Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Clinical Packet
May 14, 2014

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

P&T Charge

As defined by §22-6-122

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

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

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

Preferred Drug List/Program Definitions

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

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

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

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

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

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

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

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

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

Maximum Unit Limitations
Early Refill
Brand Limit Switchover
Therapeutic Duplication

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

Prior Authorization Criteria Definitions

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

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

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

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

External Criteria

Alzheimer's Agents

Appropriate Diagnosis

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

Prior Treatment Trials

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

Stable Therapy

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

Medical Justification

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

PA Approval Timeframes

- Approval may be given for up to 12 months.

Electronic Prior Authorization (PA)

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

Verbal PA Requests

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

Antidepressants

Appropriate Diagnosis

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

Prior Treatment Trials

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

Stable Therapy

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

Medical Justification

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

PA Approval Timeframes

- Approval may be given for up to 12 months.

Electronic Prior Authorization (PA)

- Antidepressants are included in the electronic PA program.

Verbal PA Requests

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

Cerebral Stimulants/Agents Used for ADD/ADHD

Appropriate Diagnosis

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

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

Prior Therapy

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

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

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

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

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

Stable Therapy

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

Medical Justification

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

PA Approval Timeframes

- Approval may be given for up to 12 months.

Electronic Prior Authorization (PA)

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

Verbal PA Requests

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

Anxiolytics/Sedatives/Hypnotics

Appropriate Diagnosis

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

Prior Treatment Trials

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

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

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

Stable Therapy

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

Medical Justification

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

PA Approval Timeframes

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

Electronic Prior Authorization (PA)

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

Verbal PA Requests

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

Genitourinary Smooth Muscle Relaxants

Appropriate Diagnosis

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

Prior Treatment Trials

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

Stable Therapy

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

Medical Justification

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

PA Approval Timeframes

- Approval may be given for up to 12 months.

Electronic Prior Authorization (PA)

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

Verbal PA Requests

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

AGENDA

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

May 14, 2014
9:00 a.m. – 12:00 noon

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1. Opening remarks…….....…..Chair
2. Approval of November 13, 2013 P&T Committee Meeting minutes……...….…Chair
3. Pharmacy program update…….…...….…….....…...Alabama Medicaid
4. Oral presentations by manufacturers/manufacturers' representatives (prior to each respective class review)
5. Pharmacotherapy class re-reviews from February 2014 meeting .....University of Massachusetts Clinical Pharmacy Services
   - Skin and Mucous Membrane Antibacterials – AHFS 840404
   - Skin and Mucous Membrane Antivirals – AHFS 840406
   - Skin and Mucous Membrane Antifungals – AHFS 840408
   - Skin and Mucous Membrane Scabicides and Pediculicides – AHFS 840412
   - Skin and Mucous Membrane Local Anti-infectives, Miscellaneous – AHFS 840492
   - Skin and Mucous Membrane Anti-inflammatory Agents – AHFS 840600
   - Skin and Mucous Membrane Antipruritics and Local Anesthetics – AHFS 840800
   - Skin and Mucous Membrane Astringents – AHFS 841200
   - Skin and Mucous Membrane Keratolytic Agents – AHFS 842800
   - Skin and Mucous Membrane Keratoplastic Agents – AHFS 843200
   - Skin and Mucous Membrane Agents, Miscellaneous – AHFS 849200
6. Pharmacotherapy class re-reviews…University of Massachusetts Medical School Clinical Pharmacy Services
   - Alzheimer's Agents
     - Parasympathomimetic (Cholinergic) Agents – AHFS Class 120400 (to include Aricept®, Aricept ODT®, Exelon®, Exelon Patch®, Razadyne®, and Razadyne ER® only)
     - Central Nervous System Agents, Miscellaneous – AHFS Class 289200 (to include Namenda® and Namenda XR® only)
   - Antidepressants – AHFS 281604
   - Cerebral Stimulants/Agents Used for ADHD
     - Central Alpha-Agonists – AHFS 240816 (to include Kapvay® only)
     - Amphetamines – AHFS 282004 (to include Adderall®, Adderall XR®, Desoxyn®, Dexedrine®, ProCentra®, Vyvanse® and Zenzedi® only)
     - Anorexigenic Agents and Respiratory and Cerebral Stimulants, Miscellaneous – AHFS 282032 (to include Concerta®, Daytrana®, Focalin®, Focalin XR®, Metadate CD®, Metadate ER®, Methylin®, Quillivant XR®, Ritalin®, Ritalin LA®, and Ritalin-SR® only)
     - Central Nervous System Agents, Miscellaneous – AHFS 289200 (to include Intuniv® and Strattera® only)

