InsomniaSOS026PDF.pdf.
8. Treatment of insomnia. Treat Guidel Med Lett. 2006 Feb;4(42):5-10.
9. Mayo-Smith MF. Pharmacological management of alcohol withdrawal. A meta-analysis and evidence-based practice guideline. American Society of Addiction Medicine Working Group on Pharmacological Management of Alcohol Withdrawal. JAMA. 1997 Jul 9;278(2):144-51.
10. Appleton R, Choonara I, Martland T, Phillips B, Scott R, Whitehouse W. The treatment of convulsive status epilepticus in children. The Status Epilepticus Working Party, Members of the Status Epilepticus Working Party. Arch Dis Child. 2000 Nov;83(5):415-9.
11. Wheless JW, Clarke DF, Carpenter D. Treatment of pediatric epilepsy: expert opinion, 2005. J Child Neurol. 2005 Dec;20 Suppl 1:S1-56.
12. Meierkord H, Boon P, Engelsen B, Göcke K, Shorvon S, Tinuper P, et al. EFNS guideline on the management of status epilepticus. Eur J Neurol. 2006; 13:445-50.
13. Nembutal® [package insert]. Deerfield, IL: Ovation Pharmaceuticals, Inc.; January 2007.
14. Seconal® [package insert]. In: DailyMed [database on the internet]. Bethesda, MD: National Library of Medicine [updated 2007 Jan;cited 2007 Sep 10]. Available from: http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=2846.
15. Brevital® sodium injection [package insert]. In: DailyMed [database on the internet]. Bethesda, MD: National Library of Medicine [updated 2006 Oct; cited 2007 Sep 10]. Available from: http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=2258.
16. Butisol® sodium [package insert]. In: DailyMed [database on the internet]. Bethesda, MD: National Library of Medicine [updated 2007 Aug; cited 2007 Sep 10]. Available from: http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=4889.
17. Amobarbital: drug information. In: Rose BD, editor. UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2007 [cited 2007 Aug 28]. Available from: http://www.utdol.com/utd/index.do.
18. Butabarbital: drug information. In: Rose BD, editor. UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2007 [cited 2007 Aug 28]. Available from: http://www.utdol.com/utd/index.do
19. Methohexital: drug information. In: Rose BD, editor. UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2007 [cited 2007 Aug 28]. Available from: http://www.utdol.com/utd/index.do.
20. Pentobarbital: drug information. In: Rose BD, editor. UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2007 [cited 2007 Aug 28]. Available from: http://www.utdol.com/utd/index.do.
21. Phenobarbital: drug information. In: Rose BD, editor. UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2007 [cited 2007 Aug 28]. Available from: http://www.utdol.com/utd/index.do.
22. Secobarbital: drug information. In: Rose BD, editor. UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2007 [cited 2007 Aug 28]. Available from: http://www.utdol.com/utd/index.do.

23. Mariani JJ, Rosenthal RN, Tross S, Singh P, Anand OP. A randomized, open-label, controlled trial of gabapentin and phenobarbital in the treatment of alcohol withdrawal. Am J Addict. 2006 Jan-Feb;15:76-84.
24. Mello de Paula A. Comparative study of zopiclone and pentobarbitone as hypnotics. Pharmacology. 1983;27 Suppl 2:188-95.
25. Okawa KK, Allens G. A clinical comparison of triazolam with placebo and with secobarbital in insomniac patients. J Int Med Res. 1978;6(4):343-7.
26. Painter M, Scher M, Stein A, Armatti S, Wang Z, Gardiner J, et al. Phenobarbital compared with phenytoin for the treatment of neonatal seizures. N Engl J Med. 1999 Aug 12;341(7):485-9.
27. Smith CT, Marson AG, Williamson PR. Carbamazepine versus phenobarbitone monotherapy for epilepsy [abstract]. Cochrane Database of Systematic Reviews. 2003;1.
28. Treiman D, Meyers P, Walton N, Collins J, Colling C, Rowan AJ, et al. A comparison of four treatments for generalized convulsive status epilepticus. Veterans Affairs Status Epilepticus Cooperative Study Group. N Engl J Med. 1998 Sep 17;339(12):792-8.

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Anxiolytics, Sedatives, and Hypnotics
Benzodiazepines AHFS Classes 282408
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I. Overview

Benzodiazepines have been a mainstay of pharmacological treatment for anxiety disorders and insomnia since they were first introduced in the 1960s. These agents were developed as safer and better tolerated alternatives to other drug classes such as the barbiturates, and they have largely replaced these older agents as one of the therapeutic alternatives for the management of anxiety and insomnia.[1] In addition to the short-term treatment of insomnia and anxiety disorders, benzodiazepines have been used as adjunctive therapy in seizure disorders, for the management of acute alcohol withdrawal, for preoperative sedation, and as emergency intervention to treat convulsive status epilepticus.[2-5]

When bound to benzodiazepine receptors, benzodiazepines potentiate the effects of γ-aminobutyric acid (GABA) and other inhibitory neurotransmitters. 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 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, and psychomotor impairment. Benzodiazepine receptor subtype-3 is located throughout the body as well as the glial cells and is believed to contribute to tolerance and withdrawal when activated.[2-5]

Primary insomnia, as defined by the American Psychiatric Association's (APA's) *Diagnostic and Statistical Manual of Mental Disorders,* Text Revision, 4th edition (DSM-IV-TR), is difficulty in initiating or maintaining sleep for at least one month, causing marked distress or impairment in social, occupational, or other important areas of functioning.[1] A diagnosis of primary insomnia is made after other possible mental and medical disorders have been excluded. Management of insomnia is most effective when the choice of treatment is patient-specific, taking into consideration the patient's age, the duration and severity of symptoms, and the etiology of insomnia if known.[1] For many patients, treatment of insomnia with nonpharmacological behavioral changes may be as effective as drug therapy.[1]

Besides their use as hypnotics, benzodiazepines have an important place in the treatment of various anxiety disorders. Anxiety states are a collection of conditions in which a generalized pervasive fear dominates a patient's life. Anxiety disorders, as detailed in the DSM-IV-TR, include the following: generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, posttraumatic stress, and social phobias.[6]

The benzodiazepines that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Currently, Alabama Medicaid does not cover estazolam, halazepam, midazolam, and quazepam formulations as well as the brand formulations of the other agents in the class, as benzodiazepines are an excludable drug class in accordance with the Omnibus Budget Reconciliation Act of 1990 (OBRA 90).

Table 1. Benzodiazepines Included in this Review

Generic Name	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
alprazolam	sustained-release tablet, tablet	Xanax®*‡, Xanax XR®‡	alprazolam, alprazolam XR
chlordiazepoxide	capsule, injection	Librium®*	chlordiazepoxide
clonazepam	orally disintegrating tablet, tablet	Klonopin®*	clonazepam
clorazepate	sustained-release tablet,	Tranxene SD®, Tranxene	clorazepate

Generic Name	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
	tablet	T-Tab®*,	
diazepam	injection, oral concentrate, rectal gel, solution, tablet	Valium®*‡, Diastat®	Diastat®, diazepam
flurazepam	capsule	Dalmane®*	flurazepam
lorazepam	injection, oral concentrate, tablet	Ativan®*, Lorazepam Intensol®	lorazepam
oxazepam	capsule	Serax®*	oxazepam
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.

II. Evidence-Based Medicine and Current Treatment Guidelines

Treatment guidelines that incorporate the benzodiazepines are summarized in Table 2.

Table 2. Treatment Guidelines Using the Benzodiazepines

Clinical Guideline	Recommendation
American Academy of Sleep Medicine (AASM), Standards of Practice Committee: **Practice Parameters for the Psychological and Behavioral Treatment of Insomnia: An Update (2006)**[7]	• Insomnia as a primary disorder is known as "primary insomnia," as opposed to insomnia due to or associated with another condition such as medical or psychiatric illness, substance abuse disorder, or another sleep disorder. The latter is referred to in the guideline as "secondary insomnia." • Psychological and behavioral interventions are effective and recommended in the treatment of both chronic primary insomnia and secondary insomnia. • Stimulus control is effective in the treatment of chronic insomnia and involves training that reassociates the bed and bedroom with sleep and promotes a consistent sleep-wake schedule. • Chronic insomnia is effectively treated with relaxation training (progressive muscle relaxation) and autogenic training to reduce tension, as well as reduce disruptive thoughts at bedtime. • Sleep restrictions, such as limiting time in bed to actual time asleep, are useful in chronic insomnia. • Cognitive behavior therapy, with or without relaxation therapy, is recommended in the treatment of chronic insomnia. This form of therapy focuses on changing patient beliefs and attitudes about insomnia. Stimulus control therapy, sleep restriction, relaxation training and sleep hygiene education may also be involved. • Paradoxical intention, where the patient attempts to stay awake, is effective in sleep initiation insomnia. • The use of visual or auditory biofeedback to reduce somatic arousal is useful in chronic insomnia. • There is insufficient evidence that sleep hygiene monotherapy is effective. • Imagery training has not been proven effective as monotherapy or in combination with other approaches. • There is limited evidence that cognitive therapy alone is effective in treating insomnia. • Insufficient evidence was available to recommend one single therapy over another, or to recommend single therapy versus a combination of psychological and behavioral interventions. • Psychological and behavioral interventions are effective and recommended in treating insomnia in older adults. • Psychological and behavioral interventions are effective in treating insomnia in chronic hypnotic users.

Clinical Guideline	Recommendation
National Institutes of Health (NIH), State-of-the-Science Conference Statement: **Manifestations and Management of Chronic Insomnia in Adults (2005)**[8]	Conference Statement • "Evidence supports the efficacy of cognitive-behavioral therapy and benzodiazepine receptor agonists in the treatment of this disorder [chronic insomnia], at least in the short term. Very little evidence supports the efficacy of other treatments, despite their widespread use." General Considerations • The most common treatments used by individuals with chronic insomnia are prescription medications, over-the-counter antihistamines, and alcohol. • The major forms of psychological treatments are cognitive and behavioral therapies. Prescription Medications with Food and Drug Administration (FDA) Approval for the Treatment of Insomnia • Benzodiazepine receptor agonists include benzodiazepines (eg, flurazepam, temazepam, and triazolam) as well as nonbenzodiazepine-structured anxiolytic agents acting at benzodiazepine receptors (eg, 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 (eg, 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. • 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 (eg, amitriptyline and mirtazapine) in individuals with chronic insomnia are lacking. • These guidelines were published prior to the FDA approval of ramelteon. Nonprescription Medications • Antihistamines (eg, diphenhydramine) are the most commonly used over-the-counter agents for chronic insomnia; however, there is no systematic evidence for efficacy and there are significant concerns about the risks of these medications. Behavioral and Cognitive Therapies • Behavioral methods include relaxation training, stimulus control, and sleep restriction. • Cognitive therapy methods have been added to behavioral methods and include cognitive restructuring, in which anxiety-producing beliefs and erroneous beliefs about sleep and sleep loss are specifically targeted. • The combination of cognitive methods and behavioral methods (CBT) has been found to be as effective as prescription medications for short-term treatment of chronic insomnia. The beneficial effects of CBT may last well beyond the termination of active treatment.
Treatment Guidelines from the Medical Letter on Drugs and Therapeutics: **Treatment of Insomnia (2006)**[9]	• Short-term use of a short-acting nonbenzodiazepine benzodiazepine receptor agonist (NBRA) is generally effective and safe (minimal adverse events and drug interactions), but it is not clear that NBRAs are more effective or safer than benzodiazepines. • Short-acting benzodiazepines and NBRAs may not prevent early morning awakening; when this occurs, a drug with an intermediate duration of action may be more helpful. • Nonprescription first generation antihistamines such as diphenhydramine are not recommended for treatment of insomnia; tolerance develops quickly and they can

Clinical Guideline	Recommendation
	cause next-day sedation that impairs driving skills. • Cognitive behavioral therapy is safer and in some patients may be more effective than drugs for the treatment of chronic insomnia. • Barbiturates and chloral hydrate are not recommended due to their many side effects and the possibility of physical dependence and abuse.
International Consensus Group on Depression and Anxiety: **Consensus Statement on Panic Disorder (1998)**[10]	General Considerations • The goal of treatment is full remission across the syndrome: panic attacks, anxiety, phobias, well-being, and disability. • The strongest evidence for clinical efficacy exists for selective serotonin-reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), and benzodiazepines. • Monoamine oxidase inhibitors (MAOIs) have demonstrated efficacy, though the quality of evidence is less extensive. • There is limited evidence for the use of anticonvulsants, and recommended use of valproate is confined to treatment-resistant patients. • β-Blockers should be considered an ineffective therapeutic option in panic disorder. Treatment of Choice • SSRIs are recommended as first-line treatment of panic disorder. • SSRI treatment is to be initiated at a low dose and increased slowly, as tolerated, to the target dose. • Effective treatment may be continued for 12 to 24 months with consideration for stopping only when the patient is well and in a stable life situation, after which treatment may be discontinued slowly over the course of 4 to 6 months; treatment should never be stopped abruptly. • Concomitant use of a benzodiazepine for a limited period (<8 weeks) may be used to help initiate treatment with an SSRI in some patients. Second-line Treatment • Second-line treatment is needed when a patient fails to respond to an adequate trial (8 to 12 weeks) of an SSRI at the maximum tolerated dose. • If partial response was observed and the SSRI was well tolerated, switch to another SSRI. • If an SSRI was not tolerated, initiate a trial of a benzodiazepine or a TCA. Third-line Treatment • An MAOI or valproate may be tried. Additional Pertinent Considerations • SSRIs are generally preferable to benzodiazepines or TCAs based on a review of long-term treatment data. • SSRIs may be administered in a once-daily dosing regimen (except fluvoxamine); clomipramine may be given as a single dose at bedtime; however, other TCAs require multiple dosing as do benzodiazepines. • Patients with panic disorder and a recent history of alcoholism should, except in some instances, not be prescribed benzodiazepines. • Patients who have panic disorder and a history of suicidal ideation or temporal lobe epilepsy should not be prescribed TCAs. • SSRIs are an appropriate choice of treatment for patients with panic disorders who also have concomitant depression, high suicidality, or concomitant medical illness. • SSRIs should be the preferred therapeutic option for panic disorder comorbid with other anxiety disorders (eg, obsessive-compulsive disorder) or alcoholism. • Benzodiazepines are generally well tolerated but may cause unwanted sedative effects, poor coordination, and memory problems; may potentiate the effects of alcohol; and

Clinical Guideline	Recommendation
	are associated with the risk of dependence with long-term use as well as potential difficulties with withdrawal symptoms. • TCAs are associated with poor tolerability due to their anticholinergic effects, may cause weight gain, and have the potential to cause seizures as well as other safety concerns. • SSRIs have an improved tolerability over traditional TCAs and most side effects resolve over time; some SSRIs may cause initial jitteriness.

International Consensus Group on Depression and Anxiety:
Consensus Statement on Generalized Anxiety Disorder (GAD) (2001)[11]
	<u>General Considerations</u>
	• Chronic worrying and the effects of chronic tension are the specific features that define GAD; duration of symptoms is an important factor differentiating GAD from other anxiety disorders. For a diagnosis of GAD, the symptoms of anxiety and worry should have been present for 6 months.
	• Cognitive behavioral therapy (CBT) techniques are recommended as the preferred form of psychotherapy in GAD.
	• When GAD is comorbid with depression, as it commonly is, medication is often indicated.
	
	<u>Treatment of Choice</u>
	• Antidepressants are recommended as first-line treatment of GAD. The following classes of antidepressants can be used:
	  o Selective serotonin-reuptake inhibitors (SSRIs)
	  o Serotonin-norepinephrine reuptake inhibitors (SNRIs)
	  o Nonsedating tricyclic antidepressants (TCAs)
	• Benzodiazepines may be used as adjunct agents in acute exacerbations of GAD or for sleep disturbances during the initiation of antidepressant therapy. Patients should be stabilized on antidepressant therapy for >4 weeks before benzodiazepines are slowly tapered off (over 4 to 8 weeks).
	• For patients with a long-term condition, with several comorbid conditions, and in patients with an increased risk of suicide, an SSRI or SNRI is indicated.
	
	<u>Other Therapeutic Options</u>
	• Buspirone has demonstrated efficacy in GAD in most clinical trials, although it has not shown efficacy against comorbid conditions and therefore is not recommended as first-line treatment for GAD.
	
	<u>Additional Pertinent Considerations</u>
	• The guideline indicates that the only first-line use of benzodiazepines is an acute anxiety reaction, with an expected duration of 2 to 6 weeks; benzodiazepines are not appropriate for first-line treatment of GAD, which is a condition requiring appropriate long-term treatment.
	• Benzodiazepines are appropriate for intermittent or episodic use.
	• Benzodiazepines may have a role as adjunctive therapy in acute exacerbation of GAD or in sleep disturbances during the initiation of antidepressant therapy.
	• GAD is frequently comorbid with depressive disorders, for which benzodiazepines are not desirable, or with other anxiety disorders, for which benzodiazepine therapy is not usually favored as first-line.
	• The use of benzodiazepines may be a problem in the long term, due to the risk of withdrawal reactions, or in patients with a history of drug abuse or alcoholism.
	• The guideline indicates that hydroxyzine is used in acute anxiety states, in which it is targeting symptoms rather than treating the condition itself.
	• The use of hydroxyzine is similar to that of benzodiazepines; however, hydroxyzine does not cause dependence.
	• Hydroxyzine has no demonstrated efficacy in depression, panic disorder, social phobia, or obsessive-compulsive disorder.

Clinical Guideline	Recommendation
	• Neuroleptics are not appropriate for the treatment of GAD as there is almost no clinical evidence to support their use, and they may be associated with tardive dyskinesia even in low doses.

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 (2004)**[12]	<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. More effective options are outlined below.
	• Sedating antihistamines or antipsychotics should not be prescribed for panic disorder.
	
	<u>Panic Disorder Treatment Options</u>
	Interventions with evidence for the longest duration of effect are listed in descending order, where preference of the patient should be taken into account:
	  • Psychological therapy (ie, cognitive behavioral therapy, structured problem solving, psychoeducation)
	  • Pharmacological therapy: antidepressants
	  • Self-help interventions (ie, 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 (eg, paroxetine, fluvoxamine, citalopram) licensed in the United Kingdom (UK) for panic disorder should be offered; if an SSRI is not suitable, the TCAs imipramine or clomipramine may be considered.
	• Side effects with the initiation of antidepressants may be minimized by starting at a low dose and increasing the dose slowly until a satisfactory therapeutic response is achieved.
	• 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, imipramine or clomipramine may be considered, or another form of therapy may be offered.
	
	<u>Generalized Anxiety Disorder General Considerations</u>
	• Benzodiazepines may be used for acute treatment, but they should not usually be used beyond 2 to 4 weeks.
	
	<u>Generalized Anxiety Disorder Treatment Options</u>
	Interventions with evidence for the longest duration of effect are listed in descending order, where preference of the patient should be taken into account:
	  • Psychological therapy (eg, cognitive behavioral therapy, structured problem solving, psychoeducation)
	  • Pharmacological therapy: antidepressants
	  • Self-help interventions (eg, bibliotherapy, support groups, exercise, cognitive behavioral therapy via a computer interface)
	
	<u>Generalized Anxiety Disorder Additional Considerations for Pharmacologic Therapy</u>
	• Unless otherwise indicated, an SSRI should be offered; if one SSRI is not suitable, another SSRI should be offered.
	• Side effects with the initiation of antidepressants may be minimized by starting at a low dose and increasing the dose slowly until a satisfactory therapeutic response is

Clinical Guideline	Recommendation
	achieved. • 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. • If venlafaxine is being considered, an initial electrocardiogram (ECG) and blood pressure measurement should be undertaken and the dose should be no higher than 75 mg per day; treatment should be initiated and managed under the supervision of specialist mental health medical practitioners and regular monitoring of cardiac status is advised. • A number of different drugs are considered for the treatment of GAD in the guideline, including SSRIs (eg, paroxetine, fluvoxamine, citalopram), TCAs (eg, imipramine, clomipramine), benzodiazepines (eg, diazepam, alprazolam, clonazepam, lorazepam), sedating antihistamines (eg, hydroxyzine), SNRIs (eg, venlafaxine), and buspirone. • Antidepressants are preferred over benzodiazepines due to the potential for abuse and because antidepressants may treat comorbid depression.
International Consensus Group on Depression and Anxiety: **Consensus Statement on Social Anxiety Disorder (SAD) (1998)**[13]	General Considerations • SAD appears to predispose individuals to the development of other psychiatric disorders, most notably depression. • There is some evidence for the effectiveness of cognitive behavioral treatment in SAD; however, this is based on relatively small trials as compared to that for pharmacotherapy. Treatment of Choice • Selective serotonin-reuptake inhibitors (SSRIs) are recommended as first-line treatment of SAD, with most efficacy evidence for SSRIs derived from well-controlled studies with paroxetine. • The appropriate dosage regimen for paroxetine has been defined: it should be initiated at 20 mg/day for 2 to 4 weeks, and then increased as necessary. • An adequate trial of treatment with an SSRI is 6 to 8 weeks, and if effective, treatment should be continued for at least 12 months. • Long-term treatment is indicated if symptoms are unresolved, if the patient has a comorbidity or a history of relapse, or if there was an early onset of SAD. • SSRIs are also recommended for treating patients who have failed to respond to other treatments for SAD. Other Therapeutic Options • Phenelzine, a monoamine oxidase inhibitor (MAOI), has less evidence for efficacy in SAD and is associated with concerns about its tolerability and safety, which make it an inappropriate option for first-line treatment. • The benzodiazepine clonazepam has limited but well-controlled data for the treatment of SAD; alprazolam was shown to be significantly less effective than clonazepam for SAD, and there is no evidence that benzodiazepines as a class are effective in SAD. Additional Pertinent Considerations • β-Blockers do not have a place in the management of SAD; despite the benefit of their use with normal performance anxiety, there is no controlled evidence to show that β-blockers are advantageous for the pathologic anxiety of generalized SAD. Furthermore they may have harmful effects, especially in patients with asthma. • In contrast with their efficacy in panic disorder, there are no controlled data for the efficacy of tricyclic antidepressants (TCAs) in SAD.

Clinical Guideline	Recommendation
American Society of Addiction Medicine (ASAM), Committee on Practice Guidelines: **Pharmacological Management of Alcohol Withdrawal (1997)**[14]	• 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 oversedation. • 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 (eg, 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 illness(es), 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 (eg, 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 and the elderly are the same as for adults.

Clinical Guideline	Recommendation
	• Risk versus benefit should be considered when administering benzodiazepines and barbiturates during pregnancy as they are both associated with adverse effects on the fetus.
The Status Epilepticus Working Party: **The Treatment of Convulsive Status Epilepticus in Children (2000)**[15]	• Give high flow oxygen, measure blood glucose and confirm epileptic seizure. <u>Immediate Intravenous (IV) Access</u> • If intravenous (IV) access is available give lorazepam 0.1 mg/kg IV. • Repeat lorazepam once if seizing at 10 minutes. • If seizing continues after an additional 10 minutes, administer phenytoin 18 mg/kg IV or phenobarbitone* (if already on phenytoin) 20 mg/kg IV and paraldehyde 0.4 mL/kg rectally (PR) mixed with an equal volume of olive oil. • Rapid sequence induction of anesthesia using thiopentone** 4 mg/kg IV is recommend if seizing continues for an additional 20 minutes. <u>No immediate IV Access</u> • Give diazepam 0.5 mg/kg PR. • Add lorazepam 0.1 mg/kg IV if still seizing at 10 minutes or paraldehyde 0.4 mL/kg PR if no IV access. • If seizure activity continues for another 10 minutes, give phenytoin 18 mg/kg IV or phenobarbitone* 20 mg/kg IV (or intraosseous if no IV access) in addition to paraldehyde 0.4 mL/kg mixed with same volume of olive oil, PR if not already given and contact anesthetist or intensive care medic. • Rapid sequence induction of anesthesia using thiopentone** 4 mg/kg IV is recommend if seizing continues for an additional 20 minutes after the initiation of paraldehyde.
Journal of Child Neurology: **Treatment of Pediatric Epilepsy: Expert Opinion (2005)**[16]	• Rectal diazepam is the treatment of choice for acute treatment of a prolonged febrile seizure or cluster of seizures. • Intravenous phenobarbital is the treatment of choice and intravenous lorazepam or fosphenytoin are also first line options for the initial therapy of neonatal status epilepticus. • Lorazepam is the treatment of choice and intravenous diazepam is also a first line option for the initial therapy of all types of pediatric status epilepticus. • Rectal diazepam or fosphenytoin are the first-line options for generalized tonic-clonic status epilepticus. • Benzodiazepines were not identified as being first-line or treatment of choice for the following: complex partial status epilepticus, absence status epilepticus, symptomatic myoclonic and generalized tonic-clonic seizures, complex partial seizures, infantile spasms, Lennox-Gastaut syndrome, benign childhood epilepsy with centro-temporal spikes, childhood absence epilepsy, juvenile absence epilepsy, and juvenile myoclonic epilepsy.
European Federation of Neurological Societies (EFNS): **Guideline on the Management of Status Epilepticus (2006)**[17]	<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.

Clinical Guideline	Recommendation
	• 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> • Anaesthetic 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.

*Synonym for phenobarbital
**Synonym for thiopental

III. Indications

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[2,18-27]

Indication	Alprazolam	Chlor-diazepoxide	Clonazepam	Clorazepate	Diazepam	Flurazepam	Lorazepam	Oxazepam	Temazepam	Triazolam
Acute alcohol withdrawal		✔		✔	✔			✔		
Anxiety disorders, management	✔ *	✔ *		✔ *	✔ *		✔ *‡	✔ *‡		
Insomnia							✔			
Insomnia, short-term treatment						✔			✔	✔
Muscle spasms					✔					
Panic disorder with or without agoraphobia	✔		✔							
Premedication for anesthetic procedures							✔ §			
Preoperative apprehension/anxiety		✔			✔ **					
Seizure disorders (Lennon-Gastaut, akinetic, absence and myoclonic seizure disorders), monotherapy or adjunct therapy			✔							
Seizures, adjunct therapy					✔ †					
Seizures, partial, adjunct therapy				✔						
Status epilepticus							✔ §			

*Also may be used for the short-term relief of symptoms of anxiety
†Rectal gel formulation 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 depressive symptoms
§ Recommended route of administration is intramuscular (IM) or intravenous (IV)
** For sedation, preoperative medication, endoscopic procedures, and cardioversion the intramuscular (IM) or intravenous (IV) route of administration is recommended

IV. Pharmacokinetics

The pharmacokinetic parameters for the benzodiazepines are summarized in Table 4.

Table 4. Pharmacokinetic Parameters of the Benzodiazepines[2-5, 18-27]

Drug	Duration of Action*	Bioavailability (%)	Protein Binding (%)	Metabolism	Active Metabolites	Elimination (%)	Half-Life (hours)
Alprazolam	Short	90†	80	Extensively metabolized, primarily by cytochrome P450 3A4 (CYP3A4)	Yes; alpha-hydroxy-alprazolam and 4-hydroxy-alprazolam	Renal	6.3-26.9 (IR) 10.7-15.9 (XR)
Chlor-diazepoxide	Long	Not reported	90-98	Hepatic; extensively metabolized	Yes; desmethyl-chlordiaze-poxide and demoxepam	Renal; 1-2 unchanged, 3-6 as conjugate	24-48
Clonazepam	Long	90	85	Hepatic; extensively metabolized	None	Renal; <2 unchanged	30-40
Clorazepate	Long	91	97-98	Hepatic	Yes; nordiazepam and desmethyl-diazepam	Renal (62-67); fecal (15-19)	2.3 (parent compound) 46-48 (metabolites)
Diazepam	Long	98	94-99	Hepatic; extensively metabolized	Yes; desmethyl-diazepam (major), and 3-hydroxydi-azepam and 3-hydroxy-N-diazepam (minor)	Renal (75)	0.83-2.25 days
Flurazepam	Long	Not reported	97	Hepatic; extensively metabolized	Yes; hydroxyethy l-flurazepam and desalkyl-flurazepam	Renal (up to 78)	2.3 (parent compound) 47-100 (metabolites)
Lorazepam	Short	90	85-91	Hepatic; extensively metabolized	None	Renal (88); fecal (7)	12
Oxazepam	Short	93	86-99	Hepatic; extensively metabolized	None	Renal (50); bile (<0.1)	5.7-10.9
Temazepam	Short	Not reported	96	Hepatic; extensively metabolized	None	Renal (80-90)	3.5-18.4

Drug	Duration of Action*	Bioavaila-bility (%)	Protein Binding (%)	Metabolism	Active Metabolites	Elimination (%)	Half-Life (hours)
Triazolam	Short	Not reported	89-94	Hepatic; extensively metabolized	Yes; alpha-hydroxy-triazolam	Renal (80); fecal 9	2.3

IR=immediate-release, XR=extended-release
* Classification may vary due to a wide range in the documented half-life.
† The bioavailability and pharmacokinetics of the extended-release tablets are similar to that of the immediate-release formulation, with the exception of a slower rate of absorption seen with the extended-release tablets.
IR=immediate-release formulation, XR=extended release formulation

V. Drug Interactions

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

Table 5. Significant Drug-Drug Interactions with the Benzodiazepines[3]

Drug(s)	Significance Level	Interaction	Mechanism
Benzodiazepines (all)	1	Ethanol	Increased central nervous system (CNS) effects and impaired psychomotor function have been observed. Patients should be cautioned to avoid the use of alcohol and benzodiazepines concurrently. With acute ethanol ingestion, increased benzodiazepine absorption and decreased hepatic metabolism is possible. Counsel patients about the additive or synergistic CNS effects and avoid concomitant use.
Benzodiazepines (alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, flurazepam, quazepam*, 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 resulting in large increases in serum concentrations of benzodiazepines undergoing oxidative metabolism. Coadministration of these protease inhibitors with benzodiazepines metabolized by CYP3A4 is contraindicated.
Benzodiazepines (alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, flurazepam, quazepam*, triazolam)	2	Azole antifungals	Increased and prolonged serum levels, CNS depression, and psychomotor impairment has been noted with certain benzodiazepines undergoing oxidative metabolism and may possibly continue for several days after stopping the azole antifungal agent. Consider giving a lower benzodiazepine dose or a benzodiazepine that undergoes glucuronidation (eg, lorazepam, temazepam) when giving fluconazole. Use of alprazolam or triazolam with itraconazole or ketoconazole is contraindicated.
Benzodiazepines (diazepam, triazolam)	2	Diltiazem	Increased CNS depression and prolonged effects have been observed with the use of diltiazem and certain benzodiazepines.
Benzodiazepines	2	Hydantoins	Serum hydantoin concentrations may be increased and phenytoin may increase the clearance of certain benzodiazepines. Hydantoin levels and effects should be monitored when the benzodiazepine dose is started or stopped.

Drug(s)	Significance Level	Interaction	Mechanism
Benzodiazepines (alprazolam, diazepam, triazolam)	2	Macrolides and related antibiotics (clarithromycin, erythromycin, telithromycin)	Increased CNS depression and prolonged sedation have been noted with concomitant use of certain benzodiazepines and macrolide related agents. Consider benzodiazepines undergoing conjugative metabolism that are unlikely to interact (eg, lorazepam, oxazepam, temazepam).
Benzodiazepines (alprazolam, triazolam)	2	Nonnucleoside reverse transcriptase (NNRT) inhibitors (delavirdine, efavirenz)	Nonnucleoside reverse transcriptase (NNRT) inhibitors may inhibit the hepatic metabolism (CYP3A4) of the benzodiazepine. The pharmacologic effects of certain benzodiazepines may be increased and the duration prolonged, leading to protracted sedation and respiratory depression. NNRT inhibitors should not used simultaneously with certain benzodiazepines.
Benzodiazepines (alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, flurazepam, triazolam)	2	Rifamycins	When used with rifamycins, the pharmacologic effects of certain benzodiazepines may be decreased due to an increase in the oxidative metabolism of the benzodiazepine (CYP450). Clinical response to the benzodiazepine should be monitored when starting or stopping rifamycins and the dose may be adjusted as needed.
Alprazolam	2	Carbamazepine	Carbamazepine has been shown to induce the metabolism of alprazolam, resulting in the decreased pharmacologic effects of alprazolam. During coadministration the patient should be monitored for a decrease in response and a higher dose of alprazolam may be considered if necessary.
Diazepam	2	Opioid analgesics (buprenorphine, methadone)	Increased sedation and strength of opioid effects have been observed with the concomitant use of diazepam and opioid analgesics. Patients should be advised against driving or operating machinery while taking these agents simultaneously.
Triazolam	2	Modafinil	Induction of gastrointestinal (major) and hepatic (minor) metabolism of triazolam by modafinil is suspected. Therefore reduced triazolam plasma levels and decreased pharmacologic effects have been observed with concurrent modafinil administration. Clinical response to triazolam should be observed closely if modafinil is started or stopped and the triazolam dose may be adjusted as appropriate.

*Not covered by Alabama Medicaid
Significance Level 1: Major severity
Significance Level 2: Moderate severity

VI. Adverse Drug Events

Benzodiazepines as a class share a number of adverse drug events. The most common side effects are CNS-related and include sedation, fatigue, ataxia, dizziness, confusion, and syncope. Longer acting benzodiazepines or benzodiazepines with active metabolites may have a higher incidence of residual daytime sedation, psychomotor impairment and mental impairment. This may be more pronounced in elderly patients or patients with impaired elimination of benzodiazepines (eg, hepatic insufficiency). Adverse effects are dose-related and are most pronounced during initiation of therapy.
The most common adverse drug events reported with the benzodiazepines are noted in Table 6.

In March of 2007 the FDA issued a press release regarding its request that all drug manufacturers of medications approved for the treatment of sleep disorders revise product labeling to include warnings and potential risks of adverse events. Various products containing flurazepam (Dalmane®), temazepam (Restoril®), and triazolam (Halcion®) were among the drugs targeted in the alert. These adverse events include severe allergic reaction (eg, anaphylaxis) and angioedema as well as complex sleep-related behaviors including sleep-driving, making phone calls and eating and preparing food while asleep. The FDA has also requested that consumers be informed through the development of a Patient Medication Guide.[28]

In addition to the adverse drug events noted in Table 6, misuse and dependence is also a concern associated with benzodiazepine therapy. The risk of dependence increases in the following scenarios: long-term therapy, high daily dose, use of high potency, rapid onset benzodiazepines, history of substance abuse, chronic physical illness, chronic sleep disorders, and dysthymic or personality disorders.[29,30]

Symptoms may occur upon benzodiazepine discontinuation, especially if the therapy is abruptly stopped without a taper period. Symptoms may include relapse of anxiety disorder, rebound symptoms and withdrawal syndromes. Withdrawal symptoms are typically observed only after a treatment duration of greater than 4 months, but may be seen in shorter therapies involving high doses. Withdrawal can occur within hours of discontinuation of a short-acting benzodiazepine or as late as 1-2 weeks with long-acting agents. Factors that can predict the severity of discontinuation symptoms include: long-term therapy, high daily dose, short benzodiazepine half-life, rapid taper rate, and concomitant substance abuse.[29,31] Taper schedules should be individualized to the patient and take into consideration the duration of therapy, any concomitant illness, and daily dose.

Table 6. Adverse Drug Events (%) Reported with the Benzodiazepines[2-5, 18-27]

Adverse Event	Alprazolam	Chlor-diazepoxide	Clonazepam	Clorazepate	Diazepam	Flurazepam	Lorazepam	Oxazepam	Temazepam	Triazolam
Cardiovascular										
Chest pain	10.6	-	✔	-	-	✔	-	-	-	✔
Decreased systolic blood pressure	-	-	-	✔	-	-	-	-	-	-
Dyspnea	-	-	-	-	-	-	-	-	✔	-
EEG changes	-	✔	-	-	-	-	-	-	-	-
Flushing	-	-	✔	-	-	✔	-	-	-	-
Hypotension	4.7	-	✔	-	✔	✔	✔	-	-	-
Palpitations	-	-	✔	-	-	✔	-	-	✔	-
Shortness of breath	-	-	✔	-	-	✔	-	-	-	-
Syncope	3.1-3.8	✔	-	-	-	-	-	✔	-	✔
Tachycardia	7.7-15.4	-	-	-	-	-	-	-	-	0.5-0.9

Adverse Event	Alprazolam	Chlor-diazepoxide	Clonazepam	Clorazepate	Diazepam	Flurazepam	Lorazepam	Oxazepam	Temazepam	Triazolam
Central Nervous System										
Abnormal coordination	-	-	6	-	-	-	-	-	-	-
Abnormal involuntary movement	14.8	-	-	-	-	-	-	-	-	-
Aggression	-	-	✔	-	-	-	✔	-	-	✔
Agitation	2.9	-	✔	-	-	-	✔	-	✔	-
Akathesia	1.6	-	-	-	-	-	-	-	-	-
Amnesia	-	-	✔	-	-	-	✔	-	✔	✔
Anxiety	16.6	-	✔	-	-	-	✔	-	2.0	-
Apathy	-	-	✔	-	✔	-	-	-	-	-
Aphonia	-	-	✔	-	-	-	-	-	-	-
Apprehension	-	-	-	-	-	✔	-	-	-	-
Ataxia	-	✔	5-30	✔	✔	✔	✔	✔	✔	4.6
Blurred vision	6.2-21	-	1	✔	✔	✔	✔		1.3	-
Change in libido, unspecified	7.1	-	-	-	✔	-	✔	✔	-	✔
Cognitive disorder	28.8	-	-	-	-	-	-	-	-	-
Confusion	9.9-10.4	✔	1	✔	✔	✔	✔	-	1.3	0.5-0.9
Coma	-	-	✔	-	-	✔	✔	-	-	-
Convulsions/seizure	-	-	-	-	-	-	✔	-	-	-
Decreased libido	14.4	✔	1	-	-	-	✔	-	-	-
Delusions	-	-	-	-	-	-	-	-	-	✔
Depersonalization	-	-	✔	-	-	-	-	-	-	✔
Depression	13.9	-	7	✔	✔	✔	✔	-	1.7	0.5-0.9
Derealization	1.9	-	-	-	-	-	-	-	-	✔
Difficulty focusing	-	-	-	-	-	✔	-	-	-	-
Diplopia	-	-	✔	✔	✔	-	✔	-	-	-
Disinhibition	2.7	-	✔	-	-	-	✔	-	-	-
Disorientation	-	-	-	-	-	✔	✔	-	-	✔
Dizziness	1.8-29.8	-	8	✔	-	✔	6.9	✔	4.5	7.8
Dream abnormalities	1.8	-	-	-	-	-	-	-	✔	0.5
Dreaming, excessive	-	-	✔	-	-	-	-	-	-	-
Drowsiness	41.0-76.8	✔	50	✔	✔	✔	✔	✔	9.1	14.0
Drunkenness	-	-	✔	-	-	-	-	-	-	-
Dry mouth	14.7	-	✔	✔	-	✔	-	-	1.7	0.5
Dysesthesia	-	-	-	-	-	-	-	-	-	0.5

Adverse Event	Alprazolam	Chlor-diazepoxide	Clonazepam	Clorazepate	Diazepam	Flurazepam	Lorazepam	Oxazepam	Temazepam	Triazolam
Dysarthria	23.3	-	2	-	✔	-	✔	-	-	✔
Equilibrium loss	-	-	-	-	-	-	-	-	✔	-
Euphoria	-	-	-	-	-	✔	✔	-	1.5	0.5-0.9
Excitement	-	-	✔	-	✔	✔	✔	✔	-	✔
Fear	1.4	-	-	-	-	-	-	-	-	-
Feeling warm	1.3	-	-	-	-	-	-	-	-	-
Glassy-eyed appearance	-	-	✔	-	-	-	-	-	-	-
Hallucinations	-	-	✔	-	✔	✔	✔	-	✔	✔
Head fullness	-	-	✔	-	-	-	-	-	-	-
Headache	12.9-29.2	-	✔	✔	✔	✔	✔	✔	8.5	9.7
Hemiparesis	-	-	✔	-	-	-	-	-	-	-
Hoarseness	-	-	✔	-	-	-	-	-	-	-
Hostility	-	-	✔	-	-	-	✔	-	-	-
Hypoesthesia	-	-	✔	-	-	-	-	-	-	-
Hypotonia	-	-	✔	-	-	-	-	-	-	-
Hysteria	-	-	✔	-	-	-	-	-	-	-
Illusion	-	-	✔	-	-	-	-	-	-	-
Impaired coordination	40.1	-	-	-	-	-	-	-	-	-
Impotence	-	-	1	-	-	-	✔	-	-	-
Inattention	-	-	✔	-	-	-	-	-	-	-
Increased libido	7.7	✔	✔	-	-	-	-	-	-	-
Insomnia	8.9-29.4	-	✔	✔	✔	-	✔	-	-	0.5
Intellectual ability reduced	-	-	2	-	-	-	-	-	-	-
Irritability	33.1	-	✔	✔	-	✔	-	-	-	✔
Lethargy	-	-	-	-	-	✔	-	✔	4.5	-
Lightheadedness	20.8	-	-	-	-	✔	-	-	-	4.9
Memory impairment	33.1	-	4	-	-	-	✔	-	-	0.5-0.9
Migraine	-	-	✔	-	-	-	-	-	-	-
Muscle tone disorders	6.3	-	-	-	-	-	-	-	-	-
Muscular twitching	7.9	-	-	-	-	-	-	-	-	-
Nervousness	4.1	-	3	✔	-	✔	-	-	4.6	5.2
Nightmares	-	-	✔	-	-	-	-	-	1.2	0.5
Nystagmus	-	-	✔	-	-	-	-	-	✔	-
Paresis	-	-	✔	-	-	-	-	-	-	-
Paresthesia	2.4	-	✔	-	-	-	-	-	-	0.5

Adverse Event	Alprazolam	Chlor-diazepoxide	Clonazepam	Clorazepate	Diazepam	Flurazepam	Lorazepam	Oxazepam	Temazepam	Triazolam
Psychosis	-	-	✔	-	-	-	-	-	-	-
Rage	-	-	-	-	✔	-	✔	-	-	-
Restlessness	-	-	-	-	-	✔	-	-	✔	✔
Sedation	-	-	-	-	-	✔	15.9	-	-	✔
Sexual dysfunction	7.4	-	-	-	-	-	-	-	-	-
Sleep disturbances	-	-	✔	-	✔	-	✔	-	-	✔
Slurred speech	-	-	✔	✔	✔	✔	✔	✔	-	✔
Somnolence	-	-	37	-	-	-	-	-	-	✔
Staggering	-	-	-	-	-	✔	-	-	-	-
Talkativeness	2.2	-	-	-	-	✔	-	-	-	-
Tiredness	-	-	-	-	-	-	-	-	-	0.5-0.9
Tremor	4	-	✔	✔	✔	-	✔	✔	✔	-
Unsteadiness	-	-	-	-	-	-	3.4	-	-	-
Vasomotor disturbances	2	-	-	-	-	-	-	-	-	-
Vertigo	-	-	✔	-	✔	-	✔	✔	1.2	-
Visual disturbances	-	-	✔	-	-	-	✔	-	-	0.5-0.9
Vivid dreams	-	-	✔	-	-	-	-	-	-	-
Weakness	7.1	-	-	-	-	✔	4.2	-	1.4	0.5
Dermatological										
Acne flare	-	-	✔	-	-	-	-	-	-	-
Allergic skin reactions	3.8	-	-	-	-	-	✔	-	-	0.5
Burning skin	-	-	✔	-	-	-	-	-	-	-
Contact dermatitis	-	-	✔	-	-	-	-	-	-	-
Dermatological symptoms	-	-	-	-	-	-	✔	-	-	0.5
Pruritis	-	-	✔	-	-	✔	-	-	-	✔
Pustular reaction	-	-	✔	-	-	-	-	-	-	-
Rash	10.8	-	✔	✔	✔	✔	-	✔ *	-	-
Skin disorder	-	-	✔	-	-	-	-	-	-	-
Skin eruptions	-	✔	-	-	-	-	-	-	-	-
Xeroderma	-	-	✔	-	-	-	-	-	-	-
Endocrine and Metabolic										
Edema	4.9	✔	✔ ‡	-	-	-	-	✔	-	-
Hyponatremia	-	-	-	-	-	-	✔	-	-	-
Hypothermia	-	-	-	-	-	-	✔	-	-	-
SIADH	-	-	-	-	-	-	✔	-	-	-

Adverse Event	Alprazolam	Chlor-diazepoxide	Clonazepam	Clorazepate	Diazepam	Flurazepam	Lorazepam	Oxazepam	Temazepam	Triazolam
Gastrointestinal										
Abdominal distress	18.3	-	1	-	-	-	-	-	1.5	-
Anorexia	-	-	✔	-	-	✔	-	-	✔	✔
Bowel movements, frequent	-	-	✔	-	-	-	-	-	-	-
Change in appetite	-	-	✔	-	-	-	✔	-	-	-
Constipation	10.4-26.2	✔	2	-	✔	✔	✔	-	-	0.5
Decreased appetite	27.8	-	1	-	-	-	-	-	-	-
Diarrhea	10.1-20.6	-	✔	-	-	✔	-	-	1.7	0.5
Dyspepsia	-	-	✔	-	-	-	-	-	-	-
Flatulence	-	-	✔	-	-	-	-	-	-	-
Gastritis	-	-	✔	-	-	-	-	-	-	-
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	9.6-22	✔	✔	-	✔	✔	✔	✔	3.1	4.6
Pyrosis	-	-	✔	-	-	-	-	-	-	-
Upset stomach	-	-	✔	-	-	✔	-	-	-	-
Vomiting	9.6-22	-	-	-	-	✔	-	-	✔	4.6
Genitourinary										
Bladder dysfunction	-	-	✔	-	-	-	-	-	-	-
Cystitis	-	-	✔	-	-	-	-	-	-	-
Dysmenorrhea	-	-	3	-	-	-	-	-	-	-
Dysuria	-	-	✔	-	-	-	-	-	-	-
Enuresis	-	-	✔	-	-	-	-	-	-	-