- Wakefulness Promoting Agents – AHFS 282080 (to include Nuvigil®, Provigil®, and Xyrem® only)
- Anxiolytics, Sedatives, and Hypnotics – Barbiturates – AHFS 282404
- Anxiolytics, Sedatives, and Hypnotics – Benzodiazepines – AHFS 282408
- Anxiolytics, Sedatives, and Hypnotics – Miscellaneous – AHFS 282492
- Genitourinary Smooth Muscle Relaxants – AHFS 861200

7. Results of voting announced……..…….....…….Chair
8. Next meeting date
    - August 13, 2014
9. Adjourn

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Alzheimer's Agents
Parasympathomimetic (Cholinergic) Agents, AHFS Class 120400
Central Nervous System Agents, Miscellaneous, AHFS Class 289200
May 14, 2014

I. Overview

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

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

There are four agents approved for the treatment of Alzheimer's disease, including cholinesterase inhibitors (donepezil, galantamine and rivastigmine) and an NMDA receptor antagonist (memantine).[4-12] Although none of the agents delay the progression of neurodegeneration, they do delay the progression of symptoms. The cholinesterase inhibitors enhance cholinergic function by increasing the concentration of acetylcholine through reversible inhibition of its hydrolysis by acetylcholinesterase. Memantine blocks NMDA receptors and inhibits their overstimulation by glutamate.

Since the last review an extended release capsule of memantine was approved by the Food and Drug Adminsitration.[12] Additionally, in February of 2014, Forest Laboratories notified the prescriber community that they plan to discontinue the sale of Namenda® tablets on August 15, 2014. They also note that they will continue to sell the Namenda® oral solution and Namenda XR® extended release capsules.[13]

The Alzheimer's agents that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Donepezil, galantamine and rivastigmine are available in a generic formulation. This class was last reviewed in August 2012.

Table 1. Alzheimer's Agents Included in this Review

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

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

II. Evidence-Based Medicine and Current Treatment Guidelines

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

Table 2. Treatment Guidelines Using the Alzheimer's Agents

Clinical Guideline	Recommendation(s)
European Federation of Neurological Societies: **Guidelines for the Diagnosis and Management of Alzheimer's Disease (2010)**[14]	• Patients and caregivers should be provided with education and support. • There is insufficient evidence to support the use of any drugs purely for the primary prevention of dementia. Cholinesterase inhibitors, vitamin E, gingko and oestrogens should not be used as treatments for those with mild cognitive impairment. • In patients with Alzheimer's disease, treatment with cholinesterase inhibitors (donepezil, galantamine, or rivastigmine) should be considered at the time of diagnosis, taking into account expected therapeutic benefits and potential safety issues. Benefits on cognitive and non-cognitive symptoms have been demonstrated in those with mild, moderate and severe disease. Realistic expectations for treatment effects and potential side effects should be discussed with the patient and caregivers. • In patients with moderate to severe Alzheimer's disease, treatment with memantine should be considered taking into account expected therapeutic benefits and potential safety issues. Benefits on cognitive and noncognitive symptoms are apparent, some non-cognitive symptoms (agitation, delusions) may respond better than others. Realistic expectations for treatment effects and potential side effects should be discussed with the patient and caregivers. • Regular patient follow-up should be an integral part of management. • Aspirin should not be used as a treatment for Alzheimer's disease, though it can be used in those with Alzheimer's disease who also have other indications for its use (e.g. to prevent cardiovascular events). • Vitamin E should not be used as a treatment for Alzheimer's disease. • Currently, there is insufficient evidence to support the use of other agents including, anti-inflammatory drugs, nootropics (including piracetam, nicergoline), selegiline, oestrogens, pentoxyphylin, or statins in the treatment or prevention of Alzheimer's disease. • Cognitive stimulation or rehabilitation may be considered in patients with mild to moderate Alzheimer's disease. • Management of behavioral and psychological symptoms of dementia should begin with a careful search for triggers and causative factors (i.e. physical illness). Where possible, initial treatment should be non-pharmacological. • Antipsychotics should only be used for moderate or severe behavioral and psychological symptoms of dementia causing significant distress which have either not responded to other treatments (like non-pharmacological measures or cholinesterase inhibitors) or when other treatments are not appropriate. Low dose of atypical agents should be used only after assessment of risk benefit and full discussion with patient (when capacity allows) and caregiver. • Atypical agents have fewer side effects and do not confer a greater risk of stroke or mortality than conventional drugs. • Selective serotonin reuptake inhibitors rather than tricyclic antidepressants should be used to treat depression in Alzheimer's disease.
American College of Physicians/American Academy of Family Physicians: **Current Pharmacologic Treatment of Dementia: A Clinical Practice Guideline**	• The decision to initiate therapy should be based on evaluation of benefits and risks associated with an individual patient. All of the drugs have known adverse events, and the decision to manage patients with dementia should balance harms against modest or even no benefit. • Although the evidence shows statistically significant benefits of treatment with some cholinesterase inhibitors and memantine for all kinds of dementia, these benefits, on average, are not clinically significant for cognition and are modest for global assessments. Currently, there is no way to predict which