Adverse Event	Alprazolam	Chlor-diazepoxide	Clonazepam	Clorazepate	Diazepam	Flurazepam	Lorazepam	Oxazepam	Temazepam	Triazolam
Genitourinary complaints	-	-	-	✔	-	✔	-	-	-	-
Incontinence	1.5	-	✔	-	✔	-	-	-	-	✔
Menstrual disorders/ irregularities	10.4	✔	✔	-	-	-	-	-	-	✔
Micturition difficulties	12.2	-	-	-	-	-	-	-	-	-
Micturition frequency	-	-	1	-	-	-	-	-	-	-
Nocturia	-	-	✔	-	-	-	-	-	-	-
Pelvic pain	-	-	✔	-	-	-	-	-	-	-
Polyuria	-	-	✔	-	-	-	-	-	-	-
Urine discoloration	-	-	✔	-	-	-	-	-	-	-
Urinary retention	-	-	✔	-	✔	-	-	-	-	✔
Urinary tract bleeding	-	-	✔	-	-	-	-	-	-	-
Urinary tract infection	-	-	1	-	-	-	-	-	-	-
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	-	-	-	-	-	✔	-	-	-	-

Adverse Event	Alprazolam	Chlor-diazepoxide	Clonazepam	Clorazepate	Diazepam	Flurazepam	Lorazepam	Oxazepam	Temazepam	Triazolam
Musculoskeletal										
Ankle pain	-	-	✔	-	-	-	-	-	-	-
Asthenia	-	-	-	-	-	-	✔	-	-	-
Arthralgia	-	-	✔	-	-	-	-	-	-	-
Back ache	-	-	-	-	-	-	-	-	✔	-
Back pain	-	-	✔	-	-	-	-	-	-	-
Feet pain	-	-	✔	-	-	-	-	-	-	-
Fracture, traumatic	-	-	✔	-	-	-	-	-	-	-
Hypertonia	-	-	✔	-	-	-	-	-	-	-
Increased muscle spasticity	-	-	-	-	✔	-	-	-	-	✔
Jaw pain	-	-	✔	-	-	-	-	-	-	-
Joint pain	-	-	-	-	-	✔	-	-	-	-
Knee pain	-	-	✔	-	-	-	-	-	-	-
Knee swelling	-	-	✔	-	-	-	-	-	-	-
Leg cramps	-	-	✔	-	-	-	-	-	-	-
Leg pain	-	-	✔	-	-	-	-	-	-	-
Lumbago	-	-	✔	-	-	-	-	-	-	-
Muscle cramps	2.4	-	✔	-	-	-	-	-	-	-
Muscle pain	-	-	✔	-	-	-	-	-	-	-
Muscle stiffness	2.2	-	-	-	-	-	-	-	-	-
Muscle weakness	-	-	✔	-	-	-	-	-	-	-
Myalgia	-	-	1	-	-	-	-	-	-	-
Rigidity	4.2	-	-	-	-	-	-	-	-	-
Shoulder pain	-	-	✔	-	-	-	-	-	-	-
Tendinitis	-	-	✔	-	-	-	-	-	-	-
Respiratory										
Apnea	-	-	-	-	-	-	✔	-	-	-
Asthmatic attack	-	-	✔	-	-	-	-	-	-	-
Bronchitis	-	-	1	-	-	-	-	-	-	-
Chest congestion	-	-	✔	-	-	-	-	-	-	-
Cough	-	-	2	-	-	-	-	-	-	-
Dypsnea	-	-	✔	-	-	-	-	-	-	-
Hyperventilation	9.7	-	-	-	-	-	-	-	-	-
Pharyngitis	-	-	2	-	-	-	-	-	-	-
Pleurisy	-	-	✔	-	-	-	-	-	-	-
Pneumonia	-	-	✔	-	-	-	-	-	-	-

Adverse Event	Alprazolam	Chlor-diazepoxide	Clonazepam	Clorazepate	Diazepam	Flurazepam	Lorazepam	Oxazepam	Temazepam	Triazolam
Rhinitis	-	-	2	-	-	-	-	-	-	-
Sinusitis	-	-	4	-	-	-	-	-	-	-
Sneezing, excessive	-	-	✔	-	-	-	-	-	-	-
Upper respiratory infection	4.3	-	8	-	-	-	-	-	-	-
Worsening of obstructive pulmonary disease	-	-	-	-	-	-	✔	-	-	-
Worsening of sleep apnea	-	-	-	-	-	-	✔	-	-	-
Other										
Abrasions	-	-	✔	-	-	-	-	-	-	-
Allergic reaction	-	-	2	-	-	-	-	-	-	-
Alopecia	-	-	✔	-	-	-	✔	-	-	-
Anaphylactic reactions	-	-	-	-	-	-	✔	-	-	-
Bitter taste	-	-	-	-	-	✔	-	-	-	-
Breast pain	-	-	✔	-	-	-	-	-	-	-
Chills	-	-	-	-	-	-	-	-	-	-
Colpitis	-	-	1	-	-	-	-	-	-	-
Congestion	-	-	-	-	-	-	-	-	-	0.5
Cramps	-	-	-	-	-	-	-	-	-	0.5-0.9
Dehydration	-	-	✔	-	-	-	-	-	-	-
Deterioration, general	-	-	✔	-	-	-	-	-	-	-
Earache	-	-	✔	-	-	-	-	-	-	-
Extrapyramidal symptoms	-	✔	-	-	-	-	✔	-	-	-
Eye irritation	-	-	✔	-	-	-	-	-	-	-
Eye twitching	-	-	✔	-	-	-	-	-	-	-
Faintness	-	-	-	-	-	✔	-	-	-	-
Falling	-	-	✔	-	-	-	-	-	-	✔
Fatigue	48.6	-	7	✔	✔	-	✔	-	-	✔
Glossitis	-	-	-	-	-	-	-	-	-	✔
Hangover	-	-	-	-	-	-	-	-	2.5	-
Hypersensitivity reactions	-	-	-	-	-	-	✔	-	-	-
Inappropriate behavior	-	-	25.0	-	-	-	-	-	-	✔
Infection	1.3	-	✔ §	-	-	-	-	-	-	-

Adverse Event	Alprazolam	Chlor-diazepoxide	Clonazepam	Clorazepate	Diazepam	Flurazepam	Lorazepam	Oxazepam	Temazepam	Triazolam
Influenza	-	-	4	-	-	-	-	-	-	-
Lymphadenopathy	-	-	✔	-	-	-	-	-	-	-
Malaise	-	-	✔	-	-	-	-	-	-	-
Motion sickness	-	-	✔	-	-	-	-	-	-	-
Nasal congestion	7.3-17.4	-	-	-	-	-	-	-	-	-
Nosebleed	-	-	✔	-	-	-	-	-	-	-
Pain	-	-	✔	-	-	✔	-	-	-	0.5-0.9
Salivation changes, unspecified	-	-	-	-	✔	-	-	-	-	-
Salivation, decreased	32.8	-	-	-	-	-	-	-	-	-
Salivation, increased	4.2-5.6	-	✔	-	-	✔	-	-	-	-
Shivering	-	-	✔	-	-	-	-	-	-	-
Sore gums	-	-	✔	-	-	-	-	-	-	-
Stimulation/ overstimulation	-	-	-	-	✔	✔	-	-	✔	✔
Stomatitis	-	-	-	-	-	-	-	-	-	✔
Suicidal ideation	-	-	✔	-	-	-	✔	-	-	-
Sweating	15.1	-	-	-	-	✔	-	-	-	-
Thirst	-	-	✔	-	-	-	-	-	-	-
Tinnitus	6.6	-	-	-	-	-	-	-	-	0.5
Taste alteration	-	-	✔	-	-	-	-	-	-	0.5
Thrombophlebitis	-	-	✔	-	-	-	-	-	-	-
Toothache	-	-	✔	-	-	-	-	-	-	-
Visual field defect	-	-	✔	-	-	-	-	-	-	-
Weight gain	2.7-27.2	-	✔	-	-	-	-	-	-	-
Weight loss	2.3-22.6	-	✔	-	-	-	-	-	-	-
Yawning	-	-	✔	-	-	-	-	-	-	-

✔ Percent not specified
- Event not reported or incidence <1%
* Minor diffuse skin rashes, including morbilliform, urticarial, and maculopapular
†Death from hepatic failure in a patient also receiving diuretic drugs
‡Ankle, foot, facial and periorbital edema
§Includes mycotic infection, viral infection, streptococcal infection, herpes simplex infection, mononucleosis, and moniliasis.
EEG=Electroencephalogram
SIADH=Syndrome of inappropriate antidiuretic hormone
SGOT=Serum glutamic oxaloacetic transaminase
SGPT=Serum glutamic pyruvic transaminase

VII. Dosing and Administration

The usual dosing regimens for the benzodiazepines are summarized in Table 7.

Table 7. Usual Dosing for the Benzodiazepines[2-5]

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
Alprazolam	Anxiety: Initial: immediate-release, 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: Immediate-release, 0.5 mg orally three times daily; may increase dosage by up to 1 mg every three to four days; usual dosage range is 1 to 10 mg/day (mean, 5 to 6 mg/day) Extended-release, initial, 0.5 to 1 mg orally in the morning, may increase dosage by up to 1 mg/day every three to four days; usual dosage range is 3 to 6 mg/day; maximum: 10 mg/day	Safety and efficacy in children less than 18 years old have not been established.	Orally disintegrating tablet: 0.25 mg 0.5 mg 1 mg 2 mg Tablet, immediate-release: 0.25 mg 0.5 mg 1 mg 2 mg Tablet, sustained-release: 0.5 mg 1 mg 2 mg 3 mg
Chlordiazepoxide	Alcohol Withdrawal Syndrome: 50-100 mg intramuscular (IM) or intravenous (IV) every two to four hours as needed; maximum: 300 mg in 24 hours 50-100 mg orally initially, to be followed by repeated doses as needed until agitation is controlled; maximum: 300 mg/day; dosage then may be reduced to maintenance levels 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 about Treatment, Preoperative: 5 to 10 mg orally three to four times a day on days preceding surgery	Anxiety about Treatment, Preoperative: (6 years and older) 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 Ampule: 100 mg

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
	50 to 100 mg IM one hour prior to surgery		
Clonazepam	Panic Disorder: Initial, 0.25 mg orally twice daily for three days, then 0.5 mg twice daily; maintenance, may increase dosage by 0.125 to 0.25 mg orally twice daily every three days; maximum: total daily dose of 1-4 mg (divided into two to three daily doses) Seizure: Initial, 0.5 mg orally three times daily; maintenance, may increase daily dose by 0.5 to 1 mg orally every three days; maximum: total daily dose of 20 mg (divided into three daily doses)	Seizure: Up to 10 years of age or up to 30 kg: initial, 0.01 to 0.03 mg/kg/day orally divided into two to three daily doses; maintenance, 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 (divided into three daily doses)	Tablet: 0.5 mg 1 mg 2 mg Orally disintegrating tablet: 0.125 mg 0.25 mg 0.5 mg 1 mg 2 mg
Clorazepate	Alcohol Withdrawal Syndrome: Day 1: initial 30 mg orally, then 30 to 60 mg orally for the remainder of the day in divided doses; 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 after: 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 (in divided doses) Epilepsy, Adjunct: Initial, 7.5 mg orally three times daily; maintenance, increase dose by 7.5 mg/week; maximum: 90 mg/day orally (divided doses)	Epilepsy, Adjunct: Children 9 to 12 years: initial, 7.5 mg orally twice daily; maintenance, may increase dose by 7.5 mg/week; maximum: 60 mg/day orally (divided doses)	Tablet, immediate-release: 3.75 mg 7.5 mg 15 mg Tablet, sustained-release: 11.25 mg 22.5 mg
Diazepam	Alcohol Withdrawal Syndrome: Initial, 10 mg orally three to four times a day for 1 day; maintenance, 5 mg orally three to four times a day as needed 10 mg IM or IV, then 5 to 10 mg IM or IV in three to four hours if needed Anxiety: 2 to 10 mg orally two to four times a day 2 to 10 mg IM or IV every three to four hours if needed Anxiety about Treatment–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: Initial, 1 to 2.5 mg orally three to four times daily; increase gradually as needed Seizure, Adjunct: 6 months or older: initial, 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 2 to 5 years: initial, 0.5 mg/kg	Ampule, disposable syringe, vial: 5 mg/mL Oral concentrate: 5 mg/mL Oral solution: 5 mg/5 mL Rectal gel: 2.5 mg 5 mg 12.5 mg

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
	Anxiety about Treatment–Endoscopic Procedure: 5 to 10 mg IM 30 minutes prior to procedure 10 mg or less IV immediately prior to procedure; maximum: 20 mg Seizure, Adjunct: 2 to 10 mg orally two to four times a day; if recurrent, 5 to 10 mg IV every ten to fifteen minutes as needed; maximum: 30 mg; may repeat in two to four hours if needed 0.2 mg/kg rectally; may repeat in four to twelve hours Skeletal Muscle Spasm: 2 to 10 mg orally three to four times daily 5 to 10 mg IM or IV and repeat in three to four hours if needed Status Epilepticus: Initial, 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	rectally and may repeat in four to twelve hours; 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; if refractory, 0.5 mg/kg gel rectally, may repeat in four to twelve hours 6 to 11 years, initial, 0.3 mg/kg rectally, may repeat in four to twelve hours; if severe, 1 mg IV slowly (preferred) or IM every two to five minutes up to maximum of 10 mg and repeat in two to four hours if needed; if refractory, 0.3 mg/kg gel rectally, may repeat in four to twelve hours if needed 12 years and older, initial, 0.2 mg/kg rectally, may repeat in four to twelve hours; if severe, 1 mg IV slowly (preferred) or IM every two to five minutes up to maximum of 10 mg and repeat in two to four hours if needed; if refractory, 0.2 mg/kg gel rectally, may repeat in four to twelve hours if needed Skeletal Muscle Spasm, Adjunct: 6 months or older: initial, 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 or older: 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 30 days to 5 years of age: 0.5 mg/kg rectally 5 years or older: 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	Tablet: 2 mg 5 mg 10 mg

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
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: 0.05 mg/kg IM two hours before procedure; maximum: 4 mg/dose 0.044 mg/kg IV or 2 mg (whichever is less); maximum: 0.05 mg/kg IV or 4 mg (whichever is less) Status Epilepticus: 4 mg IV (given slowly, 2 mg/minute), may repeat dose in ten to fifteen minutes if needed; IM dosing may be used, but IV dosing is preferred	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 and older: 2 to 4 mg orally at bedtime Status Epilepticus: 0.05 to 0.1 mg/kg IV; maximum: 4 mg/dose	Ampule, disposable syringe, vial: 2 mg/mL 4 mg/mL Oral solution: 2 mg/mL Tablet: 0.5 mg 1 mg 2 mg
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 and older: 15 to 30 mg orally three to four times daily Anxiety, Mild to Moderate: 12 years and older: 10 to 15 mg orally three to four times daily Anxiety, Severe: 12 years and older: 15 to 30 mg orally three to four times daily	Capsule: 10 mg 15 mg 30 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 30 mg
Triazolam	Insomnia: Initial: 0.25 mg orally at bedtime; maximum: 0.5 mg/dose	Safety and efficacy in children have not been established.	Tablet: 0.125 mg 0.25 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the benzodiazepines are summarized in Table 8.

Table 8. Comparative Clinical Trials Using the Benzodiazepines

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Alcohol Withdrawal				
Holbrook et al[32] Various benzodiazepines (chlordiazepoxide: 5 trials, diazepam: 3 trials, oxazepam: 2 trials, lorazepam: 1 trial) vs alternative active treatments, 9 trials total (bromocriptine, carbamazepine, chlorpromazine, clonidine, doxepin, ethanol, hydroxyzine, paraldehyde, propranolol, thiamine) vs placebo	MA Patients being treated for acute alcohol withdrawal	11 trials N=1,286 Duration varied (1 to 180 days)	Primary: Improvement of withdrawal symptoms, therapeutic success (CIWA-Ar score ≤10), adverse effect rates, dropout rates Secondary: Not reported	Primary: In 3 studies with a similar outcome measure, the benzodiazepines studied 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). Secondary: Not reported
Ntais et al[33] Benzodiazepines alone or in combination with other agents vs other agents (eg, anticonvulsants)	MA Patients with alcohol dependence diagnosed with appropriate standardized criteria (per	N=4,051 Durations varied or were unclear	Primary: Severity of overall alcohol withdrawal syndrome, alcohol withdrawal seizures, alcohol withdrawal delirium	Primary: Compared to placebo, there was a large benefit against alcohol withdrawal seizures seen with the benzodiazepines (*P*=0.01). 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 very limited preventing informative

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs alternate benzodiazepines vs placebo	DSM) who experienced alcohol withdrawal		Secondary: Adverse events, discontinuations due to side effects, number of withdrawals per arm, mortality,	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.
Anxiety Disorders				
Mitte et al[34] Benzodiazepines (mostly diazepam, alprazolam, lorazepam) vs azapirones (mostly buspirone) vs placebo	MA Patients with GAD	48 trials N=12,053 Not reported (minimum duration for inclusion was 14 days)	Primary: Anxiety (Hamilton Rating Scale for Anxiety [HAM-A]), depression (Hamilton Rating Scale for Depression [HAM-D]), clinical significance Secondary: Not reported	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 azapirones (*P* value not reported). Significantly fewer patients in the benzodiazepine group dropped out of the study (20.5% vs 30.7%, *P*<0.05). Secondary: Not reported
Blanco et al[35] Benzodiazepines (clonazepam, bromazepam*,	MA Patients being treated for social	23 trials N=2,954	Primary: Outcome data on the Liebowitz Social Anxiety	Primary: In terms of LSAS, no statistical difference was detected between medications or medication groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
alprazolam) or antidepressants (SSRI [fluvoxamine, paroxetine, sertraline], MAOI [phenelzine], reversible inhibitor of monoamine-oxidase-A [RIMA; moclobemide*, brofaromine*]) or β-blockers (atenolol) or gabapentin or buspirone vs placebo	anxiety disorder	Duration varied (6-20 weeks)	Scale (LSAS) or a categorical measure of status Secondary: Proportion of responders with Clinical Global Impression of Change (CGI) score of 1 or 2 (ie, "very much" or "much improved," respectively)	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] Benzodiazepines vs antidepressants vs psychological panic management	MA Patients being treated for panic disorder with or without agoraphobia	106 trials N=5,011 Duration varied	Primary: Panic, agoraphobia, depression, and general anxiety Secondary: Not reported	Primary: Antidepressants, psychological panic management and antidepressants/exposure in vivo combination demonstrated significant improvement compared to a control condition in reduction of panic, agoraphobia, depression, and anxiety. High-potency benzodiazepines showed significant improvement to control condition only in panic, agoraphobia, and anxiety. There were no significant differences in treatments for panic disorder.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs exposure in vivo vs placebo Combinations of the above treatment arms were also investigated.				Antidepressant/exposure in vivo test groups had significant improvements compared to other treatments except exposure in vivo in agoraphobia. A significantly greater improvement was noted in antidepressant/exposure in vivo compared to exposure in vivo alone and psychological panic management/exposure in vivo in treatment of depression and anxiety. Secondary: Not reported
Chessick et al[37] Benzodiazepines (alprazolam: 2 trials, bromazepam*: 1 trial, clobazam*: 1 trial, clorazepate: 1 trial, diazepam: 13 trials, lorazepam: 6 trials, oxazepam: 1 trial and benzodiazepines not specified: 1 trial) vs azapirones (buspirone: 29 trials, gepirone*: 2 trials, ipsapirone*: 4 trials, and lesopitron*: 1 trial) The meta-analysis also compared the azapirones to hydroxyzine, kava kava, placebo, venlafaxine and psychotherapy, but only the results from studies comparing the azapirones to the benzodiazepines are reported in this review.	MA, PG, PRO, RCT Outpatients diagnosed GAD	36 trials N=5,908 4-14 weeks	Primary: HAM-A, Clinical Global Impression [CGI]), acceptability (drop out rates, specific side effects) Secondary: Not reported	Primary: Using the HAM-A assessment, lorazepam (N=40, WMD: 1.1; 95% CI: 0.29 to 1.91, *P*=0.008) and alprazolam (N=39, 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 (N=19, WMD: -0.20; 95% CI: -7.45 to 7.05, *P*=0.96). Another small study (N=51) 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 (*P* values not reported). Significantly fewer participants dropped out on benzodiazepines 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, 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)

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
Insomnia				
Holbrook et al[38] Benzodiazepines (triazolam: 16 trials, flurazepam: 14 trials, temazepam: 13 trials, midazolam: 5 trials, nitrazepam*: 4 trials, estazolam: 2 trials, lorazepam, diazepam, brotizolam*, quazepam^, loprazolam* and flunitrazepam*: 1 trial) vs zopiclone*: 13 trials or diphenhydramine, glutethimide, promethazine: 1 trial or cognitive behavioral therapy: 1 trial or placebo: 4 trials	MA Patients with insomnia receiving benzodiazepines as compared to placebo or an active agent	45 trials N=2,672 Duration varied (1 day to 6 weeks, mean 12.2 days)	Primary: Sleep latency, total sleep duration, adverse effects, dropout rates, cognitive function decline Secondary: Not reported	Primary: Using sleep records, benzodiazepines demonstrated a decrease in sleep latency by 4.2 minutes compared to placebo, though not significant (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 than placebo to be associated with complaints of daytime drowsiness (OR 2.4, 95% CI: 1.8 to 3.4), dizziness or lightheadedness (OR 2.6, 95% CI: 0.7 to 10.3); 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 a nonsignificant difference in terms of adverse events (OR 1.5, 95% CI: 0.8 to 2.9). Comparisons between benzodiazepines and antihistamines did not detect any significant differences on sleep outcomes. In 1 trial where a benzodiazepine was compared to behavioral therapy, triazolam was found to be more effective in reducing sleep latency early in the trial, but efficacy decreased by the second week of treatment. Behavioral therapy efficacy was maintained throughout the 9-week follow-up. Secondary: Not reported
Smith et al[39]	MA	21 trials	Primary: Sleep latency, total	Primary: Sleep latency was reduced by 30% with pharmacological treatment

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Benzodiazepines (flurazepam, quazepam^, triazolam, lorazepam, midazolam^): 6 trials or benzodiazepine receptor agonists (zolpidem, zopiclone*): 2 trials vs behavioral treatment: 14 trials vs placebo One trial directly compared pharmacotherapy with a benzodiazepine (temazepam) and behavioral therapy.	Patients with primary insomnia for 1 month or longer	N=470 Duration varied (<1 week to 10 weeks)	sleep time, number of awakenings, wake time after sleep onset, and sleep quality before and after treatment Secondary: Not reported	compared with 43% with behavioral interventions. Pharmacotherapy increased total sleep time by 12% and behavior therapy by 6%. 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% and behavior therapy by 28% 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) Secondary: Not reported
Nowell et al[40] Benzodiazepines (estazolam^: 6 trials, flurazepam: 10 trials, lorazepam: 1 trial, quazepam^: 3 trials, temazepam: 3 trials, triazolam: 4 trials) or zolpidem (5 trials) vs placebo	MA of 22 trials (from 1978-1996); DB, PC, RCT, XO Adults <65 years with chronic insomnia	22 trials N=1,894 Median duration of 7 days, range 4 to 35 days	Primary: Sleep latency, TST, number of awakenings, sleep quality Secondary: Not reported	Primary: Zolpidem and benzodiazepines were significantly more effective than placebo with regards to sleep latency, TST, number of awakenings and sleep quality ($P<0.001$). Secondary: Not reported Note: This meta-analysis did not compare the efficacy of zolpidem to benzodiazepines.
Buscemi et al[41] Benzodiazepines (52 trials including	MA of 105 trials (up to July 2006); DB, PC,	105 trials N varied,	Primary: Sleep latency, WASO, sleep	Primary: Sleep latency assessed by PSG was significantly decreased for benzodiazepines (WMD: -10.0 minutes; 95% CI: -16.6 to -3.4),

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
brotizolam*, estazolam^, flunitrazepam*, flurazepam, loprazolam*, lorazepam, lormetazepam*, nitrazepam*, quazepam^, temazepam and triazolam) or nonbenzodiazepines (48 trials including eszopiclone, gaboxadol*, indiplon*, zaleplon, zolpidem and zopiclone*) or antidepressants (8 trials including doxepin, pivagabine*, trazodone and trimipramine) vs placebo (105 trials) Some trials had multiple treatment arms.	RCT Adults with chronic insomnia	range 6 to 1,507 Duration varied (1 night to 6 months)	efficiency, sleep quality, TST, adverse events Secondary: Not reported	nonbenzodiazepines (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), nonbenzodiazepines (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 nonbenzodiazepines 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 nonsignificantly favored antidepressants for WASO and nonsignificantly favored placebo for TST. (*P* values were not reported.) Indirect comparisons between benzodiazepines and nonbenzodiazepines resulted in no significant difference in sleep latency; however, benzodiazepines were associated with more adverse events (*P* value not reported). Indirect comparisons between benzodiazepines and antidepressants resulted in no significant difference in sleep latency or adverse events (*P* values not reported). Indirect comparisons between nonbenzodiazepines and antidepressants resulted in a significantly greater sleep latency assessed by PSG but not by sleep diary for nonbenzodiazepines. There was no significant difference in adverse events. (*P* values were not reported.) 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, nonbenzodiazepines and antidepressants, respectively, compared to placebo. The adverse events most commonly reported in these studies were headache, drowsiness, dizziness and nausea.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
Hindmarch et al[42] Zolpidem, modified release (MR) 6.25 mg vs zolpidem MR 12.5 mg vs flurazepam 30 mg vs placebo	DB, DD, RCT, XO Healthy volunteers at least 65 years of age	N=24 Single dose, treatment visits lasted 2 days and were separated by 28-42 days washout	Primary: Psychometric tests performed 8 hours after study medication (CFF, CRT, word recall, CTT, DSST), subjective evaluation of sleep (LSEQ), safety, pharmacokinetics (zolpidem MR only) Secondary: Not reported	Primary: There were no significant differences in psychometric tests between either dose of zolpidem MR 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 MR and with flurazepam (all $P<0.05$). Neither zolpidem MR nor flurazepam modified perception of well-being on awakening (*P* values not reported). 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. Secondary: Not reported
Okawa et al[43] 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	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 Secondary: Not reported	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.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	3 or more awakenings			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. Nineteen patients reported drowsiness, dizziness, nausea and lightheadedness. Secondary: Not reported
Seizures				
Pavlidou et al[44] Intermittent rectal diazepam 0.33 mg/kg every 8 hours (first day) followed by every 12 hours on the next day (maximum 7.5 mg/dose) 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 Secondary: Not reported	Primary: The 36-month recurrence rates in the no treatment group compared to the diazepam group were: 83% vs 38% (high risk patients; $P=0.005$), 55% vs 35% (intermediate risk patients; $P=0.341$), and 46% vs 33% (low risk patients; $P=0.412$). Secondary: Not reported
Appleton et al[45] Lorazepam intravenously or rectally (dose not specified) vs diazepam intravenously or rectally (dose not specified)	MA Children between ages 1 month to 16 years presenting to an Accident and Emergency department or to	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,	Primary: 1-2 intravenous doses stopped the convulsion in 70% (19/27) of lorazepam-treated patients compared to 65% (22/34) 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% (6/27) of intravenous lorazepam-treated children and 35% (12/34) of intravenous diazepam-treated children experienced a

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	a hospital ward in an acute tonic-clonic convulsion		admission to intensive care unit) Secondary: Not reported	further convulsion within 24 hours after presentation (RR 0.63 [95% CI: 0.27 to 1.46]). Approximately 4% (1/27) versus 15% (5/34) of patients receiving intravenous lorazepam compared to intravenous diazepam, respectively, 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% (1/27) compared to 21% (7/34) in the diazepam-treated group (RR 0.18 [95% CI: 0.02 to 1.37]). Secondary: Not reported
Treiman et al[46] Phenobarbital 15 mg/kg vs diazepam 0.15 mg/kg followed by phenytoin 18 mg/kg vs lorazepam 0.1 mg/kg vs phenytoin 18 mg/kg	DB, MC, 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 Secondary: Not reported	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. Secondary: Not reported
Adverse Events				
Leufkens et al[47] alprazolam extended-release (XR) 1 mg vs	DB, PC, XO Healthy individuals aged 20-45 years	N=18 Up to 5.5 hours after administra-tion	Primary: Comparison of effects on actual driving ability (as assessed in a standard on-the-	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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
alprazolam immediate-release (IR) 1 mg vs placebo			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	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 (*P* value not reported).

*Agent not available in the US
^Product not covered by Alabama Medicaid
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, SSRI=Selective serotonin reuptake inhibitor, XR=extended-release

Additional Evidence

Dose Simplification
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Stable Therapy
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Impact on Physician Visits
An evidence-based medicine literature search 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 Benzodiazepines

Generic Name	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
alprazolam	sustained-release tablet, tablet	Xanax®*‡, Xanax XR®‡	$$$-$$$$	$
chlordiazepoxide	capsule, injection	Librium®*	$$$-$$$$$	$
clonazepam	orally disintegrating tablet, tablet	Klonopin®*	$$$$	$
clorazepate	sustained-release tablet, tablet	Tranxene SD®, Tranxene T-Tab®*,	$$$$$	$$$
diazepam	injection, oral concentrate, rectal gel, solution, tablet	Valium®*‡, Diastat®	$$$$$	$
flurazepam	capsule	Dalmane®*	$$$	$
lorazepam	injection, oral concentrate, tablet	Ativan®*, Lorazepam Intensol®	$$$-$$$$	$
oxazepam	capsule	Serax®*	$$$$	$$
temazepam	capsule	Restoril®*	$$$$	$
triazolam	tablet	Halcion®*	$$$	$

*Generic is available in at least one dosage form or strength.
†Brand is no longer available.
‡Product is currently not covered by Alabama Medicaid.
N/A=not available

X. Conclusions

While the long-term use of benzodiazepines is generally discouraged due to concerns about dependence and side effects, they still maintain an important place in therapy for certain patients. Benzodiazepines are used primarily for the treatment of anxiety disorders, for the short-term treatment of insomnia, and as an adjunct therapy for epilepsy. In addition, some of these agents are FDA approved for treatment of acute alcohol withdrawal and as muscle relaxants. According to the most current clinical guidelines, benzodiazepines may be considered as a first-line therapy option in panic disorders and generalized anxiety disorders when the patient is experiencing acute anxiety reactions. These same guidelines recognize that a preponderance of clinical evidence supports the use of SSRI antidepressants, rather than benzodiazepines, in anxiety states, and that the SSRI medications have a more favorable safety profile.

In regards to the treatment of insomnia, almost half of the agents within this review are indicated for the short-term treatment of insomnia. Currently, there are no guidelines that recommend one particular pharmacological agent as a first-line therapy choice in the treatment of insomnia. Cognitive behavioral therapy is a nonpharmacological treatment option that may be more effective than drug therapy.[8] A meta-analysis conducted by Smith et al of 21 trials concluded that behavioral therapy is more effective than benzodiazepines in latency to sleep onset and equally effective in total sleep time, number of awakenings, wake time after sleep onset, and sleep quality.[39] Current guidelines for the management of chronic insomnia recommend behavioral therapy as a first-line therapy.

Benzodiazepines are recommended over nonbenzodiazepine sedative hypnotics for the management of alcohol withdrawal that is classified as moderate-to-severe in nature, or in patients with a history of withdrawal seizures or serious comorbid conditions. No particular benzodiazepine was found to be safer or more efficacious in the relief of symptoms, nor is any particular benzodiazepine recommended in the relevant clinical guidelines.[14,32,33]

Benzodiazepines are also considered to be a first-line agent for the treatment of patients with convulsive status epilepticus. In an outpatient scenario where there may be no IV access, and where the medication may be administered by a nonhealthcare professional, the rectal administration of diazepam is the preferred initial intervention. Currently, the only available rectal benzodiazepine formulation is the brand Diastat®.

All of the benzodiazepines included in this review are available generically in at least one oral dosage form. Direct-comparison trials within this class are limited and there is insufficient evidence that demonstrates that one benzodiazepine is more effective than another. Diastat® provides a beneficial route of administration over generic agents for its primary indication, status epilepticus.

Therefore, with the exception of Diastat®, all brand products within the class reviewed are comparable to each other and to the generics and over-the-counter products in this class and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

With the exception of diazepam rectal gel, no brand benzodiazepine is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

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

References

1. Dubovsky S. Benzodiazepine receptor agonists and antagonists. In: Sadock B, Sadock V, editors. Kaplan & Sadock's comprehensive textbook of psychiatry [monograph on the internet]. 8th ed. Philadelphia: Lippincott Williams & Wilkins; 2005 [cited 2007 Jul 16].. Available from: http://www.r2library.com/marc_frame.aspx?ResourceID=214.
2. Micromedex® Healthcare Series [database on the internet]. Greenwood Village (CO): Thomson Micromedex, 2007 [cited 2007 Jul 16]. Available from: http://www.thomsonhc.com/.
3. Drug Facts and Comparisons 4.0 [database on the internet]. St. Louis: Wolters Kluwer Health, Inc.; 2007 [cited 2007 Jul 16]. Available from: http://online.factsandcomparisons.com.
4. Central nervous system agents 28:00, Anticonvulsants 28:12, Benzodiazepines 28:12.08. In: McEvoy GK, editor; American Hospital Formulary Service. AHFS drug information 2007 [monograph on the Internet]. Bethesda (MD): American Society of Health-System Pharmacists; 2007 [cited 2007 Aug 9]. Available from: http://online.statref.com.
5. Central nervous system agents 28:00, Anxiolytics, Sedatives, and Hypnotics 28:24, Benzodiazepines 28:24.08. In: McEvoy GK, editor; American Hospital Formulary Service. AHFS drug information 2007 [monograph on the Internet]. Bethesda (MD): American Society of Health-System Pharmacists; 2007 [cited 2007 Aug 9]. Available from: http://online.statref.com.
6. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th ed, text revision. [monograph on the internet]. Washington: American Psychiatric Association, 2000 [cited 2007 Jul 16]. Available from: http://online.statref.com/.
7. Morgenthaler T, Kramer M, Alessi C, Friedman L, Boehlecke B, Brown T, et al; American Academy of Sleep Medicine. Practice parameters for the psychological and behavioral treatment of insomnia: an update. An American Academy of Sleep Medicine report. Sleep. 2006 Nov 1;29(11):1415-9. Available from: http://www.aasmnet.org/PracticeParameters.aspx?cid=109.
8. NIH State-of-the-Science Conference statement on manifestations and management of chronic insomnia in adults. NIH Consens Sci Statements [serial on the Internet]. 2005 Jun 13-15 [cited 2007 Aug 8]; 22(2) 1-30. Available from: http://consensus.nih.gov/2005/2005InsomniaSOS026PDF.pdf.
9. Treatment of insomnia. Treat Guidel Med Lett. 2006 Feb;4(42):5-10.
10. Ballenger J, Davidson J, Lecrubier Y, Nutt D, Baldwin D, den Boer J, et al. Consensus statement on panic disorder from the International Consensus Group on Depression and Anxiety. J Clin Psychiatry. 1998;59 Suppl 8:47-54.
11. Ballenger J, Davidson J, Lecrubier Y, Nutt DJ, Borkovec T, Rickels K, et al. Consensus statement on generalized anxiety disorder from the International Consensus Group on Depression and Anxiety. J Clin Psychiatry. 2001;62 Suppl 11:53-8.
12. McIntosh A, Cohen A, Turnbull N, Esmonde L, Dennis P, Eatock J, et al. Clinical guidelines for the management of anxiety. Management of anxiety (panic disorder, with or without agoraphobia, and generalized anxiety disorder) in adults in primary, secondary and community care [guideline on the internet]. London (UK): National Institute for Clinical Excellence (NICE); 2004 Dec [cited 2007 Jul 30]. Available from: http://guidance.nice.org.uk/CG22/guidance/pdf/English.
13. Ballenger J, Davidson J, Lecrubier Y, Nutt D, Bobes J, Beidel D, Ono Y, et al. Consensus statement on social anxiety disorder from the International Consensus Group on Depression and Anxiety. J Clin Psychiatry. 1998;59 Suppl 17:54-60.
14. Mayo-Smith MF. Pharmacological management of alcohol withdrawal. A meta-analysis and evidence-based practice guideline. American Society of Addiction Medicine Working Group on Pharmacological Management of Alcohol Withdrawal. JAMA. 1997 Jul 9;278(2):144-51.
15. Appleton R, Choonara I, Martland T, Phillips B, Scott R, Whitehouse W. The treatment of convulsive status epilepticus in children. The Status Epilepticus Working Party, Members of the Status Epilepticus Working Party. Arch Dis Child. 2000 Nov;83(5):415-9.
16. Wheless JW, Clarke DF, Carpenter D. Treatment of pediatric epilepsy: expert opinion, 2005. J Child Neurol. 2005 Dec;20 Suppl 1:S1-56.
17. Meierkord H, Boon P, Engelsen B, Göcke K, Shorvon S, Tinuper P, et al. EFNS guideline on the management of status epilepticus. Eur J Neurol. 2006; 13:445-50.
18. Xanax® (alprazolam) [package insert]. New York (NY): Pfizer, Inc.; March 2006.
19. Librium® (chlordiazepoxide) [package insert]. Costa Mesa (CA): ICN Pharmaceuticals, Inc.; September 2001.
20. Klonopin® (clonazepam) [package insert]. Nutley (NJ): Roche Laboratories, Inc.; July 2001.
21. Tranxene® (clorazepate) [package insert]. Deerfield (IL): Ovation Pharmaceuticals, Inc.; April 2005.
22. Valium® (diazepam) [package insert]. Nutley (NJ): Roche Laboratories, Inc.; March 2000.
23. Dalmane® (flurazepam) [package insert]. Costa Mesa (CA): ICN Pharmaceuticals, Inc.; September 2001.
24. Ativan® (lorazepam) [package insert]. Philadelphia (PA): Wyeth Laboratories; October 2002.
25. Oxazepam [package insert]. Princeton (NJ): Sandoz, Inc.; July 2006.

26. Restoril® (temazepam) [package insert]. St. Louis (MO): Mallinckrodt, Inc.; April 2007.
27. Halcion® (triazolam) [package insert]. New York (NY): Pharmacia & Upjohn Company (Pfizer, Inc.); 2007 May.
28. FDA news. FDA requests label change for all sleep disorder drug products. Rockville, MD: US Food and Drug Administration; 2007 Mar 14 [cited 2007 Aug 14] Available from: http://www.fda.gov/bbs/topics/NEWS/2007/NEW01587.html.
29. Roth T, Roehrs TA. A review of the safety profiles of benzodiazepine hypnotics. J Clin Psychiatry. 1991 Sep;52 Suppl:38-41.
30. Moller HJ. Effectiveness and safety of benzodiazepines. J Clin Psychopharmacol. 1999 Dec;19(6 Suppl 2):2S-11S.
31. Rickels K, DeMartinis N, Rynn M, Mandos L. Pharmacologic strategies for discontinuing benzodiazepine treatment. J Clin Psychopharmacol. 1999 Dec;19(6 Suppl 2):12S-6S.
32. Holbrook A, Crowther R, Lotter A, Cheng C, King D. Meta-analysis of benzodiazepine use in the treatment of acute alcohol withdrawal. CMAJ. 1999 Mar 9;160(5):649-55.
33. Ntais C, Pakos E, Kyzas P, Ioannidis JP. Benzodiazepines for alcohol withdrawal. Cochrane Database Syst Rev. 2005 Jul 20;(3):CD005063.
34. Mitte K, Noack P, Steil R, Hautzinger M. A meta-analytic review of the efficacy of drug treatment in generalized anxiety disorder. J Clin Psychopharmacol. 2005 Apr;25(2):141-50.
35. Blanco C, Schneier F, Schmidt A, Blanco-Jerez C, Marshall R, Sanchez-Lacay A et al. Pharmacological treatment of social anxiety disorder: a meta-analysis. Depress Anxiety. 2003;18(1):29-40.
36. van Balkom AJ, Bakker A, Spinhoven P, Blaauw BM, Smeenk S, Ruesink B. A meta-analysis of the treatment of panic disorder with or without agoraphobia: a comparison of psychopharmacological, cognitive-behavioral, and combination treatments. J Nerv Ment Dis. 1997 Aug;185(8):510-6.
37. Chessick CA, Allen MH, Thase M, Batista Miralha da Cunha AB, Kapczinski FF, de Lima MS, et al. Azapirones for generalized anxiety disorder. Cochrane Database Syst Rev. 2006 Jul 19;3:CD006115.
38. Holbrook A, Crowther R, Lotter A, Cheng C, King D. Meta-analysis of benzodiazepine use in the treatment of insomnia. CMAJ. 2000 Jan 25;162(2):225-33.
39. Smith MT, Perlis ML, Park A, Smith MS, Pennington J, Giles DE, Buysse DJ. Comparative meta-analysis of pharmacotherapy and behavior therapy for persistent insomnia. Am J Psychiatry. 2002 Jan;159(1):5-11.
40. Nowell PD, Mazumdar S, Buysse DJ, Dew MA, Reynolds CF, Kupfer DJ. Benzodiazepines and zolpidem for chronic insomnia. A meta-analysis of treatment efficacy. JAMA. 1997 Dec 24/31;278(24):2170-7.
41. Buscemi N, Vandermeer B, Friesen C, Bialy L, Tubman M, Ospina M, Klassen TP, Witmans M. The efficacy and safety of drug treatments for chronic insomnia in adults: a meta-analysis of RCTs. J Gen Intern Med. 2007 Sep;22(9):1335-50.
42. Hindmarch I, Legangneux E, Stanley N, Emegbo S, Dawson J. A double-blind, placebo-controlled investigation of the residual psychomotor and cognitive effects of zolpidem-MR in healthy elderly volunteers. Br J Clin Pharmacol. 2006;62(5):538-45.
43. Okawa KK, Allens G. A clinical comparison of triazolam with placebo and with secobarbital in insomniac patients. J Int Med Res. 1978;6(4):343-7.
44. Pavlidou E, Tzitiridou M, Panteliadis. Effectiveness of intermittent diazepam prophylaxis in febrile seizures: Long-term prospective controlled study. J Child Neurol. 2006; 21:1036-40.
45. Appleton R, Martland T, Phillips B. Drug management for acute tonic-clonic convulsions including convulsive status epilepticus in children. Cochrane Database Syst Rev. 2002;(4):CD001905.
46. Treiman D, Meyers P, Walton N, Collins J, Colling C, Rowan AJ, et al. A comparison of four treatments for generalized convulsive status epilepticus. Veterans Affairs Status Epilepticus Cooperative Study Group. N Engl J Med. 1998 Sep 17;339(12):792-8.
47. Leufkens TR, Vermeeren A, Smink BE, van Ruitenbeek P, Ramaekers JG. Cognitive, psychomotor and actual driving performance in healthy volunteers after immediate and extended release formulations of alprazolam 1 mg. Psychopharmacology. 2007; 191:951-9

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Anxiolytics, Sedatives, and Hypnotics
Miscellaneous Anxiolytics, Sedatives, and Hypnotics AHFS Class 282492
November 14, 2007

I. Overview

The American Hospital Formulary Service (AHFS) class of miscellaneous anxiolytics, sedatives, and hypnotics includes medications not classified as barbiturates or benzodiazepines that are used primarily for the treatment of insomnia, induction of sedation and relief of anxiety disorders. There are 11 agents in this class and they differ in their structures, mechanisms of action, and pharmacologic profiles.

Primary insomnia is poor-quality sleep or difficulty in initiating or maintaining sleep that lasts for at least one month, causing marked distress or impairment in occupational, social, or other important areas of functioning.[1] In primary insomnia, the sleep disturbance is not due to another sleep disorder (eg, narcolepsy), mental illness, medication(s), drug of abuse, or general medical condition.[1] Insomnia may be further classified as transient insomnia (1-3 nights), short-term insomnia (3 nights to 1 month), and chronic insomnia ($\geq$1 month), based upon the duration of symptoms.[2] In the United States (US), at least one-third of adults are estimated to have experienced intermittent symptoms of insomnia, with at least 10% experiencing chronic insomnia.[2] Management of insomnia is most effective when the choice of treatment is patient specific, taking into consideration the patient's age, duration and severity of symptoms, and etiology of insomnia if known.[3] All pharmacotherapy should be used with appropriate caution, at minimum effective doses and for a minimum duration of time.[2] Nonpharmacologic strategies have been shown to be effective in the treatment of insomnia, and for some patients may be more effective than drugs for the treatment of chronic insomnia.[2,4,5]

Anxiety states are a collection of conditions in which a generalized pervasive fear dominates a patient's life. Anxiety disorders include the following: generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, post-traumatic stress, and social phobias.[1]

Traditional benzodiazepines exhibit their sedative-hypnotic properties through a nonselective binding to the receptors on the gamma-aminobutyric acid$_A$ ($GABA_A$) receptor complex.[2,3,6-8] As a result, these drugs have both desirable therapeutic properties (eg, anxiolytic, sedative, anticonvulsant, and muscle-relaxant properties) and undesirable effects (eg, central nervous system depression, cognitive and psychomotor impairment, residual daytime sedation, tolerance and withdrawal). Newer, nonbenzodiazepine benzodiazepine receptor agonists (eg, eszopiclone, zaleplon, and zolpidem) are more selective when binding to the $GABA_A$ complex. Ramelteon, on the other hand, has no affinity for the $GABA_A$ receptor complex.[6] Ramelteon is a melatonin receptor, full-agonist that is more selective for the melatonin type 1 (MT_1) and type 2 (MT_2) receptors compared to the type 3 (MT_3) receptor in the suprachiasmatic nucleus of the hypothalamus. 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. Tolerance, rebound insomnia or withdrawal effects have not been observed with ramelteon, and ramelteon is not a controlled substance.[5]

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, and zolpidem are available in at least one generic dosage form.