Clinical Guideline	Recommendation(s)
(2008)[15]	patients might have a clinically important response. The evidence does not support prescribing these medications for every patient with dementia. • Evidence is insufficient to determine the optimal duration of therapy. No evidence demonstrates when it is appropriate to stop the treatment if the patient becomes unresponsive or shows decline in various domains of dementia. If slowing decline is no longer a goal, treatment with memantine or a cholinesterase inhibitor is no longer appropriate. • The evidence is insufficient to compare the effectiveness of different pharmacologic agents for the treatment of dementia. Because few trials compare one drug with another, evidence about effectiveness is insufficient to support the choice of specific drugs for the treatment of dementia. Assessment of the effectiveness of combination therapy is lacking. • Clinicians should base the choice of pharmacologic agents on tolerability, adverse effect profile and ease of use.
American Psychiatric Association: **Practice Guideline for the Treatment of Patients with Alzheimer's Disease and other Dementias (2007)**[16]	• The primary goal of medication treatment for cognitive symptoms in dementia is to delay the progression of symptoms, with the hope that this delay will translate into a preservation of functional ability, maintaining the patient for as long as possible at a particular level of symptom severity. However, no medication treatment has been shown to delay the progression of neurodegeneration. • Given the evidence from randomized controlled trials for modest improvement in some patients treated with cholinesterase inhibitors and the lack of established alternatives, it is appropriate to offer a trial of one of these agents for patients with mild or moderate Alzheimer's disease for whom the medication is not contraindicated. • Results of the numerous large placebo-controlled trials of individual cholinesterase inhibitors have suggested similar degrees of efficacy, although tolerability may differ among the medications. Currently available data do not allow a fair, unbiased direct comparison among the cholinesterase inhibitors. There is also no data on whether or how to switch from one cholinesterase inhibitor to another. • Reversible, direct medication-induced hepatotoxicity with hepatocellular injury is a unique property of tacrine. Because of this hepatotoxicity, tacrine is very uncommonly used. Hepatotoxicity has not been associated with donepezil, rivastigmine, or galantamine. • Donepezil, rivastigmine and galantamine are preferred over tacrine because of reversible hepatic toxicity and the requirement that it be given four times per day. • It is uncertain how long patients should be treated with cholinesterase inhibitors. The decision whether to continue treatment with cholinesterase inhibitors is highly individualized. Reasons that patients choose to stop taking these medications include side effects, adverse events, lack of motivation and lack of perceived efficacy. • Memantine should be considered for the treatment of patients with moderate to severe Alzheimer's disease. Memantine can be prescribed for people either currently taking or not taking a cholinesterase inhibitor. There is modest evidence that the combination of memantine and donepezil is better than donepezil alone, but there is no evidence that this combination is better than memantine alone. • Vitamin E (α-tocopherol) is no longer recommended for the treatment of cognitive symptoms of dementia because of limited evidence for its efficacy as well as safety concerns. • Nonsteroidal anti-inflammatory agents, statin medications, and estrogen supplementation (with conjugated equine estrogens) have shown a lack of efficacy and safety in placebo-controlled trials in patients with Alzheimer's

Clinical Guideline	Recommendation(s)
	disease and therefore are not recommended. • Cholinesterase inhibitors should be considered for patients with mild to moderate dementia associated with Parkinson's disease. Only rivastigmine has been approved by the Food and Drug Administration for this indication, but there is no reason to believe the benefit is specific to this cholinesterase inhibitor. Dosing and titration are similar to those for patients with Alzheimer's disease.
American Academy of Neurology: **Practice Parameter: Management of Dementia (An Evidence-Based Review) (2001; reaffirmed 2003)**[17]	<u>Pharmacologic treatment of Alzheimer's disease</u> • Cholinesterase inhibitors should be considered in patients with mild-to-moderate Alzheimer's disease, although studies suggest a small average degree of benefit. • Vitamin E (1,000 IU by mouth twice a day) should be considered in an attempt to slow progression of Alzheimer's disease. • There is insufficient evidence to support the use of other antioxidants, anti-inflammatory or other putative disease-modifying agents specifically to treat Alzheimer's disease because of the risk of significant side effects in the absence of demonstrated benefits. • Estrogen should not be prescribed to treat Alzheimer's disease. • Some patients with unspecified dementias may benefit from ginkgo biloba, but evidence-based efficacy data are lacking. <u>Pharmacologic treatment for noncognitive symptoms of dementia</u> • Antipsychotics should be used to treat agitation or psychosis in patients with dementia where environmental manipulation fails. Atypical agents may be better tolerated compared to traditional antipsychotics. • Selected antidepressants (e.g., selective serotonin-reuptake inhibitors and tricyclics) should be considered in the treatment of depression in individuals with dementia with side effect profiles guiding the choice of agent. <u>Educational Interventions for patients with dementia and/or caregivers</u> • Short-term programs directed toward educating family caregivers about Alzheimer's disease should be offered to improve caregiver satisfaction. • Intensive long-term education and support services should be offered to caregivers of patients with Alzheimer's disease to delay time to nursing home placement. • Staff of long-term care facilities should receive education about Alzheimer's disease to reduce the use of unnecessary antipsychotics. • As part of this practice guideline, additional interventions other than education for patients and caregivers are available for functional behaviors, problem behaviors, and care environment alterations.
American Academy of Neurology: **Practice Parameter: Evaluation and Treatment of Depression, Psychosis, and Dementia in Parkinson Disease (2006)**[18]	• For patients with Parkinson's disease dementia or dementia with Lewy bodies, rivastigmine is probably effective in improving cognitive function. However, the magnitude of the benefit is modest and tremor may be exacerbated. • For patients with Parkinson's disease dementia, donepezil is probably effective in improving cognitive function. However, the magnitude of the benefits is modest. Donepezil should be considered for the treatment of dementia in Parkinson's disease.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the Alzheimer's agents are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical

significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided, are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Alzheimer's Agents[4-12]

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

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

IV. Pharmacokinetics

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

Table 4. Pharmacokinetic Parameters of the Alzheimer's Agents[4-12]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Parasympathomimetic (Cholinergic Agents)					
Donepezil	% not reported	96	Liver	Renal (57) Feces (15)	70
Galantamine	90	18	Liver	Renal (95) Feces (5)	7
Rivastigmine	Oral: 36	40	Liver, extensive Brain, extensive	Renal (>90)	Oral: 1.5 Transdermal: 3.0
Central Nervous System Agents, Miscellaneous					
Memantine	Well absorbed	45	Liver, partial	Renal (48)	60 to 80

V. Drug Interactions

There are no significant drug interactions reported with the Alzheimer's agents.[4]

VI. Adverse Drug Events

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

Table 5. Adverse Drug Events (%) Reported with the Alzheimer's Agents[4-12]

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

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

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

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

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

VII. Dosing and Administration

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

Table 6. Usual Dosing Regimens for the Alzheimer's Agents[4-12]

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

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Dementia of the Alzheimer's type (moderate to severe): Tablet: initial, 5 mg daily; may increase to 10 mg daily after four to six weeks; may increase to 23 mg daily after three months on 10 mg daily dose Orally disintegrating tablet: initial, 5 mg daily; may increase to 10 mg daily after four to six weeks		10 mg 23 mg
Galantamine	Mild-to-moderate dementia of the Alzheimer's type: Extended-release capsule: initial, 8 mg daily; maintenance, 16 to 24 mg daily Tablet and oral solution: initial, 4 mg twice a day with the morning and evening meals; maintenance: 8 to 12 mg twice a daily	Safety and efficacy not established in the pediatric population.	Extended release capsule: 8 mg 16 mg 24 mg Solution: 4 mg/mL Tablet: 4 mg 8 mg 12 mg
Rivastigmine	Mild-to-moderate dementia of the Alzheimer's type: Capsule and solution: initial, 1.5 mg twice daily with the morning and evening meals; maintenance, 3 to 6 mg twice daily Transdermal patch: initial, 4.6 mg/24 hours; maintenance, 9.5 or 13.36 mg/24 hours Severe dementia of the Alzheimer's type: Transdermal patch: initial, 4.6 mg/24 hours; maintenance, 13.36 mg/24 hours Mild-to-moderate dementia associated with Parkinson's disease: Capsule and solution: Initial, 1.5 mg twice daily with the morning and evening meals; maintenance, 3 to 6 mg twice daily Transdermal patch: initial, 4.6 mg/24 hours; maintenance, 9.5 or 13.36 mg/24 hours	Safety and efficacy not established in the pediatric population.	Capsule: 1.5 mg 3 mg 4.5 mg 6 mg Solution: 2 mg/mL Transdermal patch: 4.6 mg/24 hours 9.5 mg/24 hours 13.3 mg/24 hours

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Central Nervous System Agents, Miscellaneous			
Memantine	Moderate-to-severe dementia of the Alzheimer's type: Solution and tablet: initial, 5 mg once daily, increase dose by 5 mg at weekly intervals (twice daily dosing); maintenance, 10 mg twice daily Extended release capsule: initial, 7 mg once daily; maintenance, 28 mg once daily	Safety and efficacy not established in the pediatric population.	Extended release capsule: 7 mg 14 mg 21 mg 28 mg Extended release capsule dose pack: 7 mg (7 count)-14 mg (7 count)-21 mg (7 count)-28 mg (7 count) Solution: 10 mg/5 mL Tablet: 5 mg 10 mg Tablet dose pack: 5 mg (28 count)-10 mg (21 count)