Table 1. Miscellaneous Anxiolytics, Sedatives, and Hypnotics Included in this Review

Generic Name	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
buspirone	tablet	Buspar®*	buspirone
chloral hydrate	capsule, rectal suppository, syrup	Aquachloral®, Somnote®	chloral hydrate*
dexmedetomidine	injection	Precedex®	none
droperidol	injection	Inapsine®*	droperidol

Generic Name	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
eszopiclone	tablet	Lunesta®	Lunesta®
hydroxyzine hydrochloride	injection, syrup, tablet	Atarax®*†	hydroxyzine hydrochloride
hydroxyzine pamoate	capsule, oral suspension	Vistaril®*	hydroxyzine pamoate
meprobamate	tablet	Miltown®*	meprobamate
ramelteon	tablet	Rozerem®	Rozerem®
zaleplon	capsule	Sonata®	none
zolpidem	extended-release tablet, tablet	Ambien®*, Ambien® CR	Ambien® CR, zolpidem

*Generic is available in at least one dosage form or strength.
†Brand is no longer available.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate 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 Academy of Sleep Medicine (AASM), Standards of Practice Committee: **Practice Parameters for the Psychological and Behavioral Treatment of Insomnia: An Update (2006)**[4]	• Insomnia as a primary disorder is known as "primary insomnia," as opposed to insomnia due to or associated with another condition such as medical or psychiatric illness, substance abuse disorder, or another sleep disorder. The latter is referred to in the guideline as "secondary insomnia." • Psychological and behavioral interventions are effective and recommended in the treatment of both chronic primary insomnia and secondary insomnia. • Stimulus control is effective in the treatment of chronic insomnia and involves training that reassociates the bed and bedroom with sleep and promotes a consistent sleep-wake schedule. • Chronic insomnia is effectively treated with relaxation training (progressive muscle relaxation) and autogenic training to reduce tension, as well as reduce disruptive thoughts at bedtime. • Sleep restrictions, such as limiting time in bed to actual time asleep, are useful in chronic insomnia. • Cognitive behavior therapy, with or without relaxation therapy, is recommended in the treatment of chronic insomnia. This form of therapy focuses on changing patient beliefs and attitudes about insomnia. Stimulus control therapy, sleep restriction, relaxation training and sleep hygiene education may also be involved. • Paradoxical intention, where the patient attempts to stay awake, is effective in sleep initiation insomnia. • The use of visual or auditory biofeedback to reduce somatic arousal is useful in chronic insomnia. • There is insufficient evidence that sleep hygiene monotherapy is effective. • Imagery training has not been proven effective as monotherapy or in combination with other approaches. • There is limited evidence that cognitive therapy alone is effective in treating insomnia. • Insufficient evidence was available to recommend one single therapy over another, or to recommend single therapy versus a combination of psychological and behavioral interventions. • Psychological and behavioral interventions are effective and recommended in treating insomnia in older adults. • Psychological and behavioral interventions are effective in treating insomnia in chronic hypnotic users.

Clinical Guideline	Recommendation(s)
National Institutes of Health (NIH), State-of-the-Science Conference Statement: **Manifestations and Management of Chronic Insomnia in Adults (2005)**[9]	Conference Statement • "Evidence supports the efficacy of cognitive-behavioral therapy and benzodiazepine receptor agonists in the treatment of this disorder [chronic insomnia], at least in the short term. Very little evidence supports the efficacy of other treatments, despite their widespread use." General Considerations • The most common treatments used by individuals with chronic insomnia are prescription medications, over-the-counter antihistamines, and alcohol. • The major forms of psychological treatments are cognitive and behavioral therapies. Prescription Medications with Food and Drug Administration (FDA) Approval for the Treatment of Insomnia • Benzodiazepine receptor agonists include benzodiazepines (eg, flurazepam, temazepam, and triazolam) as well as nonbenzodiazepine-structured anxiolytic agents acting at benzodiazepine receptors (eg, 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 (eg, 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. • 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 (eg, amitriptyline and mirtazapine) in individuals with chronic insomnia are lacking. • These guidelines were published prior to the FDA approval of ramelteon. Nonprescription Medications • Antihistamines (eg, diphenhydramine) are the most commonly used over-the-counter agents for chronic insomnia; however, there is no systematic evidence for efficacy and there are significant concerns about the risks of these medications. Behavioral and Cognitive Therapies • Behavioral methods include relaxation training, stimulus control, and sleep restriction. • Cognitive therapy methods have been added to behavioral methods and include cognitive restructuring, in which anxiety-producing beliefs and erroneous beliefs about sleep and sleep loss are specifically targeted. • The combination of cognitive methods and behavioral methods (CBT) has been found to be as effective as prescription medications for short-term treatment of chronic insomnia. The beneficial effects of CBT may last well beyond the termination of active treatment.
Treatment Guidelines from the Medical Letter on Drugs and Therapeutics: **Treatment of Insomnia (2006)**[5]	• Short-term use of a short-acting nonbenzodiazepine benzodiazepine receptor agonist (NBRA) is generally effective and safe (minimal adverse events and drug interactions), but it is not clear that NBRAs are more effective or safer than benzodiazepines. • Short-acting benzodiazepines and NBRAs may not prevent early morning awakening; when this occurs, a drug with an intermediate duration of action may be more helpful. • Nonprescription first generation antihistamines such as diphenhydramine are not recommended for treatment of insomnia; tolerance develops quickly and they can

Clinical Guideline	Recommendation(s)
	cause next-day sedation that impairs driving skills. • Cognitive behavioral therapy is safer and in some patients may be more effective than drugs for the treatment of chronic insomnia. • Barbiturates and chloral hydrate are not recommended due to their many side effects and the possibility of physical dependence and abuse.
International Consensus Group on Depression and Anxiety: **Consensus Statement on Panic Disorder (1998)**[10]	General Considerations • The goal of treatment is full remission across the syndrome: panic attacks, anxiety, phobias, well-being, and disability. • The strongest evidence for clinical efficacy exists for selective serotonin-reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), and benzodiazepines. • Monoamine oxidase inhibitors (MAOIs) have demonstrated efficacy, though the quality of evidence is less extensive. • There is limited evidence for the use of anticonvulsants, and recommended use of valproate is confined to treatment-resistant patients. • β-Blockers should be considered an ineffective therapeutic option in panic disorder. Treatment of Choice • SSRIs are recommended as first-line treatment of panic disorder. • SSRI treatment is to be initiated at a low dose and increased slowly, as tolerated, to the target dose. • Effective treatment may be continued for 12 to 24 months with consideration for stopping only when the patient is well and in a stable life situation, after which treatment may be discontinued slowly over the course of 4 to 6 months; treatment should never be stopped abruptly. • Concomitant use of a benzodiazepine for a limited period (<8 weeks) may be used to help initiate treatment with an SSRI in some patients. Second-line Treatment • Second-line treatment is needed when a patient fails to respond to an adequate trial (8 to 12 weeks) of an SSRI at the maximum tolerated dose. • If partial response was observed and the SSRI was well tolerated, switch to another SSRI. • If an SSRI was not tolerated, initiate a trial of a benzodiazepine or a TCA. Third-line Treatment • An MAOI or valproate may be tried. Additional Pertinent Considerations • SSRIs are generally preferable to benzodiazepines or TCAs based on a review of long-term treatment data. • SSRIs may be administered in a once-daily dosing regimen (except fluvoxamine); clomipramine may be given as a single dose at bedtime; however, other TCAs require multiple dosing as do benzodiazepines. • Patients with panic disorder and a recent history of alcoholism should, except in some instances, not be prescribed benzodiazepines. • Patients who have panic disorder and a history of suicidal ideation or temporal lobe epilepsy should not be prescribed TCAs. • SSRIs are an appropriate choice of treatment for patients with panic disorders who also have concomitant depression, high suicidality, or concomitant medical illness. • SSRIs should be the preferred therapeutic option for panic disorder comorbid with other anxiety disorders (eg, obsessive-compulsive disorder) or alcoholism. • Benzodiazepines are generally well tolerated but may cause unwanted sedative effects, poor coordination, and memory problems; may potentiate the effects of alcohol; and are associated with the risk of dependence with long-term use as well as

Clinical Guideline	Recommendation(s)
	potential difficulties with withdrawal symptoms. • TCAs are associated with poor tolerability due to their anticholinergic effects, may cause weight gain, and have the potential to cause seizures as well as other safety concerns. • SSRIs have an improved tolerability over traditional TCAs and most side effects resolve over time; some SSRIs may cause initial jitteriness.

International Consensus Group on Depression and Anxiety:
Consensus Statement on Generalized Anxiety Disorder (GAD) (2001)[11]
	General Considerations
	• Chronic worrying and the effects of chronic tension are the specific features that define GAD; duration of symptoms is an important factor differentiating GAD from other anxiety disorders. For a diagnosis of GAD, the symptoms of anxiety and worry should have been present for 6 months.
	• Cognitive behavioral therapy (CBT) techniques are recommended as the preferred form of psychotherapy in GAD.
	• When GAD is comorbid with depression, as it commonly is, medication is often indicated.
	
	Treatment of Choice
	• Antidepressants are recommended as first-line treatment of GAD. The following classes of antidepressants can be used:
	  o Selective serotonin-reuptake inhibitors (SSRIs)
	  o Serotonin-norepinephrine reuptake inhibitors (SNRIs)
	  o Nonsedating tricyclic antidepressants (TCAs)
	• Benzodiazepines may be used as adjunct agents in acute exacerbations of GAD or for sleep disturbances during the initiation of antidepressant therapy. Patients should be stabilized on antidepressant therapy for >4 weeks before benzodiazepines are slowly tapered off (over 4 to 8 weeks).
	• For patients with a long-term condition, with several comorbid conditions, and in patients with an increased risk of suicide, an SSRI or SNRI is indicated.
	
	Other Therapeutic Options
	• Buspirone has demonstrated efficacy in GAD in most clinical trials, although it has not shown efficacy against comorbid conditions and therefore is not recommended as first-line treatment for GAD.
	
	Additional Pertinent Considerations
	• The guideline indicates that the only first-line use of benzodiazepines is an acute anxiety reaction, with an expected duration of 2 to 6 weeks; benzodiazepines are not appropriate for first-line treatment of GAD, which is a condition requiring appropriate long-term treatment.
	• Benzodiazepines are appropriate for intermittent or episodic use.
	• Benzodiazepines may have a role as adjunctive therapy in acute exacerbation of GAD or in sleep disturbances during the initiation of antidepressant therapy.
	• GAD is frequently comorbid with depressive disorders, for which benzodiazepines are not desirable, or with other anxiety disorders, for which benzodiazepine therapy is not usually favored as first-line.
	• The use of benzodiazepines may be a problem in the long term, due to the risk of withdrawal reactions, or in patients with a history of drug abuse or alcoholism.
	• The guideline indicates that hydroxyzine is used in acute anxiety states, in which it is targeting symptoms rather than treating the condition itself.
	• The use of hydroxyzine is similar to that of benzodiazepines; however, hydroxyzine does not cause dependence.
	• Hydroxyzine has no demonstrated efficacy in depression, panic disorder, social phobia, or obsessive-compulsive disorder.
	• Neuroleptics are not appropriate for the treatment of GAD as there is almost no clinical evidence to support their use, and may be associated with tardive dyskinesias.

Clinical Guideline	Recommendation(s)
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 (2004)**[12]	Panic Disorder General Considerations • Benzodiazepines are associated with a less effective outcome in the long term and should not be prescribed for panic disorder. More effective options are outlined below. • Sedating antihistamines or antipsychotics should not be prescribed for panic disorder. Panic Disorder Treatment Options Interventions with evidence for the longest duration of effect are listed in descending order, where preference of the patient should be taken into account: • Psychological therapy (ie, cognitive behavioral therapy, structured problem solving, psychoeducation) • Pharmacological therapy: antidepressants • Self-help interventions (ie, bibliotherapy, support groups, exercise, cognitive behavioral therapy via a computer interface) Panic Disorder Additional Considerations for Pharmacologic Therapy • 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 (eg, paroxetine, fluvoxamine, citalopram) licensed in the United Kingdom (UK) for panic disorder should be offered; if an SSRI is not suitable, the TCAs imipramine or clomipramine may be considered. • Side effects with the initiation of antidepressants may be minimized by starting at a low dose and increasing the dose slowly until a satisfactory therapeutic response is achieved. • 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, imipramine or clomipramine may be considered, or another form of therapy may be offered. Generalized Anxiety Disorder General Considerations • Benzodiazepines may be used for acute treatment, but they should not usually be used beyond 2 to 4 weeks. Generalized Anxiety Disorder Treatment Options Interventions with evidence for the longest duration of effect are listed in descending order, where preference of the patient should be taken into account: • Psychological therapy (eg, cognitive behavioral therapy, structured problem solving, psychoeducation) • Pharmacological therapy: antidepressants • Self-help interventions (eg, bibliotherapy, support groups, exercise, cognitive behavioral therapy via a computer interface) Generalized Anxiety Disorder Additional Considerations for Pharmacologic Therapy • Unless otherwise indicated, an SSRI should be offered; if one SSRI is not suitable, another SSRI should be offered. • Side effects with the initiation of antidepressants may be minimized by starting at a low dose and increasing the dose slowly until a satisfactory therapeutic response is achieved. • If the patient is showing improvement the medication should be continued for at least

Clinical Guideline	Recommendation(s)
	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. • If venlafaxine is being considered, an initial electrocardiogram (ECG) and blood pressure measurement should be undertaken and the dose should be no higher than 75 mg per day; treatment should be initiated and managed under the supervision of specialist mental health medical practitioners and regular monitoring of cardiac status is advised. • A number of different drugs are considered for the treatment of GAD in the guideline, including SSRIs (eg, paroxetine, fluvoxamine, citalopram), TCAs (eg, imipramine, clomipramine), benzodiazepines (eg, diazepam, alprazolam, clonazepam, lorazepam), sedating antihistamines (eg, hydroxyzine), SNRIs (eg, venlafaxine), and buspirone. • Antidepressants are preferred over benzodiazepines due to the potential for abuse and because antidepressants may treat comorbid depression.
International Consensus Group on Depression and Anxiety: **Consensus Statement on Social Anxiety Disorder (SAD) (1998)**[13]	General Considerations • SAD appears to predispose individuals to the development of other psychiatric disorders, most notably depression. • There is some evidence for the effectiveness of cognitive behavioral treatment in SAD; however, this is based on relatively small trials as compared to that for pharmacotherapy. Treatment of Choice • Selective serotonin-reuptake inhibitors (SSRIs) are recommended as first-line treatment of SAD, with most efficacy evidence for SSRIs derived from well-controlled studies with paroxetine. • The appropriate dosage regimen for paroxetine has been defined: it should be initiated at 20 mg/day for 2 to 4 weeks, and then increased as necessary. • An adequate trial of treatment with an SSRI is 6 to 8 weeks, and if effective, treatment should be continued for at least 12 months. • Long-term treatment is indicated if symptoms are unresolved, if the patient has a comorbidity or a history of relapse, or if there was an early onset of SAD. • SSRIs are also recommended for treating patients who have failed to respond to other treatments for SAD. Other Therapeutic Options • Phenelzine, a monoamine oxidase inhibitor (MAOI), has less evidence for efficacy in SAD and is associated with concerns about its tolerability and safety, which make it an inappropriate option for first-line treatment. • The benzodiazepine clonazepam has limited but well-controlled data for the treatment of SAD; alprazolam was shown to be significantly less effective than clonazepam for SAD, and there is no evidence that benzodiazepines as a class are effective in SAD. Additional Pertinent Considerations • β-Blockers do not have a place in the management of SAD; despite the benefit of their use with normal performance anxiety, there is no controlled evidence to show that β-blockers are advantageous for the pathologic anxiety of generalized SAD. Furthermore they may have harmful effects, especially in patients with asthma. • In contrast with their efficacy in panic disorder, there are no controlled data for the efficacy of tricyclic antidepressants (TCAs) in SAD. • There is no evidence for the efficacy of buspirone in SAD.

III. Indications

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[6-8,14-25]

Drug	Alcohol Withdrawal Syndrome	Anxiety Disorders	Anxiety Symptoms, Short-Term Relief	Anxiety Due to Drug Withdrawal	Insomnia	Insomnia, Short-Term	Nausea and Vomiting	Pruritus	Sedation
Buspirone		✔ *	✔ *						
Chloral hydrate	✔			✔ (eg, narcotics, barbiturates)		✔			✔ (routine, preoperative, prior to electroenceph-alographic evaluation)
Dexmedetomidine									✔ (initially intubated and mechanically ventilated patients in an intensive care setting)
Droperidol							✔ (associated with surgical or diagnostic procedures)		
Eszopiclone					✔ † (decreased sleep latency and improved sleep maintenance)				
Hydroxyzine hydrochloride	✔		✔ *‡				✔ (excluding pregnancy)	✔ *	✔ § (pre- or postoperative, pre- or postpartum)
Hydroxyzine			✔ *					✔ *	✔ (premedication or

Drug	Alcohol Withdrawal Syndrome	Anxiety Disorders	Anxiety Symptoms, Short-Term Relief	Anxiety Due to Drug Withdrawal	Insomnia	Insomnia, Short-Term	Nausea and Vomiting	Pruritus	Sedation
pamoate									following general anesthesia)
Meprobamate		✔ *	✔ *						
Ramelteon					✔ ‖ (characterized by difficulty with sleep onset)				
Zaleplon						✔ ¶ (decreased time to sleep onset)			✔ (routine or preoperative)
Zolpidem immediate-release						✔ # (characterized by difficulty with sleep initiation)			
Zolpidem, extended-release					✔ ^ (characterized by difficulties with sleep onset and/or sleep maintenance)				

*Effectiveness in long-term use (more than 3 to 4 weeks for buspirone and more than 4 months for hydroxyzine hydrochloride or pamoate or meprobamate) has not been demonstrated in controlled clinical trials.
†The clinical trials performed in support of efficacy were up to 6 months in duration. Studies were conducted in patients with transient and chronic insomnia.
‡Agent can be used to manage the acutely disturbed or hysterical patient.
§Agent can be used pre- or postoperative, pre- or postpartum to allay anxiety, permit reduction in narcotic dosage, and control emesis.
‖The clinical trials reported in the product labeling were conducted in patients with transient and chronic insomnia and lasted up to 35 days in duration.
¶The clinical trials performed in support of efficacy ranged from single night to 5 weeks in duration. Studies were conducted in patients with transient and chronic insomnia.
#The clinical trials performed in support of efficacy were 4-5 weeks in duration and conducted in patients with transient and chronic insomnia.
^The clinical trials performed in support of efficacy were both 3 weeks in duration, although the final formal assessments of sleep latency and maintenance were performed after 2 weeks of treatment. The studies were conducted in patients with chronic primary insomnia.

IV. Pharmacokinetics

The pharmacokinetic parameters for the miscellaneous anxiolytics, sedatives, and hypnotics are summarized in Table 4.

Table 4. Pharmacokinetic Parameters of the Miscellaneous Anxiolytics, Sedatives, and Hypnotics[2,6-8, 14-25]

Drug	Bioavailability (%)	Protein Binding (%)	Metabolism	Active Metabolites	Elimination (%)	Half-Life (hours)
Buspirone	90	86	Hepatic (CYP3A4)	Yes; 1-pyrimidinyl-piperazine	Fecal (18-38), renal (29-63)	2-3
Chloral hydrate	Well absorbed orally and rectally	70-80	Hepatic	Yes; trichloroethanol	Biliary (N/A), renal (N/A)	8-11
Dexmedetomidine	73 (Intramuscular)	94	Hepatic (CYP2A6)	None	Fecal (4), renal (95)	2
Droperidol	Not reported	Extensive	Hepatic	None	Fecal (22), renal (75)	2
Eszopiclone	80%	52-59	Hepatic (CYP3A4 and CYP 2E1)	Yes; (S)-N-desmethylzopiclone	Not reported	6
Hydroxyzine	Not reported	Not reported	Hepatic	Yes; cetirizine	Not reported	3-20
Meprobamate	Not reported	0-30	Hepatic	None	Renal (10-12 unchanged within 24 hours)	9-11
Ramelteon	Total absorption is at least 84%; however, absolute oral bioavailability is 1.8%	82	Hepatic (CYP1A2)	Yes; M-II	Fecal (4), renal (84)	1-2.6
Zaleplon	30	60	Hepatic (aldehyde oxidase and CYP3A4)	None	Fecal (17), renal (71)	1
Zolpidem	70	93	Hepatic (mainly CYP3A4, also CYP1A1 and CYP2D6)	None	Biliary (N/A), fecal (N/A), renal (N/A)	2.5 (immediate-release) 2.8 (controlled-release)

N/A=not available

V. Drug Interactions

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

Table 5. Significant Drug-Drug Interactions with the Miscellaneous Anxiolytics, Sedatives, and Hypnotics[7,8]

Drug(s)	Significance Level	Interaction	Mechanism
Buspirone	1	Monoamine oxidase inhibitors	Concurrent administration of buspirone with monoamine oxidase inhibitors (MAOIs) is not recommended. Cases of hypertensive

Drug(s)	Significance Level	Interaction	Mechanism
		(isocarboxazid, pargyline, phenelzine, procarbazine, selegiline, tranylcypromine)	crisis have occurred when MAOIs have been administered simultaneously with buspirone. This interaction may be mediated by the affinity of buspirone for serotonin receptors. Allow 14 days to elapse between withdrawal of the MAOI and administration of buspirone.
Droperidol	1	Ziprasidone	Ziprasidone is contraindicated in patients receiving droperidol due to the increased risk of life-threatening cardiac arrhythmias, including torsades de pointes. The combination may have synergistic or additive prolongation of the QT interval.
Ramelteon	1	Fluvoxamine	Fluvoxamine is a strong inhibitor of CYP1A2, the main metabolizing enzyme for ramelteon. Ramelteon should not be used in combination with fluvoxamine.
Buspirone	2	Azole antifungals (fluconazole, itraconazole, ketoconazole, miconazole)	Azole antifungals may inhibit the CYP3A4 isozyme responsible for first-pass metabolism of buspirone, resulting in elevated plasma levels and increased pharmacologic and adverse effects.
Buspirone	2	Diltiazem	Diltiazem may enhance the bioavailability of buspirone by reducing the first-pass metabolism (CYP3A4) of buspirone. The pharmacologic and adverse effects of buspirone may be increased.
Buspirone	2	Macrolide and related antibiotics (clarithromycin, erythromycin, telithromycin)	Macrolide and related antibiotics may inhibit the CYP3A4 isozyme responsible for first-pass metabolism of buspirone, resulting in elevated plasma levels and increased pharmacologic and adverse effects
Buspirone	2	Rifamycins (rifabutin, rifampin, rifapentine)	Rifamycins may induce first-pass metabolism (CYP3A4) of buspirone. Buspirone plasma concentrations and pharmacologic effects may be decreased.
Buspirone	2	Verapamil	Verapamil may enhance the bioavailability of buspirone by reducing the first-pass metabolism (CYP3A4) of buspirone. The pharmacologic and adverse effects of buspirone may be increased.
Chloral hydrate	2	Ethanol	Concurrent ingestion of chloral hydrate and ethanol synergistically increases central nervous system (CNS) depression. Disulfiram-like reactions, while rare, have been reported when alcohol is consumed after chloral hydrate.
Eszopiclone	2	Ketoconazole	Concomitant use of eszopiclone and ketoconazole may result in increased plasma concentrations of eszopiclone due to the CYP3A4-mediated inhibition of eszopiclone metabolism by ketoconazole. Increased eszopiclone plasma concentrations may result in increased side effects.
Meprobamate	2	Ethanol	Acute ethanol ingestion results in decreased clearance of drugs through inhibition of hepatic metabolic systems. With chronic ethanol ingestion, one may manifest tolerance presumably due to enhanced metabolic capacity. The combination may result in enhanced CNS depressant effects affecting coordination and judgment.
Ramelteon	2	Fluconazole, ketoconazole	Fluconazole and ketoconazole inhibit CYP2C9 and CYP3A4, respectively, resulting in increased exposure to ramelteon and increased risk of side effects.
Zaleplon	2	Cimetidine	Cimetidine may inhibit the metabolism (aldehyde oxidase and CYP3A4) of zaleplon resulting in a potentiation of zaleplon effects.

Drug(s)	Significance Level	Interaction	Mechanism
Zaleplon	2	Rifampin	Rifampin may induce the CYP3A4 metabolism of zaleplon resulting in a reduction in efficacy for zaleplon.
Zolpidem	2	Azole antifungals (fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole)	Azole antifungal agents may interfere with the major route of zolpidem metabolism (CYP3A4). Plasma concentrations and therapeutic effects of zolpidem may be increased. The effects on zolpidem appear to be greatest with ketoconazole.
Zolpidem	2	Bupropion, desipramine, fluoxetine, sertraline, venlafaxine	Hallucinations after concurrent use of zolpidem and antidepressant medication have been reported. The hallucination episodes all lasted longer than one hour, but resolved without further sequelae.
Zolpidem	2	Rifampin	Rifampin may increase the metabolism of zolpidem resulting in decreased plasma levels and pharmacodynamic effects of zolpidem.
Zolpidem	2	Ritonavir	Ritonavir may inhibit the hepatic metabolism of zolpidem leading to possibly severe sedation and respiratory depression. Concurrent administration of zolpidem and ritonavir is contraindicated.

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 noted in Table 6. A black box warning regarding droperidol is noted in Table 7 and for chloral hydrate in Table 8.

In March of 2007 the FDA issued a press release regarding its request that all drug manufacturers of medications approved for the treatment of sleep disorders revise product labeling to include warnings and potential risks of adverse events. Various products containing eszopiclone, ramelteon, zaleplon, and zolpidem were among the drugs targeted in the alert. These adverse events include severe allergic reaction and angioedema, as well as complex sleep-related behaviors including sleep-driving, making phone calls and eating and preparing food while asleep. The FDA has also requested that consumers be informed through the development of a Patient Medication Guide.[26]

Table 6. Common Adverse Events (%) Reported with the Miscellaneous Anxiolytics, Sedatives, and Hypnotics[6-8,14-25]

Adverse Event	Buspirone	Chloral Hydrate	Dexmede-tomidine	Droper-idol	Eszopi-clone	Hydroxy-zine HCl	Hydroxy-zine Pamoate	Mepro-bamate	Ramelteon	Zaleplon	Zolpidem IR	Zolpidem ER
Cardiovascular												
Arrhythmia	-	-	≤1	-	-	-	-	✔	-	-	-	-
Atrial fibrillation	-	-	4	-	-	-	-	-	-	-	-	-
Bradycardia	-	-	7	-	-	-	-	-	-	-	-	-
Cardiac arrest	-	-	≤1	✔	-	-	-	-	-	-	-	-
Cerebrovascular disorder	-	-	-	-	-	-	-	-	-	-	≤1	≤1
Chest pain	≥1	-	-	-	≥1	-	-	-	-	≥1	1	≤1
ECG changes, transient	-	-	-	-	-	-	-	✔	-	-	-	-
Hypertension	≤1	-	16	✔	-	-	-	-	-	-	≤1	≤1
Hypotension (includes postural)	≤1	-	28	✔	-	-	-	✔	-	-	≤1	≤1
Migraine	-	-	-	-	≥1	-	-	-	-	≥1	≤1	≤1
Palpitation	1	-	-	✔	-	-	-	✔	-	-	2	2
Peripheral edema	-	-	-	-	≥1	-	-	✔	-	≤1	-	≤1
QT interval prolongation	-	-	-	✔	-	-	-	-	-	-	-	-
Syncope	≤1	-	-	✔	-	-	-	✔	-	-	≤1	≤1
Tachycardia	1	-	3	✔	-	-	-	✔	-	-	≤1	≤1
Torsades de pointes	-	-	-	✔	-	-	-	-	-	-	-	-

Adverse Event	Buspirone	Chloral Hydrate	Dexmede-tomidine	Droper-idol	Eszopi-clone	Hydroxy-zine HCl	Hydroxy-zine Pamoate	Mepro-bamate	Ramelteon	Zaleplon	Zolpidem IR	Zolpidem ER
Ventricular tachycardia	-	-	≤1	✔	-	-	-	-	-	-	-	-
Central Nervous System												
Agitation	-	-	2	-	-	-	-	-	-	-	≤1	≤1
Akathisia	≤1	-	-	✔	-	-	-	-	-	-	-	-
Amnesia/ memory disorder	-	-	-	-	-	-	-	-	-	2-4	1	1-3
Anger/hostility	2	-	-	-	-	-	-	-	-	-	-	-
Anxiety	-	-	-	✔	1-3	-	-	-	-	≥1	1	2-3
Ataxia	-	✔	-	-	-	-	-	✔	-	-	>1	1
Confusion	2	✔	≤1	-	≤3	-	-	-	-	≤1	>1	3
Convulsions	≤1	-	-	-	-	✔	✔	-	-	-	-	-
Decreased concentration	2	-	-	-	-	-	-	-	-	≥1	≤1	2
Delirium	-	-	≤1	-	-	-	-	-	-	-	-	-
Depersonalization	≤1	-	-	-	-	-	-	-	-	≤2	≤1	1
Depression	2	-	-	✔	1-4	-	-	-	2	≥1	2	1-2
Disinhibition	-	-	-	-	-	-	-	-	-	-	-	1
Dissociative reaction	≤1	-	-	-	-	-	-	-	-	-	-	-
Dizziness	12	✔	≤1	✔	1-7	-	-	✔	5	7-9	1-5	8-12
Dream disturbances	≥1	-	-	-	1-3	-	-	-	-	-	1	≤1
Drowsiness	10	-	-	✔	-	✔	✔	✔	-	-	2-8	>1
Dysphoria	≤1	-	-	✔	-	-	-	-	-	-	-	-
Dystonia	-	-	-	✔	-	-	-	-	-	-	-	-
Emotional lability	-	-	-	-	-	-	-	-	-	-	≤1	1
Euphoria	≤1	-	-	-	-	-	-	✔	-	-	>1	1
Excitement	2	✔	-	-	-	-	-	✔	-	-	-	-
Extrapyramidal symptoms	-	-	-	✔	-	-	-	-	-	-	-	-
Falling	-	-	-	-	-	-	-	-	-	-	≤1	≤1
Fast EEG activity	-	-	-	-	-	-	-	✔	-	-	-	-

Adverse Event	Buspirone	Chloral Hydrate	Dexmede-tomidine	Droper-idol	Eszopi-clone	Hydroxy-zine HCl	Hydroxy-zine Pamoate	Mepro-bamate	Ramelteon	Zaleplon	Zolpidem IR	Zolpidem ER
Fatigue	4	-	-	-	-	-	-	-	4	-	1	3
Fearfulness	≤1	-	-	-	-	-	-	-	-	-	-	-
Hallucinations	≤1	✔	≤1	✔	1-3	-	✔	-	-	≤1	≤1	4
Headache	6	-	≤1	-	13-21	✔	✔	✔	7	30-42	7-19	14-19
Hyperactivity	-	-	-	✔	-	-	-	-	-	-	-	-
Hypesthesia	-	-	-	-	-	-	-	-	-	≤2	-	-
Hypertonia	-	-	-	-	-	-	-	-	-	1	-	-
Hypoesthesia	-	-	-	-	-	-	-	-	-	-	≤1	2
Illusion	-	-	≤1	-	-	-	-	-	-	-	≤1	≤1
Incoordination	1	✔	-	-	-	-	-	-	-	-	-	2
Insomnia	3	-	-	-	-	-	-	-	3	-	>1	>1
Involuntary movements	≤1	-	-	-	-	✔	✔	-	-	-	-	-
Lethargy	-	-	-	-	-	-	-	-	-	-	3	>1
Libido decreased	≤1	-	-	-	≤3	-	-	-	-	-	-	-
Libido increased	≤1	-	-	-	-	-	-	-	-	-	-	-
Lightheadedness	3	✔	-	-	-	-	-	-	-	-	2	>1
Malaise	≤1	-	-	-	-	-	-	-	-	≤2	≤1	≤1
Nervousness	5	-	-	-	≤5	-	-	-	-	≥1	1	≤1
Neuralgia	-	-	≤1	-	≤3	-	-	-	-	-	-	-
Neuritis	-	-	≤1	-	-	-	-	-	-	-	-	-
Numbness/ paresthesia	1-2	-	-	-	-	-	-	✔	-	3	≤1	≤1
Oculogyric crisis	-	-	-	✔	-	-	-	-	-	-	-	-
Overstimulation	-	-	-	-	-	-	-	✔	-	-	-	-
Psychomotor retardation	≤1	-	-	-	-	-	-	-	-	-	-	2
Restlessness	-	-	-	✔	-	-	-	-	-	-	-	-
Sedation, residual	-	✔	-	-	-	-	-	-	-	-	3	>1
Sleep disorder	-	-	-	-	-	-	-	-	-	-	1	≤1
Somnolence	10	✔	-	✔	8-10	✔	✔	✔	5	5-6	3	6-15
Speech disorder	-	-	≤1	-	-	-	-	✔	-	-	≤1	≤1

Adverse Event	Buspirone	Chloral Hydrate	Dexmede-tomidine	Droper-idol	Eszopi-clone	Hydroxy-zine HCl	Hydroxy-zine Pamoate	Mepro-bamate	Ramelteon	Zaleplon	Zolpidem IR	Zolpidem ER
Stupor	-	-	-	-	-	-	-	-	-	-	≤1	≤1
Suicidal ideation	≤1	-	-	-	-	-	-	-	-	-	-	-
Tremor	1	-	-	-	-	✔	✔	-	-	2	≤1	1
Vertigo	-	-	-	-	-	-	-	✔	-	≤1	>1	2
Dermatological												
Angioedema	-	✔	-	-	-	-	-	-	-	-	✔	✔
Bullous lesions	-	✔	-	-	-	-	-	-	-	-	-	-
Dry skin	≤1	-	-	-	-	-	-	-	-	-	-	-
Ecchymosis	≤1	-	-	-	-	-	-	✔	-	-	-	-
Eczema	-	✔	-	-	-	-	-	-	-	-	-	-
Edema	≤1	-	-	-	-	-	-	-	-	-	≤1	≤1
Erythema multiforme	-	✔	-	-	-	-	-	-	-	-	-	-
Hair loss	≤1	-	-	-	-	-	-	-	-	-	-	-
Pallor	-	-	-	-	-	-	-	-	-	-	≤1	≤1
Petechiae	-	-	-	-	-	-	-	✔	-	-	-	-
Photosensitivity reaction	-	-	-	-	-	-	-	-	-	≤1	-	-
Pruritis	≤1	-	-	-	1-4	-	✔	✔	-	≥1	≤1	≤1
Purpura	-	✔	-	-	-	-	-	✔	-	-	-	-
Rash	1	✔	-	-	3-4	-	✔	✔	-	≥1	2	1
Skin wrinkling	-	-	-	-	-	-	-	-	-	-	-	1
Urticaria	-	✔	-	-	-	-	✔	✔	-	-	-	1
Endocrine and Metabolic												
Acidosis	-	-	2	-	-	-	-	-	-	-	-	-
Acidosis, respiratory	-	-	≤1	-	-	-	-	-	-	-	-	-
Blood cortisol decreased	-	-	-	-	-	-	-	-	1	-	-	-
Hyperglycemia	-	-	2	-	-	-	-	-	-	-	≤1	≤1
Hyperkalemia	-	-	≤1	-	-	-	-	-	-	-	-	-

Adverse Event	Buspirone	Chloral Hydrate	Dexmede-tomidine	Droper-idol	Eszopi-clone	Hydroxy-zine HCl	Hydroxy-zine Pamoate	Mepro-bamate	Ramelteon	Zaleplon	Zolpidem IR	Zolpidem ER
Gastrointestinal												
Abdominal pain	2	✔	≤1	-	✔	-	-	-	-	6	2	>1
Anorexia/ weight loss	≤1	-	-	-	-	-	-	-	-	≤2	1	≤1
Appetite disorder	-	-	-	-	-	-	-	-	-	-	-	1
Appetite increased/ weight gain	≤1	-	-	-	-	-	-	-	-	-	-	-
Colitis	≤1	-	-	-	-	-	-	-	-	≤1	-	-
Constipation	1	-	-	-	-	-	-	-	-	≥1	2	2
Diarrhea	2	✔	≤1		2-4	-		✔	2	-	1-3	>1
Dry mouth	3	-	3	-	3-7	✔	✔	-	-	≥1	3	>1
Dyspepsia	-	-	-	-	2-6	-	-	-	-	≥1	5	>1
Dysphagia	-	-	-	-	-	-	-	-	-	-	≤1	≤1
Flatulence	≤1	-	-	-	-	-	-	-	-	-	≤1	1
Gastroenteritis	-	-	-	-	-	-	-	-	-	-	≤1	1
Hiccup	-	-	-	-	-	-	-	-	-	-	>1	>1
Nausea	8	✔	11	-	4-5	-	-	✔	3	6-8	2-6	7
Salivation	≤1	-	-	-	-	-	-	-	-	-	-	-
Rectal bleeding	≤1	-	-	-	-	-	-	-	-	-	-	-
Thirst	-	-	2	-	-	-	-	-	-	-	≤1	≤1
Vomiting	1	✔	4	-	≤3	-	-	✔	-	-	1	1
Hematologic												
Agranulocytosis	-	-	-	-	-	-	-	✔	-	-	-	-
Anemia	-	-	3	-	-	-	-	-	-	-	-	-
Aplastic anemia	-	-	-	-	-	-	-	✔	-	-	-	-
Eosinophilia	-	-	-	-	-	-	-	✔	-	-	-	-
Leukopenia	-	-	-	-	-	-	-	✔	-	-	-	-
Laboratory Test Abnormalities												
Abnormal hepatic function	-	-	-	-	-	-	-	-	-	-	≤1	≤1
Alkaline phosphatase increased	-	-	≤1	-	-	-	-	-	-	-	-	-

Adverse Event	Buspirone	Chloral Hydrate	Dexmede-tomidine	Droper-idol	Eszopi-clone	Hydroxy-zine HCl	Hydroxy-zine Pamoate	Mepro-bamate	Ramelteon	Zaleplon	Zolpidem IR	Zolpidem ER
GGT elevation	-	-	≤1	-	-	-	-	-	-	-	-	-
SGOT elevation	≤1	-	≤1	-	-	-	-	-	-	-	-	-
SGPT elevation	≤1	-	≤1	-	-	-	-	-	-	-	≤1	≤1
Musculoskeletal												
Arthralgia	≤1	-	-	-	-	-	-	-	2	≥1	4	>1
Arthritis	-	-	-	-	-	-	-	-	-	≥1	≤1	≤1
Back pain	-	-	-	-	✔	-	-	-	-	≥1	3	4
Leg/muscle cramps	≤1	-	-	-	-	-	-	-	-	-	≤1	2
Myalgia	1	-	-	-	✔	-	-	-	2	≥1	1-7	4
Neck pain	-	-	-	-	-	-	-	-	-	-	-	1-2
Weakness	2	-	-	-	✔	-	-	✔	-	5-7	>1	>1
Respiratory												
Apnea	-	-	≤1	-	-	-	-	-	-	-	-	-
Bronchitis	-	-	-	-	-	-	-	-	-	≥1	≤1	≤1
Bronchospasm	-	-	≤1	✔	-	-	-	-	-	-	-	-
Coughing	-	-	-	-	-	-	-	-	-	-	≤1	≤1
Dyspnea	-	-	≤1	-	-	-	-	-	-	-	≤1	≤1
Epistaxis	-	-	-	-	-	-	-	-	-	≤1	-	-
Hypercapnia	-	-	≤1	-	-	-	-	-	-	-	-	-
Hyperventilation	≤1	-	-	-	-	-	-	-	-	-	-	-
Hypoventilation	-	-	≤1	-	-	-	-	-	-	-	-	-
Hypoxia	-	-	4	-	-	-	-	-	-	-	-	-
Laryngospasm	-	-	-	✔	-	-	-	-	-	-	-	-
Lower respiratory tract infection	-	-	-	-	-	-	-	-	-	-	-	1
Pharyngitis	-	-	-	-	✔	-	-	-	-	-	3	6
Pleural effusion	-	-	2	-	-	-	-	-	-	-	-	-
Pulmonary congestion	≤1	-	≤1	-	-	-	-	-	-	-	-	-
Respiratory depression	-	-	-	✔	-	-	-	-	-	-	-	-
Rhinitis	-	-	-	-	✔	-	-	-	-	-	1	≤1
Shortness of breath	≤1	-	-	-	-	-	-	-	-	-	-	-

Adverse Event	Buspirone	Chloral Hydrate	Dexmede-tomidine	Droper-idol	Eszopi-clone	Hydroxy-zine HCl	Hydroxy-zine Pamoate	Mepro-bamate	Ramelteon	Zaleplon	Zolpidem IR	Zolpidem ER
Sinusitis	-	-	-	-	-	-	-	-	-	-	4	>1
Throat sore/ irritation	≥1	-	-	-	-	-	-	-	-	-	-	1
Upper respiratory tract infection	-	-	-	-	5-10	-	-	-	3	-	5	>1
Special Senses												
Conjunctivitis	≤1	-	-	-	-	-	-	-	-	≥1	-	-
Dysgeusia/ taste perversion	≤1	-	-	-	8-34	-	-	-	2	≥1	≤1	≤1
Ear pain	-	-	-	-	-	-	-	-	-	≤1	-	-
Eye pain	-	-	-	-	-	-	-	-	-	3-4	≤1	≤1
Eye redness/itching	≤1	-	-	-	-	-	-	-	-	-	≤1	2
Hyperacusis	≤1	-	-	-	-	-	-	-	-	1-2	-	-
Labyrinthitis	-	-	-	-	-	-	-	-	-	-	-	1
Nasal congestion	≥1	-	-	-	-	-	-	-	-	-	-	-
Parosmia	≤1	-	-	-	-	-	-	-	-	≤2	-	-
Photopsia	-	-	≤1	-	-	-	-	-	-	-	-	-
Scleritis	-	-	-	-	-	-	-	-	-	-	≤1	≤1
Tinnitus	≥1	-	-	-	-	-	-	-	-	-	≤1	1
Visual disturbance	2	-	≤1	-	-	-	-	✔	-	≤2	>1	1-3
Other												
Accidental injury/ trauma	-	-	-	-	≤3	-	-	-	-	-	≤1	1
Adenopathy	-	-	-	-	-	-	-	✔	-	-	-	-
Allergic reactions	-	-	-	-	-	-	✔	✔	-	-	4	>1
Anaphylaxis	-	-	-	✔	-	-	-	-	-	✔	-	-
Anesthesia, light	-	-	≤1	-	-	-	-	-	-	-	-	-
Chills/rigors	-	-	2	✔	-	-	-	-	-	-	-	-
Cross reaction to carisoprodol	-	-	-	-	-	-	-	✔	-	-	-	-
Cystitis	-	-	-	-	-	-	-	-	-	-	≤1	≤1
Dysuria	≤1	-	-	-	-	-	-	-	-	-	-	-

Adverse Event	Buspirone	Chloral Hydrate	Dexmede-tomidine	Droper-idol	Eszopi-clone	Hydroxy-zine HCl	Hydroxy-zine Pamoate	Mepro-bamate	Ramelteon	Zaleplon	Zolpidem IR	Zolpidem ER
Exacerbation of porphyric symptoms	-	-	-	-	-	-	-	✔	-	-	-	-
Fever/hyperpyrexia	≤1	✔	2-5	-	-	-	-	✔	-	≥1	≤1	1
Flu syndrome	-	-	-	-	✔	-	-	-	1	-	2	3
Gynecomastia (males)	-	-	-	-	≤3	-	-	-	-	-	-	-
Hemorrhage	-	-	3	-	-	-	-	-	-	-	-	-
Hypovolemia	-	-	≤1	-	-	-	-	-	-	-	-	-
Infection	-	-	-	-	-	-	-	-	-	-	1	≤1
Menstrual irregularities	≤1	-	-	-	≤3	-	-	-	-	3-4	≤1	1
Oliguria	-	-	2	-	-	-	-	-	-	-	-	-
Pain (nonspecific)	-	-	2	-	4-5	-	-	-	-	-	-	-
Photopsia	-	-	≤1	-	-	-	-	-	-	-	-	-
Sore throat	≥1	-	-	-	-	-	-	-	-	-	-	-
Sweating/ clamminess	1	-	≤1	-	-	-	-	-	-	-	≤1	≤1
Urinary frequency/ incontinence	≤1	-	-	-	-	-	-	-	-	-	≤1	≤1
Urinary hesitancy	≤1	-	-	-	-	-	-	-	-	-	-	-
Urinary tract infection	-	-	-	-	≤3	-	-	-	-	-	2	>1
Vaginitis	-	-	-	-	-	-	-	-	-	-	≤1	≤1
Viral infection	-	-	-	-	3	-	-	-	-	-	-	-

-Event not reported or incidence <1%

✔ Percent not specified

ECG=electrocardiogram, EEG=electroencephalogram, ER=extended release, GGT= gamma-glutamyl transferase, HCl=hydrochloride, IR=immediate release, SGOT=serum glutamic oxaloacetic transaminase (aspartate aminotransferase), SGPT=serum glutamic pyruvic transaminase (alanine aminotransferase)

Table 7. Black Box Warning for Droperidol[17]

WARNING
Cases of QT prolongation and/or torsades 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, droperidol should be reserved 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 (see CONTRAINDICTAIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS). Cases of QT prolongation and serious arrhythmias (eg, torsades de pointes) have been reported in patients treated with droperidol. Based on these reports, all patients should undergo a 12-lead electrocardiogram (ECG) prior to administration of droperidol to determine if a prolonged QT interval (eg, QTc greater than 440 msec for males or 450 msec for females) is present. If there is a prolonged QT interval, droperidol should NOT be administered. For patients in whom the potential benefit of droperidol treatment is felt to outweigh the risks of potentially serious arrhythmias, ECG monitoring should be performed prior to treatment and continued for 2-3 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. Droperidol should be administered with extreme caution to patients who may be at risk for development of prolonged QT syndrome (eg, 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 over 65 years, alcohol abuse, and use of agents such as benzodiazepines, volatile anesthetics, and intravenous opiates. Droperidol should be initiated at a low dose and adjusted upward, with caution, as needed to achieve the desired effect.