VIII. Effectiveness

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

Table 7. Comparative Clinical Trials with the Alzheimer's Agents

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Alzheimer's Disease				
Geldmacher et al.[19] (2003) Donepezil 5 mg/day	OS Patients with Alzheimer's disease	N=1,115 Variable duration	Primary: Time to nursing home placement Secondary: Not reported	Primary: Use of donepezil of 5 mg/day or more was associated with significant delays in nursing home placement. A cumulative dose-response relationship was observed between longer-term sustained donepezil use and delay of nursing home placement. When donepezil was taken at effective doses for at least nine to 12 months, conservative estimates of the time gained before nursing home placement were 21.4 months for first-dementia-related nursing home placement and 17.5 months for permanent nursing home placement. Secondary: Not reported
Burns et al.[20] (2007) Donepezil 5 to 10 mg/day	MC, OL Patients ≥50 years of age with mild-to-moderate Alzheimer's disease	N=579 132 weeks	Primary: ADAS-cog, CDR-SB, IDDD, QoLS, and adverse events Secondary: Not reported	Primary: Mean changes in ADAS-cog scores of all patients were improved by approximately two points after six weeks (cumulative week 36) and one point after 12 weeks (cumulative week 42), with improvement compared to the start of OL treatment. At week 24 (cumulative week 54), mean ADAS-cog scores still showed improvement (approximately 0.5 points) compared to those scores reported at the start of OL treatment. From 24 weeks, ADAS-cog scores declined over the remainder of the study. At the end of 132 weeks of OL treatment (162 weeks total follow-up), the change from DB baseline was 15.6 points for all patients. No difference was seen between patients who had previously received placebo in the DB phase vs those receiving donepezil for the entire treatment period. CDR-SB scores improved slightly over the first 12 weeks (up to cumulative week 42) of OL treatment and then slowly declined for the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				remainder of the study period (up to cumulative week 162). Mean IDDD total scores were maintained over the first 24 weeks of OL treatment to within approximately 1 point relative to those at the beginning of this study period. Mean IDDD scores were 138.1 at week 0, 136.9 at week 12, 138.9 at week 24 and 170.8 at week 132 (162 weeks of total follow-up). At the start of the OL extension, QoLS scores were improved compared to baseline, with a mean change of 3.03. The scores remained above the baseline level at weeks six and 12 of OL treatment. At the end of 132 weeks of OL treatment, the decline from the baseline for the DB study was -46.2. Overall, 85% of patients experienced at least one treatment-emergent adverse event. The most common adverse events included diarrhea (12%), nausea (11%), infection (11%) and accidental injury (10%). Nonfatal all-causality and treatment-related serious adverse events were reported for 25 and 7% of patients, respectively. Seventeen patients died during the study or within four weeks after discontinuation of donepezil. The most common causes of death were pneumonia (seven patients) and cerebrovascular accident (two patients). Fifteen deaths were considered unrelated to donepezil. Two deaths, one due to a cerebral hemorrhage diagnosed on day five of treatment and another due to a suspected myocardial infarction on day 55, were considered by the investigators to be possibly related to donepezil. Secondary: Not reported
Hashimoto et al.[21] (2009) Donepezil 5 mg/day	OS, PRO Patients with Alzheimer's disease	N=416 12 weeks	Primary: MMSE Secondary: Not reported	Primary: There were significant changes in mean scores on the MMSE (0.9; P<0.01) from baseline to week 12. There was a significant decrease in the personal strain score at week 12 (P=0.002). There was no significant improvement was in role strain.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There was no significant decrease in the time spent supervising Alzheimer's disease patients. Secondary: Not reported
Homma et al.[22] (2009) Donepezil 10 mg/day	OL Japanese patients ≥50 years of age with severe Alzheimer's disease (modified Hachinski Ischemic Score ≤6, FAST ≥6, MMSE score of 1 to 12	N=189 52 weeks	Primary: SIB, and BEHAVE-AD Secondary: Not reported	Primary: The mean change in SIB scores during the OL study showed improvement until week 24, followed by a decline by week 36. For those patients receiving 52 weeks of treatment, the mean change in SIB from baseline (enrollment in OL study) was –6.1. The mean change in SIB declined more rapidly after 24 weeks. For the BEHAVE-AD, little change was observed during the OL study. The change from baseline to week 24 and week 52 was 0.7 and 0.5, respectively. The level of behavioral symptoms in the study population was low. Overall, 177 patients (93.7%) experienced at least one adverse event. Severe adverse events were reported by 15 patients (7.9%) and serious adverse events were reported by 33 patients (17.5%). The most common adverse events were nasopharyngitis, diarrhea, nausea and vomiting. Secondary: Not reported
Courtney et al.[23] (2004) Donepezil 5 to 10 mg/day vs placebo	DB, RCT Patients with Alzheimer's disease	N=565 156 weeks	Primary: MMSE, BADLS, time to entering institution Secondary: Not reported	Primary: Cognition averaged 0.8 MMSE points better (95% CI, 0.5 to 1.2; P<0.0001) and functionality 1.0 BADLS points better (95% CI, 0.5 to 1.6; P<0.0001) with donepezil over the first two years. No significant benefits were seen with donepezil compared to placebo in institutionalization (42 vs 44% at three years; P=0.4) or progression of disability (58 vs 59% at three years; P=0.4). The RR of entering institutional care in the donepezil group compared to placebo was 0.97 (95% CI, 0.72 to 1.30; P=0.8); the RR of progression of disability or entering institutional care was 0.96 (95% CI, 0.74 to 1.24; P=0.7).

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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			changes in weight, electrocardiogram, vital signs, and laboratory parameters; and discontinuation due to adverse events all at months three, six, nine, and 12 Secondary: Not reported	Patients who had increased donepezil dose from 10 mg/day to 23 mg/day had slightly higher rates of adverse events than patients who were already receiving 23 mg (78.0 and 16.9 vs 72.8 and 14.0%, respectively). The incidence of new adverse events declined rapidly after the first two weeks and remained low throughout the duration of the study. Secondary: Not reported
Winblad et al.[26] (2006) RCT Donepezil 10 mg/day vs placebo OL Donepezil 5 mg daily for 28 days, then 10 mg/day per clinician's judgment	DB, OL, PC Patients 40 to 90 years of age with a probable or possible diagnosis of Alzheimer's disease	N=286 52-week RCT with a 2-year OL extension phase	Primary: GBS Secondary: MMSE, GDS, PDS, NPI	Primary: The GBS total scores indicate that both the continuous-treatment group and delayed-start groups had declined, with the difference between the two groups favoring the continuous-donepezil group, over the three-year period (P=0.056). Secondary: The MMSE declined significantly less in the continuous-treatment group than in the delayed-start group over the course of the study (P=0.004, P=0.057, respectively). GDS declined significantly less over the three-year study period in patients in the continuous-treatment group than in those in the delayed-start group (P=0.0231). There was a trend favoring continuous-donepezil treatment over delayed-start treatment on the PDS, although it was not statistically significant (P=0.091). NPI results showed no significant treatment differences between the groups.
Rogers et al.[27] (1998)	DB, MC, PC, RCT Patients with mild-	N=473 24 weeks	Primary: ADAS-Cog, CIBIC	Primary: Out of 473 patients, 80% of placebo patients, 85% of 5 mg patients and 68% of 10 mg patients completed the study. Those that discontinued due