Table 8. Black Box Warning for Chloral Hydrate[23]

WARNING
Chloral hydrate is genotoxic and may be carcinogenic in mice. Do not use chloral hydrate when less potentially dangerous agents would be effective.

Drug Abuse and Dependence

Chloral hydrate, meprobamate, eszopiclone, zaleplon and zolpidem are categorized as schedule C-IV by the Drug Enforcement Agency (DEA) because of their abuse potential. The risk of abuse and dependence increases with the dose and duration of treatment and concomitant use of other psychoactive drugs. The risk is also greater for patients who have a history of alcohol or drug abuse or history of psychiatric disorders. There are limited studies that have evaluated the long-term safety and efficacy of these agents. 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.[2] The longest placebo-controlled studies with zaleplon were 4 weeks in duration.[2] 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.[2]

Buspirone has shown no potential for abuse or diversion and there is no evidence that it causes tolerance, or either physical or psychological dependence.[16] Tolerance, rebound insomnia or withdrawal effects have not been observed with ramelteon.[5]

VII. Dosing and Administration

The usual dosing regimens for the miscellaneous anxiolytics, sedatives, and hypnotics are summarized in Table 9.

Table 9. Usual Dosing for the Miscellaneous Anxiolytics, Sedatives, and Hypnotics[6-8,14-25]

Drug	DEA Schedule	Usual Adult Dose	Usual Pediatric Dose	Availability
Buspirone	Not a controlled substance	Anxiety: Initial,15 mg daily (7.5 mg twice daily); dosage may be increased 5 mg per day every two to three days as needed; maximum daily dose: not to exceed 60 mg per day	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	IV	Alcohol Withdrawal Syndrome: 500 mg-1 g orally or rectally every six hours as needed; generally single doses or daily dosage should not exceed 2 g Hypnotic Dose: 500 mg-1 g orally or rectally 15-30 minutes before bedtime or, when used as a preoperative medication, 30 minutes before surgery Sedative Dose: 250 mg three times a day after meals; generally single doses or daily dosage should not exceed 2 g	Hypnotic Dose: 50 mg/kg or 1.5 g/m^2 orally or rectally; maximum single dose: 1 g Sedative Dose: 8 mg/kg or 250 mg/m^2 three times a day; maximum dose: 500 mg three times a day Premedication for Electroencephalographic Evaluation: 20-25 mg/kg	Capsule: 500 mg Suppository: 324 mg 500 mg Syrup: 500 mg/5 mL
Dexmedetomidine	Not a controlled substance	Sedation: 1 mcg/kg 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.	Vial: 200 mcg/2 mL
Droperidol	Not a controlled substance	Nausea and Vomiting: Maximum initial dose of 2.5 mg intramuscularly (IM) or slow intravenously (IV); additional 1.25 mg doses may be given to achieve desired effect	Nausea and Vomiting: Ages 2-12 years: maximum initial dose of 0.1 mg/kg; additional doses should be administered with caution, and only if potential benefit outweighs the potential risks	Ampule/Vial: 2.5 mg/mL
Eszopiclone	IV	Insomnia: Nonelderly adults: initial, 2 mg immediately before bedtime; dose may be increased to 3 mg Elderly adults: initial, 1 mg immediately before bedtime if main complaint is difficulty falling asleep; 2 mg immediately before bedtime if main complaint is difficulty staying asleep Severe hepatic impairment: initial, 1 mg	Safety and efficacy in children <18 years have not been established.	Tablet: 1 mg 2 mg 3 mg
Hydroxyzine hydrochloride	Not a controlled substance	Anxiety, Acutely Disturbed or Hysterical Patients or Alcohol Withdrawal: 50-100 mg IM and every four to six hours as needed Nausea and Vomiting (Excluding	Nausea and Vomiting (Excluding Pregnancy Associated): 0.5 mg/lb IM Sedation, Adjunctive Medication Pre- and	Syrup: 10 mg/5 mL Tablet: 10 mg 25 mg 50 mg

Drug	DEA Schedule	Usual Adult Dose	Usual Pediatric Dose	Availability
		Pregnancy Associated): 25-100 mg IM Sedation, Adjunctive Medication Pre- and Postoperative and Pre- and Postpartum: 25-100 mg IM	Postoperative: 0.5 mg/lb IM	Vial: 25 mg/mL 50 mg/mL
Hydroxyzine pamoate	Not a controlled substance	Anxiety: 50-100 mg four times daily Pruritis: 25 mg three or four times a day Sedation, Premedication or Following General Anesthesia: 50-100 mg	Anxiety: 6 years and older: 50-100 mg daily in divided doses Under 6 years: 50 mg daily in divided doses Pruritus: 6 years and older: 50-100 mg daily in divided doses Under 6 years: 50 mg daily in divided doses Sedation, Premedication or Following General Anesthesia: 0.6 mg/kg	Capsule: 25 mg 50 mg 100 mg Suspension: 25 mg/5 mL
Meprobamate	IV	Anxiety: 1,200-1,600 mg per day in three or four divided doses; maximum: 2,400 mg per day	Anxiety: 6-12 years: 200-600 mg per day in two or three divided doses Not recommended for children <6 years of age.	Tablet: 200 mg 400 mg
Ramelteon	Not a controlled substance	Insomnia: 8 mg taken within 30 minutes before going to bed	Safety and efficacy in children have not been established.	Tablet: 8 mg
Zaleplon	IV	Insomnia: Nonelderly adults: 10 mg at bedtime; maximum dose: 20 mg Elderly patients and debilitated patients: 5 mg at bedtime; maximum dose: 10 mg Patients with mild-to-moderate hepatic impairment: 5 mg at bedtime	Safety and efficacy in children have not been established.	Capsule: 5 mg 10 mg
Zolpidem	IV	Insomnia: Nonelderly adults: 10 mg IR tablet or 12.5 mg ER tablet immediately before bedtime Elderly, debilitated patients or patients with hepatic insufficiency: 5 mg IR tablet or 6.25 mg ER tablet immediately before bedtime	Safety and efficacy in children <18 years old have not been established.	Tablet, immediate-release (IR): 5 mg 10 mg Tablet, extended-release (ER): 6.25 mg 12.5 mg

VIII. Effectiveness

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

Table 10. Comparative Clinical Trials Using the Miscellaneous Anxiolytics, Sedatives, and Hypnotics

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Anxiety				
Gammans et al[27] Buspirone (doses varied with range 10-60 mg/day) vs placebo	DB, MA, PG, RCT Adult outpatients with GAD HAM-A total score ≥18	8 trials N=509 4 weeks double-blind treatment	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 Secondary: Not reported	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). Secondary: Not reported
Chessick et al[28] Azapirones (buspirone: 29 trials, gepirone*: 2 trials, ipsapirone*: 4 trials, lesopitron*: 1 trial)	MA, PG, PRO, RCT Outpatients diagnosed with GAD	36 trials N=5,908 4-14 weeks	Primary: Efficacy (HAM-A, CGI), acceptability (drop out rates, specific side effects) Secondary:	Primary: Overall, azapirones 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 azapirones was 4.4 (95% CI: 2.16 to 15.4). Using the HAM-A assessment, lorazepam (N=40, WMD: 1.1; 95% CI: 0.29 to 1.91, P=0.008) and alprazolam (N=39, WMD: 1.1; 95% CI: 0.28

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs benzodiazepines (26 trials), hydroxyzine (1 trial), kava kava (1 trial), placebo (22 trials), venlafaxine XR (1 trial) or psychotherapy (1 trial) Trials may have had more than 2 arms.			Not reported	to 1.92, *P*=0.009) were more effective than buspirone, but diazepam was comparable in efficacy to buspirone (N=19, WMD: -0.20; 95% CI: -7.45 to 7.05, *P*=0.96). Another small study (N=51) 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 (*P* values not reported). 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 (no *P* value reported). The meta-analysis was not able to conclude if buspirone was more effective than kava kava (*P*=0.3) or psychotherapy (*P* value not reported). 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 drop out 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				benzodiazepines, while those on benzodiazepines reported less nausea (*P*=0.03) and dizziness (*P*=0.02) compared to buspirone. In the trial that discontinued either diazepam or buspirone at either 6 or 12 weeks, neither group had worsening symptoms of anxiety, but those on diazepam did show withdrawal symptoms at 6 weeks compared to those on buspirone (*P*<0.001). In the one extension trial with a taper off, 25% of patients on ipsapirone showed rebound anxiety symptoms compared to 40% of patients on lorazepam (*P*<0.001). Patients on buspirone reported less dry mouth (*P*=0.03) compared to venlafaxine XR while those on venlafaxine XR reported less dizziness (*P*<0.00001) compared to buspirone. No differences in side effects were reported between buspirone and kava kava (*P*=0.5). Secondary: Not reported
Mitte et al[29] Benzodiazepines (mostly diazepam, alprazolam, lorazepam) vs azapirones (mostly buspirone) vs placebo	MA Patients with GAD	48 trials N=12,053 Not reported (minimum duration for inclusion was 14 days)	Primary: Anxiety (HAM-A, HAM-D), clinical significance Secondary: Not reported	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 azapirones (*P* value not reported). Significantly fewer patients in the benzodiazepine group dropped out of the study (20.5% vs 30.7%, *P*<0.05). Secondary: Not reported
Blanco et al[30] Benzodiazepines (clonazepam, bromazepam*,	MA Patients being treated for social	23 trials N=2,954	Primary: Outcome data on the Liebowitz Social Anxiety Scale (LSAS)	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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
alprazolam) or antidepressants (SSRI [fluvoxamine, paroxetine, sertraline], MAOI [phenelzine], reversible inhibitor of monoamine-oxidase-A [RIMA; moclobemide*, brofaromine*]) or β-blockers (atenolol) or gabapentin or buspirone vs placebo	anxiety disorder	Duration varied (6-20 weeks)	or a categorical measure of status Secondary: Proportion of responders with CGI score change of 1 or 2 (eg, "very much" or "much improved," respectively)	(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] Buspirone 20 mg/day (5 mg in AM and midday, 10 mg in PM)	DB, MC, PC, PG, RCT Adult outpatients with GAD HAM-A total	N=244 6 weeks	Primary: HAM-A scores Secondary: CGI, Montgomery-Asberg Depression	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 (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs hydroxyzine (salt not specified) 50 mg/day (12.5 mg in AM and midday, 25 mg in PM) vs placebo	score ≥20		Rating Scale (MADRS), Hospital Anxiety and Depression (HAD) Scale, Echelle Dyscontrole Comportemental (EDC), Ferreri Anxiety Rating Diagram (FARD), Tyrer Withdrawal Symptom Scale	Secondary: Significantly (*P*<0.02) more patients on hydroxyzine improved CGI scores than placebo. There was no significant difference between buspirone and placebo (*P* values not reported). 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] Hydroxyzine (salt not specified) 50 mg/day (12.5 mg in AM and noon, 25 mg PM)	DB, MC, PG, RCT Adult outpatients with GAD HAM-A total score ≥20	N=334 18 weeks	Primary: HAM-A scores Secondary: Responder and remission rates, change in Clinical	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:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
or bromazepam* 6 mg/day (1.5 mg in AM and noon, 3 mg in PM) vs placebo			Global Impressions-Severity (CGI-S) scale score and HAD scale score, maintenance of treatment efficacy, evaluation of rebound and withdrawal symptoms, safety	Results at endpoint for percentage of responders (*P*=0.003), remission rates (*P*=0.028), change in CGI-S scale score (*P*=0.001), HAD scale score (*P*=0.008), and maintenance of efficacy (*P*=0.022) on day 84 also confirmed the efficacy of hydroxyzine over placebo. The study showed no statistically significant difference between hydroxyzine and bromazepam; however, the study was not designed or powered to detect differences between these 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%) (*P* values not reported). There were no statistically significant differences between each treatment group with regards to rebound effect (*P* values not reported). 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				
Piccione et al[33] Chloral hydrate 250 mg vs chloral hydrate 500 mg	DB, XO Elderly (>60 years) patients with insomnia	N=27 5 days	Primary: Efficacy (questionnaire with subjective estimates of sleep latency, total sleep time [TST], number of	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 (*P* values not reported). 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.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs triazolam 0.25 mg vs triazolam 0.50 mg vs placebo Participants received each of the 5 treatments on 5 consecutive nights.			awakenings, overall quality of sleep), side effects Secondary: Not reported	There was no significant difference in sleep latency, TST and number of awakenings between placebo and either dose of chloral hydrate (*P* values not reported). Triazolam 0.25 mg significantly decreased sleep latency and increased TST compared to placebo (both $P<0.05$). Triazolam 0.50 mg significantly decreased the number of awakenings compared to placebo ($P<0.01$). Patients estimated their TST to be longer following the use of triazolam 0.25 mg as compared to chloral hydrate 250 mg or 500 mg (both $P<0.05$). There were no significant differences in reported side effects between the active treatments and placebo. Secondary: Not reported
Zammit et al[34] Eszopiclone 2 mg or 3 mg vs placebo	DB, MC, PC, RCT Adults aged 21-64 years 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 Secondary: Not reported	Primary: Eszopiclone 2 mg and 3 mg had significantly less time to sleep onset ($P\leq0.001$ and $P\leq0.0001$, respectively), more TST ($P\leq0.01$ and $P\leq0.0001$), better sleep efficiency ($P\leq0.001$ and $P\leq0.0001$), and enhanced quality and depth of sleep (both $P<0.05$) across the double-blind period compared with placebo. Eszopiclone 3 mg ($P\leq0.01$) 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.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
Scharf et al[35] Eszopiclone 1 mg or 2 mg vs placebo	DB, MC, PC, RCT Community-dwelling elderly patients (mean age 72.3 years) with primary insomnia	N=231 2 weeks	Primary: Patient-reported efficacy (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 of life (Quality of Life Enjoyment and Satisfaction Questionnaire [Q-LES-Q]), safety	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 ($P=0.058$). 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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] Eszopiclone 3 mg (N=593) vs placebo (N=195)	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 Secondary: Not reported	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 $P \leq 0.003$). Monthly ratings of next-day function, alertness, and sense of physical well-being were also significantly better with the use of eszopiclone than with placebo (all $P \leq 0.002$). There was no evidence of tolerance and the most common adverse events were unpleasant taste and headache. Secondary: Not reported
Walsh et al[37] Eszopiclone 3 mg (N=550) vs placebo (N=280)	DB, MC, PC, RCT Adults aged 21-64 years 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-being, and ability to function), Insomnia Severity Index, Fatigue Severity Scale, Epworth Sleepiness	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 ($P<0.05$). SF-36 domains of Physical Functioning, Vitality, and Social Functioning were improved with eszopiclone vs placebo for the Month 1-6 average

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			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) Secondary: Not reported	(*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, *P* value not reported). Unpleasant taste (19.7% vs 1.1%; *P*<0.001), somnolence (8.8% vs 3.2%; *P*=0.0029), and myalgia (6.0% vs 2.9; *P*=0.047) were reported in significantly more patients receiving eszopiclone than placebo. Secondary: Not reported
Rosenberg et al[38] Eszopiclone 1 mg, 2 mg, 3 mg or 3.5 mg vs placebo	DB, PC, RCT Healthy adult volunteers with transient insomnia	N=436 1 night	Primary: Efficacy and next-morning effects evaluated by PSG, DSST and self report Secondary: Not reported	Primary: Patients treated with eszopiclone had significantly less PSG latency to persistent sleep (all doses except 1 mg; *P*≤0.0001), WASO (all doses; *P*≤0.05) and number of awakenings (3 and 3.5 mg doses; *P*<0.005), and greater sleep efficiency (all doses; *P*≤0.02) compared with placebo. Self-reported efficacy results were similar to PSG. Self-reported morning sleepiness scores were significantly better for eszopiclone 3 and 3.5 mg compared with placebo (*P*<0.05). Treatment was well tolerated by patients, and the most common treatment-related adverse event was unpleasant taste.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
Johnson et al[39] Ramelteon 16mg, 80 mg or 160 mg vs triazolam 0.25 mg, 0.5 mg or 0.75 mg vs placebo	DB, XO Adults with 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) Secondary: Not reported	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. Secondary: Not reported
Roth et al[40] Ramelteon 16 mg vs ramelteon 64 mg vs placebo Doses were given 30 minutes before bedtime.	DB, PC, MC, RCT Healthy adult volunteers with transient insomnia (aged 35-60 years with total sleep duration of 6.5-8.5 hours, a usual sleep latency of 30 minutes or less, a habitual bedtime between 8:30	N =375 1 night	Primary: Mean latency to persistent sleep (LPS) as measured by PSG Secondary: TST, WASO, percentage of sleep time in each sleep stage, number of awakenings, residual effects assessed by DSST and postsleep questionnaire, safety	Primary: Participants who had received either ramelteon dosage had significantly shorter LPS relative to placebo (both *P*<0.001). Secondary: Participants who had received ramelteon 16 mg or 64 mg had significantly longer TST compared with placebo (*P*=0.007 and *P*=0.033, respectively). There were no significant differences between the ramelteon groups and placebo with regards to WASO, percentage of sleep time in each sleep stage, and number of awakenings. No significant differences in DSST scores were reported among the groups, but ramelteon 64 mg was associated with statistically significant declines in subjective levels of alertness (*P*=0.020) and ability to concentrate (*P*=0.043) compared to placebo.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	PM and midnight)			No serious adverse events were reported.
Roth et al[41] Ramelteon 4 mg vs ramelteon 8 mg vs placebo Doses were given at night.	DB, PC, RCT Patients aged 64-93 years 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 (eg, 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] Ramelteon 4 mg, 8 mg, 16 mg or 32 mg vs	DB, MC, PC, RCT, 5-period XO Men and non-pregnant, non-	N =107 2 nights per treatment	Primary: Mean LPS Secondary: TST, WASO, percentage of sleep	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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo Patients received all 5 treatments, with a 5- to 12-day washout between treatments. Medication was administered 30 minutes before bedtime.	lactating women between 18-64 years of age with chronic insomnia		time in each sleep stage, subjective sleep quality, next-day performance and alertness, safety	in TST compared with placebo (*P*=0.001). No significant differences in WASO (*P*=0.470), percentage of time spent in the different sleep stages and subjective sleep quality (*P*=0.525) were reported between the ramelteon groups and placebo. There were no differences between placebo and any ramelteon dose group on next-day performance and alertness (*P* values not reported). The safety of ramelteon at each dose was similar to that of placebo and the most commonly reported adverse events were headache, somnolence, and sore throat.
Danjou et al[43] Zaleplon 10 mg vs zolpidem 10 mg vs placebo	DB, XO Healthy volunteers, mean age 29.5 years	N=36 13 days	Primary: Subjective and objective measurements of residual effects when study drug was given 5, 4, 3, or 2 hours before morning awakening, tests included DSST, Critical Flicker Fusion (CFF) threshold, Choice Reaction Time (CRT), Memory Test, Sternberg Memory Scanning Task, Leeds Analogue Rating Scales (LARS), Leeds Sleep Evaluation Questionnaire (LSEQ), adverse events	Primary: No residual effects were demonstrated after zaleplon 10 mg, when administered as little as 2 hours before waking, on either subjective or objective assessments. Zolpidem 10 mg showed significant residual effects on DSST and memory after administration up to 5 hours before waking and CRT, CFF threshold and Sternberg Memory Scanning Task after administration up to 4 hours before waking. Residual effects of zolpidem were apparent in all objective and subjective measurements when the drug was administered later in the night. There were no serious adverse experiences during the study; all adverse events were mild-to-moderate. Overall, the number of subjects who reported any adverse experience after administration of study drug was similar for zaleplon and placebo (11% and 33% regardless of the time of drug administration) but was significantly higher following zolpidem (56% to 72%) when zolpidem was administered 2, 3, 4, and 5 hours before awakening (*P* values not reported). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Secondary: Not reported	
Verster et al[44] Zaleplon 10 mg vs zaleplon 20 mg vs zolpidem 10 mg vs zolpidem 20 mg vs placebo This was a 2-part study with the first part evaluating the effect of ethanol and the second part evaluating the effects of zaleplon and zolpidem. Only the second part of the study was reported in this review.	DB, XO Healthy volunteers with mean age 24.0 years	N=30 Single dose with at least a 5-day washout period	Primary: Driving ability (standard deviation of the lateral position [SDLP], standard deviation of speed [SDS], memory, psychomotor performance) (subjects given study medication 5 hours after going to bed and awakened 3 hours after dose, driving test performed 4 hours after awakened, memory and psychomotor tests performed 6 hours after awakened) Secondary: Not reported	Primary: Zaleplon 10 and 20 mg did not significantly impair driving ability 4 hours after middle-of-the-night administration (significant difference defined as $P<0.0125$). Relative to placebo, after zolpidem 10 mg, SDLP (amount of weaving of the car) was significantly elevated but the magnitude of the difference was small and not likely to be of clinical importance (difference was 2.87 cm; $P<0.005$). SDS (speed variability) was not significantly different for zolpidem 10 mg than placebo ($P=0.256$). Zolpidem 20 mg significantly increased SDLP and speed variability (both $P<0.001$). Memory and psychomotor test performances were unaffected after both doses of zaleplon and zolpidem 10 mg. Zolpidem 20 mg significantly impaired performance on psychomotor and memory tests. (Note: the recommended dose for zolpidem is 10 mg immediately before bedtime.) Secondary: Not reported
Dunbar et al[45] Zaleplon 5 mg to 20 mg	MA, DB, PG, RCT, XO	6 trials N=1,539	Primary: Sleep onset latency, TST, quality of sleep,	Primary: Of the 2 studies that directly compared sleep onset latency, 1 study reported a significantly shorter sleep latency with zaleplon ($P<0.001$),