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Donepezil 5 mg/day vs donepezil 10 mg/day vs placebo	to-moderate Alzheimer's disease		Secondary: Not reported	to adverse effects were 7, 6, and 16% in the placebo, 5 and 10 mg groups, respectively. Primary outcome measure was mean change in scores from baseline to endpoint in the ADAS-Cog. Both donepezil doses were statistically better than placebo (P<0.0001). Global functioning as measured by the CIBIC plus were statistically better for both donepezil groups compared to placebo at endpoint (P<0.005). Donepezil 5 and 10 mg treatment showed no statistical difference in improvements. Secondary: Not reported
Winblad et al.[28] (2006) Donepezil 10 mg/day vs placebo	DB, PC, PG Patients ≥50 years of age with severe Alzheimer's disease (MMSE score of 1 to 10 and a FAST rating of stage 5 to 7c)	N=248 6 months	Primary: SIB Secondary: MMSE, NPI, and CGI-I	Primary: At six months, patients assigned donepezil had significantly better mean change from baseline scores than those taking placebo for SIB (P<0.05). Secondary: CGI-I scores and the mean change from screening scores on the MMSE at six- month follow-up favored donepezil treatment over placebo (all P<0.05). There was no significant difference between treatment groups on the NPI for the modified intention-to-treat population (P=0.43).
Black et al.[29] (2007) Donepezil 10 mg/day vs placebo	DB, MC, PC, RCT Patients ≥50 years of age with severe Alzheimer's disease (MMSE score of 1 to 12, modified Hachinski Ischemic score ≤6, and FAST score ≥6)	N=343 24 weeks	Primary: SIB and CIBIC-Plus Secondary: ADCS-ADL-sev, NPI, MMSE, CBQ, RUSP	Primary: Donepezil was more efficacious when compared to placebo on SIB score change from baseline to endpoint, as well as on CIBIC-Plus score (P<0.05 for all results). Secondary: On the ADCS-ADL-sev, both the donepezil group and the placebo group declined from baseline, and the treatment difference was NS (P=0.3574). On the NPI, donepezil was not significantly different from placebo (P=0.4612).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The donepezil group showed significant improvement from screening to endpoint on the MMSE compared to placebo (P=0.0267). The CBQ stress measure showed no significant change from baseline for either group. The RUSP scores also had low average responses with little movement from baseline and no significant differences.
Homma et al.[30] (2008) Donepezil 5 to 10 mg/day vs placebo	DB, MC, PC, RCT Japanese patients ≥50 years of age with severe Alzheimer's disease (modified Hachinski Ischemic Score ≤6, FAST ≥6, MMSE score of 1 to 12 and diagnosis confirmed by neuroimaging)	N=302 24 weeks	Primary: SIB and CIBIC-Plus Secondary: ADCS-ADL-sev and BEHAVE-AD	Primary: Donepezil 5 and 10 mg/day were more effective than placebo on the SIB. At week 24, patients in the donepezil 5 mg/day group had a significant change from baseline of 2.5 points and those in the donepezil 10 mg/day group had a significant change from baseline of 4.7 points. Patients in the placebo group showed significant worsening (–4.2 points) during the course of the study (P<0.001 vs placebo). For the CIBIC-Plus, the analysis was performed on the seven categories of change as well as the three collapsed categories of improved, no change and worsened. In the seven-category analysis, the distribution of CIBIC-Plus scores in the donepezil 10 mg/day group was better than placebo (P=0.003); however, there was no difference with 5 mg/day (P=0.151). In the collapsed-category analysis, the distribution of CIBIC-Plus scores in the donepezil 10 mg/day group was better than placebo (P=0.001); however, there was no difference with 5 mg/day (P=0.129). Secondary: For the ADCS-ADL-sev, there was no significant differences between donepezil and placebo (placebo group, –1.1 points; donepezil 5 mg/day group, –0.1 points; donepezil 10 mg/day group, –0.3 points). For the BEHAVE-AD, there was no significant differences between donepezil and placebo (placebo group, –0.5; donepezil 5 mg/day group, –0.5; donepezil 10 mg/ day group, –0.1). Treatment-emergent adverse events were reported by 73.3% of placebo patients, 78.2% of donepezil 5 mg/day patients and 83.3% of donepezil 10

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				mg/day patients. There was no significant difference in adverse events between the donepezil groups and the placebo group. The most common adverse events reported are consistent with the known cholinergic side effects of donepezil. Serious adverse events were reported by 15 placebo patients (14.3%), 12 donepezil 5 mg/day patients (11.9%) and 10 donepezil 10 mg/day patients (10.4%). Five patients died during the treatment period. The causes of death were acute pneumonia (placebo group), acute myocardial infarction (donepezil 5 mg/day group), suspected stomach cancer (donepezil 5 mg/day group; the patient died 80 days after discontinuation), vomit-induced tracheal occlusion (donepezil 10 mg/day group; the patient died seven days after completion) and arrhythmia (donepezil 10 mg/day group).
Birks et al.[31] (2006) Donepezil 5 to 10 mg/day vs placebo	MA Patients with Alzheimer's disease	N=5,796 (24 trials) 12 to 60 weeks	Primary: ADAS-Cog, MMSE, CIBIC-Plus, ADL, withdrawals and adverse events Secondary: Not reported	Primary: A significant difference was seen on the ADAS-Cog scale for patients treated with donepezil 5 mg at 24 weeks (WMD, -2.02 points; 95% CI, -2.77 to -1.26; P<0.00001) and 10 mg at 24 weeks (WMD,–2.81 points; 95% CI, –3.55 to –2.06; P<0.00001). A significant difference was seen on the MMSE for patients treated with donepezil 10 mg/day as compared to placebo at 52 weeks (WMD, 1.84 points; 95% CI, 0.53 to 3.15; P=0.006). Global Clinical State, CIBIC-Plus scores showed significant benefit in patients treated with donepezil 5 and 10 mg/day (OR, 2.38; 95% CI, 1.78 to 3.19; P<0.00001 and OR, 1.82; 95% CI, 1.42 to 2.35; P<0.00001). Improvements were seen in ADL scores for patients in the donepezil group over those in the placebo group (P<0.01 for all scales used). Significantly more patients treated with donepezil 10 mg/day withdrew from treatment (24 vs 20%; P=0.003); however, there was no difference in withdrawal rates between the 5 mg/day and placebo group (P=0.56). Adverse events that occurred significantly more frequently in both the 5 and 10 mg/day treatment groups as compared to placebo are: anorexia, diarrhea, and muscle cramps.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Wallin et al.[32] (2007) Donepezil 5 to 10 mg/day vs historical data	MC, PRO Patients ≥40 years of age with probable Alzheimer's disease	N=435 3 years	Primary: MMSE, ADAS-Cog, CIBIC, IADL Secondary: Not reported	Primary: For the MMSE, patients had a mean score of 22.0 at baseline and 19.1 at 36 months. After 36 months of donepezil treatment, the mean decline was 3.8 points (95% CI, 3.0 to 4.7). For ADAS-Cog, patients had a mean score of 20.7 at baseline and 26.1 at 36 months. After 36 months, the mean increase was 8.2 points (95% CI, 6.4 to 10.0). A modeling equation predicts an increase in ADAS-Cog to be 4 to 9 points in 12 months without treatment. Scores for the treatment group were significantly better than predicted scores for non-treatment (95% CI, 14.5 to 16.6). For CIBIC, at two months, 34% of patients were considered improved, 59% unchanged and 7% were worse. At six months, 28% of patients were considered improved, 46% unchanged and 26% were worse. At 12 months, 20% of patients were considered improved, 29% unchanged and 51% were worse. At 36 months, 30% of patients were considered improved or unchanged. The IADL change from baseline at six months was 1.01, at 12 months 2.19, and at 36 months 6.18. Secondary: Not reported
Farlow et al.[33] (2010) Donepezil 10 mg/day vs donepezil 23 mg/day	DB, MC, RCT Patients 45 to 90 years of age with moderate-to-severe Alzheimer's disease who took donepezil 10 mg/day ≥12 weeks	N=1,467 24 weeks	Primary: Efficacy as measured by SIB-cognition and CIBIC-global function rating; tolerability Secondary: Not reported	Primary: After 24 weeks, the change in SIB-cognition score was significantly greater with donepezil 23 mg/day compared to donepezil 10 mg/day (2.6 vs 0.4, respectively; P<0.001). There was no significant different in CIBIC score with donepezil 23 mg/day compared to donepezil 10 mg/day (4.23 vs 4.29, respectively). In a post-hoc analysis, the least square mean changes in SIB score and CIBIC treatment effect at end point were greater with donepezil 23 mg/day compared to donepezil 10 mg/day in patients with more advanced