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs zolpidem 5 mg to 10 mg The complete meta-analysis included 24 studies in 3,909 patients of which 17 studies compared zaleplon, zolpidem or zopiclone* to a benzodiazepine, 1 study compared zolpidem to zopiclone* and 6 studies compared zaleplon to zolpidem. Only the results of the studies comparing zaleplon to zolpidem are included in this review.	Patients aged 16-85 years with insomnia	Duration varied (2 nights to 4 weeks)	adverse events, rebound insomnia Secondary: Not reported	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, *P* value not reported). 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). Secondary: Not reported
Elie et al[46] Zaleplon 5, 10 or 20 mg or zolpidem 10 mg	DB, MC, PC, RCT Adults with primary	N=615 4 weeks	Primary: Patient's assessment of sleep latency Secondary:	Primary: Median sleep latency was significantly lower with zaleplon 10 mg and 20 mg than with placebo during all 4 weeks of treatment, and with zaleplon 5 mg and zolpidem 10 mg for the first 3 weeks.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo After 28 days, all treatments were followed by placebo for 3 nights.	insomnia or insomnia associated with mild nonpsychotic psychiatric disorders		Patient's assessment of sleep duration, sleep quality, number of awakenings, rebound insomnia, withdrawal effects, safety	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 (*P* values not reported). 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	Sample Size and Study Duration	End Points	Results
Roth et al[47] Zolpidem 5, 7.5, 10, 15, 20 mg vs placebo Statistical analyses were primarily performed between zolpidem 7.5 and 10 mg and placebo.	DB, PC, PG, RCT Healthy adult volunteers with transient insomnia	N=462 Single dose	Primary: Sleep latency, sleep duration, sleep efficiency (total sleep time divided by time in bed) number of awakenings (sleep maintenance), effect on sleep stages, next day psychomotor performance and alertness (DSST, Symbol Copying Tests, Visual Analog Scales on the Morning Questionnaire) Secondary: Not reported	Primary: Compared to placebo, zolpidem 7.5 and 10 mg significantly decreased sleep latency, increased sleep duration and efficiency, and reduced the number of awakenings (all $P<0.05$). Subjective quality of sleep was also rated significantly better with both doses of zolpidem compared to placebo (both $P<0.001$). Increasing the dose above 10 mg did not result in a corresponding increase in hypnotic efficacy. Treatment with zolpidem had no effect on stage 1, stage 2 and stages 3-4 sleep. Significantly less rapid eye movement (REM) sleep was reported in the zolpidem groups compared to the placebo group (both $P<0.001$). Zolpidem 7.5 or 10 mg had no significant effect on next day psychomotor performance and alertness. No statistically significant differences in the overall side effects were found between zolpidem doses of 7.5 mg (4.9%) or 10 mg (6.7%) and placebo (7.8%). Higher doses of zolpidem were associated with more side effects (17.6% with 15 mg [$P=0.069$ vs placebo] and 31.4% with 20 mg [$P<0.001$ vs placebo]). Secondary: Not reported
Scharf et al[48] Zolpidem 10 or 15 mg vs placebo Patients were randomized to receive either zolpidem or placebo for 35 nights,	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 Secondary: Not reported	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.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
followed by placebo for 3 additional nights.				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 withdrew from the study: 1 patient experienced drowsiness, dizziness, and nausea; and 1 patient experienced visual disturbance and oversedation. The 15-mg zolpidem dosage provided no clinical advantage over the 10 mg zolpidem dosage. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Hindmarch et al[49] Zolpidem, modified release (MR) 6.25 mg vs zolpidem MR 12.5 mg vs flurazepam 30 mg vs placebo	DB, DD, RCT, XO Healthy volunteers at least 65 years of age	N=24 Single dose, treatment visits lasted 2 days and were separated by 28-42 days washout	Primary: Psychometric tests performed 8 hours after study medication (CFF, CRT, word recall, CTT, DSST), subjective evaluation of sleep (LSEQ), safety, pharmacokinetics (zolpidem MR only) Secondary: Not reported	Primary: There were no significant differences in psychometric tests between either dose of zolpidem MR 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 MR and with flurazepam (all $P<0.05$). Neither zolpidem MR nor flurazepam modified perception of well-being on awakening (*P* values not reported). 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. Secondary: Not reported
Smith et al[50] Benzodiazepines (flurazepam, quazepam^, triazolam, lorazepam, midazolam^): 6 trials or benzodiazepine receptor agonists (zolpidem, zopiclone*): 2 trials	MA Patients with primary insomnia for 1 month or longer	21 trials N=470 Duration varied (<1 week to 10 weeks)	Primary: Sleep latency, TST, number of awakenings, WASO, and sleep quality before and after treatment Secondary: Not reported	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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs behavioral treatment: 14 trials vs placebo One trial directly compared pharmacotherapy with a benzodiazepine (temazepam) and behavioral therapy.				28%. Overall, there were no differences in TST, number of awakenings, WASO, 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) Secondary: Not reported
Nowell et al[51] Benzodiazepines (estazolam^: 6 trials, flurazepam: 10 trials, lorazepam: 1 trial, quazepam^: 3 trials, temazepam: 3 trials, triazolam: 4 trials) or zolpidem: (5 trials) vs placebo	MA of 22 trials (from 1978-1996); DB, PC, RCT, XO Adults <65 years with chronic insomnia	22 trials N=1,894 Median duration of 7 days, range 4 to 35 days	Primary: Sleep latency, TST, number of awakenings, sleep quality Secondary: Not reported	Primary: Zolpidem and benzodiazepines were significantly more effective than placebo with regards to sleep latency, TST, number of awakenings and sleep quality ($P<0.001$). Secondary: Not reported Note: This meta-analysis did not compare the efficacy of zolpidem to benzodiazepines.
Buscemi et al[52] Benzodiazepines (52 trials including brotizolam*, estazolam^, flunitrazepam*, flurazepam, loprazolam*, lorazepam, lormetazepam*, nitrazepam*, quazepam^,	MA of 105 trials (up to July 2006); DB, PC, RCT Adults with chronic insomnia	105 trials N varied, range 6 to 1,507 Duration varied (1 night to 6 months)	Primary: Sleep latency, WASO, sleep efficiency, sleep quality, TST, adverse events Secondary: Not reported	Primary: Sleep latency assessed by PSG was significantly decreased for benzodiazepines (WMD: -10.0 minutes; 95% CI: -16.6 to -3.4), nonbenzodiazepines (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),

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
temazepam and triazolam) or nonbenzodiazepines (48 trials including eszopiclone, gaboxadol*, indiplon*, zaleplon, zolpidem and zopiclone*) or antidepressants (8 trials including doxepin, pivagabine*, trazodone and trimipramine) vs placebo (105 trials) Some trials had multiple treatment arms.				nonbenzodiazepines (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 nonbenzodiazepines 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 nonsignificantly favored antidepressants for WASO and nonsignificantly favored placebo for TST. (*P* values were not reported.) Indirect comparisons between benzodiazepines and nonbenzodiazepines resulted in no significant difference in sleep latency; however, benzodiazepines were associated with more adverse events (*P* value not reported). Indirect comparisons between benzodiazepines and antidepressants resulted in no significant difference in sleep latency or adverse events (*P* values not reported). Indirect comparisons between nonbenzodiazepines and antidepressants resulted in a significantly greater sleep latency assessed by PSG but not by sleep diary for nonbenzodiazepines. There was no significant difference in adverse events. (*P* values were not reported.) 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, nonbenzodiazepines and antidepressants, respectively, compared to placebo. The adverse events most commonly reported in these studies were headache, drowsiness, dizziness and nausea. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Not reported

*Not available in the United States
^Product not covered by Alabama Medicaid
Drug regimen abbreviations: AM=morning, BID=twice daily, HS=bedtime, MAOI=monoamine oxidase inhibitor, PM=evening, QD=once daily, QID=four times daily, 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, EDC=Echelle Dyscontrole Comportemental, 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

Tolerance

There are limited studies that have evaluated the long-term safety and efficacy of these agents. Chloral hydrate has been found to lose effectiveness for both inducing and maintaining sleep by the end of a 2-week period of drug administration.[23] 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.[2] The longest placebo-controlled studies with zaleplon were 4 weeks in duration.[2] 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 administered at the recommended dosages.[2]

Buspirone has shown no potential for abuse or diversion and there is no evidence that it causes tolerance, or either physical or psychological dependence.[16] Tolerance, rebound insomnia or withdrawal effects have not been observed with ramelteon when administered nightly for up to 6 months.[5,22]

Additional Evidence

Dose Simplification
The agents indicated to treat insomnia can all be administered as a single dose at bedtime. Agents within this review that are indicated to treat anxiety require more frequent administration. An evidence-based medicine literature search did not reveal data pertinent to this topic.

Stable Therapy
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Impact on Physician Visits
An evidence-based medicine literature search 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 11. Relative Cost of the Miscellaneous Anxiolytics, Sedatives, and Hypnotics

Generic Name	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
buspirone	tablet	Buspar®*	$$$$	$$
chloral hydrate	capsule, rectal suppository, syrup	Aquachloral®, Somnote®	$-$$	$
dexmedetomidine	injection	Precedex®	$$	N/A
droperidol	injection	Inapsine®*	$	$
eszopiclone	tablet	Lunesta®	$$$$	N/A
hydroxyzine hydrochloride	injection, syrup, tablet	Atarax®*†	N/A	$
hydroxyzine pamoate	capsule, oral suspension	Vistaril®*	$$$	$
meprobamate	tablet	Miltown®*	No available AWP	$$$
ramelteon	tablet	Rozerem®	$$$	N/A
zaleplon	capsule	Sonata®	$$$$	N/A
zolpidem	extended-release tablet, tablet	Ambien®*, Ambien® CR	$$$-$$$$	$

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

X. Conclusions

The miscellaneous anxiolytic, sedative, and hypnotic medications are primarily used for the treatment of anxiety disorders, induction of sedation and treatment of insomnia. Currently, none of these agents are considered to be first-line for any of the anxiety disorders, primarily due to questions of their tolerability and safety. In addition, these guidelines recognize that more clinical evidence supports the use of SSRI antidepressants in anxiety states and that SSRI medications are generally better tolerated.

Chloral hydrate, zaleplon, and zolpidem immediate-release tablets are FDA approved for the short-term treatment of insomnia, while eszopiclone, ramelteon and zolpidem extended-release tablets are labeled for insomnia (without a time restriction). Clinical studies have shown that eszopiclone, ramelteon and zolpidem extended-release tablets retained their efficacy out to 12 months, 6 months and 3 weeks, respectively. Currently, there are no guidelines that recommend one pharmacological agent as a first-line therapy choice in treatment of insomnia. Behavioral therapy has been shown to be effective and is recommended as an option for the management of chronic insomnia.[2,4,5] A review of 21 trials concluded that behavioral therapy was more effective than benzodiazepine receptor agonists in latency to sleep onset and equally effective in total sleep time, number of awakenings, wake time after sleep onset, and sleep quality.[50]

Direct comparison trials of the agents within this class are limited and there is insufficient evidence that demonstrates that any agent in the class is safer or more effective than another. Buspirone, chloral hydrate, droperidol, hydroxyzine hydrochloride and pamoate, meprobamate and zolpidem are available in at least one generic dosage form or strength.

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and over-the-counter products in this class 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 cost effective products and possibly designate one or more preferred brands.

References

1. American Psychiatric Association: diagnostic and statistical manual of mental disorders, 4th ed, text revision. [monograph on the internet]. Washington: American Psychiatric Association, 2000 [cited 2007 Jul 16]. Available from: http://online.statref.com/Document/Document.aspx?DocID=1&StartDoc=1&EndDoc=1&FxID=37&offset=151&level=2&State=False&SessionId=9FD39DGSXWDOTZNU.
2. Morin AK, Jarvis CI, Lynch AM. Therapeutic options for sleep-maintenance and sleep-onset insomnia. Pharmacotherapy. 2007;27(1):89-110.
3. Jackson SC, Curtis JL. Sleep disorders. In: DiPiro JT, Talbert RL, Yee CG, Matzke GR, Wells BG, Posey LM, editors. Pharmacotherapy: A Pathophysiologic Approach. 6th Edition. New York: McGraw-Hill;2005:1321-32.
4. Morgenthaler T, Kramer M, Alessi C, Friedman L, Boehlecke B, Brown T, et al; American Academy of Sleep Medicine. Practice parameters for the psychological and behavioral treatment of insomnia: an update. An American Academy of Sleep Medicine report. Sleep. 2006 Nov 1;29(11):1415-9. Available from: http://www.aasmnet.org/PracticeParameters.aspx?cid=109.
5. Treatment of insomnia. Treat Guidel Med Lett. 2006 Feb;4(42):5-10.
6. McEvoy GK, editor. AHFS Drug Information: Central Nervous System Agents 28:00: Anxiolytics, Sedatives, and Hypnotics 28:24, Benzodiazepines 28:24.08 [monograph on the Internet]. Bethesda (MD): American Society of Health-System Pharmacists; 2007 [cited 2007 Jul 16]. Available from: http://online.statref.com/Document/Document.aspx?DocID=568&StartDoc=568&EndDoc=568&FxID=1&offset=7&SessionId=9FD552TLLUWZNNQS.
7. Drug Facts and Comparisons 4.0 [database on the internet]. St. Louis: Wolters Kluwer Health, Inc.; 2007 [cited 2007 Jul 16]. Available from: http://online.factsandcomparisons.com.
8. Micromedex® Healthcare Series [database on the internet]. Greenwood Village (CO): Thomson Micromedex, 2007 [cited 2007 Jul 16]. Available from: http://www.thomsonhc.com/.
9. NIH state-of-the-science conference statement on manifestations and management of chronic insomnia in adults. [internet] NIH Consens Sci Statements. 2005 [cited 2007 Jul 16]. Jun 13-15; 22(2) 1-30. Available from: http://consensus.nih.gov/2005/2005InsomniaSOS026main.htm.
10. Ballenger J, Davidson J, Lecrubier Y, Nutt D, Baldwin D, den Boer J, et al. Consensus statement on panic disorder from the International Consensus Group on Depression and Anxiety. J Clin Psychiatry. 1998;59 Suppl 8:47-54.
11. Ballenger J, Davidson J, Lecrubier Y, Nutt DJ, Borkovec T, Rickels K, et al. Consensus statement on generalized anxiety disorder from the International Consensus Group on Depression and Anxiety. J Clin Psychiatry. 2001;62 Suppl 11:53-8.
12. McIntosh A, Cohen A, Turnbull N, Esmonde L, Dennis P, Eatock J, et al. Clinical guidelines for the management of anxiety. Management of anxiety (panic disorder, with or without agoraphobia, and generalized anxiety disorder) in adults in primary, secondary and community care [guideline on the internet]. London (UK): National Institute for Clinical Excellence (NICE); 2004 Dec [cited 2007 Jul 30]. Available from: http://guidance.nice.org.uk/CG22/guidance/pdf/English.
13. Ballenger J, Davidson J, Lecrubier Y, Nutt D, Bobes J, Beidel D, Ono Y, et al. Consensus statement on social anxiety disorder from the International Consensus Group on Depression and Anxiety. J Clin Psychiatry. 1998;59 Suppl 17:54-60.
14. Ambien® [package insert]. Bridgewater (NJ): Sanofi-Aventis US. March 2007.
15. Ambien CR® [package insert]. Bridgewater (NJ): Sanofi-Aventis US; April 2007.
16. Buspar® [package insert]. Princeton (NJ): Bristol-Myers Squibb; March 2007.
17. Droperidol [package insert]. Shirley (NY): American Regent Laboratories; January 2002.
18. Hydroxyzine hydrochloride injection [package insert]. Shirley (NY): American Regent Laboratories; October 2001.
19. Lunesta® [package insert]. Marlborough (MA): Sepracor; April 2007.
20. Meprobamate tablet [package insert]. Corona (CA): Watson Laboratories; April 2004.
21. Precedex® [package insert]. Lake Forest (IL): Hospira; April 2004.
22. Rozerem® [package insert]. Lincolnshire (IL): Takeda Pharmaceuticals America; April 2006.
23. Somnote® [package insert]. Boca Raton (FL): Breckenridge Pharmaceutical; December 2004.
24. Sonata® [package insert]. Bristol (TN): King Pharmaceuticals; March 2006.
25. Vistaril® [package insert]. New York (NY): Pfizer Labs; April 2004.
26. FDA requests label change for all sleep disorder drug products [press release on the Internet]. Rockville (MD): US Food and Drug Administration, 2007 Mar 14 [cited 2007 Aug 9]. Available from: http://www.fda.gov/bbs/topics/NEWS/2007/NEW01587.html.

27. Gammans RE, Stringfellow JC, Hvizdos AJ, Seidehamel RJ, Cohn JB, Wilcox CS, et al. Use of buspirone in patients with generalized anxiety disorder and coexisting depressive symptoms. A meta-analysis of eight randomized, controlled studies. Neuropsychobiology. 1992;25(4):193-201.
28. Chessick CA, Allen MH, Thase M, Batista Miralha da Cunha AB, Kapczinski FF, de Lima MS, et al. Azapirones for generalized anxiety disorder. Cochrane Database Syst Rev. 2006 Jul 19;3:CD006115.
29. Mitte K, Noack P, Steil R, Hautzinger M. A meta-analytic review of the efficacy of drug treatment in generalized anxiety disorder. J Clin Psychopharmacol. 2005 Apr;25(2):141-50.
30. Blanco C, Schneier F, Schmidt A, Blanco-Jerez C, Marshall R, Sanchez-Lacay A et al. Pharmacological treatment of social anxiety disorder: a meta-analysis. Depress Anxiety. 2003;18(1):29-40.
31. Lader M, Scotto JC. A multicentre double-blind comparison of hydroxyzine, buspirone and placebo in patients with generalized anxiety disorder. Psychopharmacology. 1998 Oct;139(4):402-6.
32. Llorca PM, Spadone C, Sol O, Danniau A, Bougerol T, Corruble E, et al. Efficacy and safety of hydroxyzine in the treatment of generalized anxiety disorder: a 3-month double-blind study. J Clin Psychiatry. 2002 Nov;63(11):1020-7.
33. Piccione P, Zorick F, Lutz T, Grissom T, Kramer M, Roth T. The efficacy of triazolam and chloral hydrate in geriatric insomniacs. J Int Med Res. 1980;8(5):361-7.
34. Zammit G, McNabb L, Caron J, Amato D, Roth T. Efficacy and safety of eszopiclone across 6 weeks of treatment for primary insomnia. Curr Med Res Opin. 2004 Dec;20(12):1979-91.
35. Scharf M, Erman M, Rosengerg R, Seiden D, McCall WV, Amato D, Wessel TC. A 2-week efficacy and safety study of eszopiclone in elderly patients with primary insomnia. Sleep. 2005;28(6):720-7.
36. Krystal AD, Walsh JK, Laska E, Caron J, Amato DA, Wessel TC, Roth T. Sustained efficacy of eszopiclone over 6 months of nightly treatment: results of a randomized, double-blind, placebo-controlled study in adults with chronic insomnia. Sleep. 2003 Nov 1;26(7):793-9.
37. Walsh JK, Krystal AD, Amato DA, Rubens R, Caron J, Wessel TC, Schaefer K, Roach J, Wallenstein F, Roth T. Nightly treatment of primary insomnia with eszopiclone for six months: effect on sleep, quality of life, and work limitations. Sleep. 2007:30(8):959-68.
38. Rosenberg R, Caron J, Roth T, Amato D. An assessment of the efficacy and safety of eszopiclone in the treatment of transient insomnia in healthy adults. Sleep Med. 2005;6:15-22.
39. Johnson MW, Suess PE, Griffiths RR. Ramelteon: a novel hypnotic lacking abuse liability and sedative adverse effects. Arch Gen Psych. 2006 Oct;63:1149-57.
40. Roth T, Stubbs C, Walsh JK. Ramelteon (TAK-375), a selective MT1/MT2-receptor agonist, reduces latency to persistent sleep in a model of transient insomnia related to a novel sleep environment. Sleep. 2005;28(3):303-7.
41. Roth T, Seiden D, Sainati S, Wang-Weigand S, Zhang J, Zee P. Effects of ramelteon on patient-reported sleep latency in older adults with chronic insomnia. Sleep Med. 2006 Jun;7(4):312-8.
42. Erman M, Seiden D, Zammit G, Sainati S, Zhang J. An efficacy, safety, and dose response study of ramelteon in patients with chronic primary insomnia. Sleep Med. 2006;7:17-24.
43. Danjou P, Paty I, Fruncillo R, Worthington P, Unruh M, Cevallos W, Martin P. A comparison of the residual effects of zaleplon and zolpidem following administration 5 to 2 h before awakening. Br J Clin Pharmacol. 1999;48:367-74.
44. Verster JC, Volkerts ER, Schreuder AHCML, Eijken EJE, van Heuckelum JHG, Veldhuijzen DS, Verbaten MN, Paty I, Darwish M, Danjou P, Patat A. Residual effects of middle-of-the-night administration of zaleplon and zolpidem on driving ability, memory functions, and psychomotor performance. J Clin Psychopharmacol. 2002 Dec;22(6):576-83.
45. Dundar Y, Dodd S, Strobl J, Boland A, Dickson R, Walley T. Comparative efficacy of newer hypnotic drugs for the short-term management of insomnia: a systematic review and meta-analysis. Hum Psychopharmacol Clin Exp. 2004:19:305-22.
46. Elie R, Ruther E, Farr I, Emilien G, Salinas E. Sleep latency is shortened during 4 weeks of treatment with zaleplon, a novel nonbenzodiazepine hypnotic. Zaleplon Clinical Study Group. J Clin Psychiatry. 1999 Aug;60(8):536-44.
47. Roth T, Roehrs T, Vogel G. Zolpidem in the treatment of transient insomnia: a double-blind, randomized comparison with placebo. Sleep. 1995 May;18(4):246-51.
48. Scharf M, Roth T, Vogel G, Walsh J. A multicenter, placebo-controlled study evaluating zolpidem in the treatment of chronic insomnia. J Clin Psychiatry. 1994 May;55(5):192-9.
49. Hindmarch I, Legangneux E, Stanley N, Emegbo S, Dawson J. A double-blind, placebo-controlled investigation of the residual psychomotor and cognitive effects of zolpidem-MR in healthy elderly volunteers. Br J Clin Pharmacol. 2006;62(5):538-45.
50. Smith M, Perlis M, Park A, Smith M, Pennington J, Giles D, et al. Comparative meta-analysis of pharmacotherapy and behavior therapy for persistent insomnia. Am J Psychiatry. 2002 Jan;159(1):5-11.
51. Nowell PD, Mazumdar S, Buysse DJ, Dew MA, Reynolds CF, Kupfer DJ. Benzodiazepines and zolpidem for chronic insomnia. A meta-analysis of treatment efficacy. JAMA. 1997 Dec 24/31;278(24):2170-7.

52. Buscemi N, Vandermeer B, Friesen C, Bialy L, Tubman M, Ospina M, Klassen TP, Witmans M. The efficacy and safety of drug treatments for chronic insomnia in adults: a meta-analysis of RCTs. J Gen Intern Med. 2007 Sep;22(9):1335-50.