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Alzheimer's disease compared to less impaired patients (SIB, 1.6 vs -1.5, respectively; P<0.001; CIBIC, 4.31 vs 4.42; P=0.028). Treatment emergent adverse events were reported in 73.7% of patients who received donepezil 23 mg/day and in 63.7% of patients who received donepezil 10 mg/day. Adverse events were reported as follows with donepezil 23 mg/day: mild (30.8%), moderate (34.5%), and severe (8.4%). The most common treatment emergent adverse events were nausea (6.1%), vomiting (5%) and diarrhea (3.2%). Severe treatment emergent adverse events that were reported included nausea (0.9%), dizziness (0.7%) and vomiting (0.6%). Adverse events were reported as follows with donepezil 10 mg/day: mild (31.2%), moderate (25.3%), and severe (7.2%). The most common treatment emergent adverse events were nausea (1.9%), vomiting (0.8%) and diarrhea (1.5%). Severe treatment emergent adverse events that were reported included nausea (0.2%) and dizziness (0.2%). Secondary: Not reported
Ferris et al.[34] (2011) Donepezil 10 mg/day vs donepezil 23 mg/day	DB, MC, RCT (post-hoc analysis) Patients 45 to 90 years of age with moderate-to-severe Alzheimer's disease who took donepezil 10 mg/day ≥12 weeks	N=1,467 24 weeks	Primary: SIB-Language scale and 21-item SIB-derived language scale Secondary: Correlation of SIB-Language scale and SIB-derived language scale with ADCS-ADL-sev, CIBIC-plus/CIBIC-plus, and MMSE	Primary: At week 24, there was an improvement in language noted with donepezil 23 mg/day compared to a decline in language function with donepezil 10 mg/day (SIB-Language scale treatment difference, 0.8; P=0.0013, SIB-derived language scale treatment difference, 0.8; P=0.0009). Secondary: At week 24, SIB-Language scale and SIB-derived language scale scores were moderately correlated with scores on the ADCS-ADL-sev and CIBIC-plus. Results were similar in both moderate (MMSE, 17 to 20) and severe (MMSE, 0 to 16) Alzheimer's disease patients.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Farlow et al.[35] (2011) Donepezil 10 mg/day vs donepezil 23 mg/day	DB, MC, RCT (post-hoc analysis) Patients 45 to 90 years of age with moderate-to-severe Alzheimer's disease who took donepezil 10 mg/day ≥12 weeks	N=1,434 24 weeks	Primary: Safety and tolerability Secondary: Not reported	Primary: Of the 963 patients receiving donepezil 23 mg/day and 471 patients receiving donepezil 10 mg/day, a total of 71.1 and 84.7% completed the study, respectively. The most common adverse events causing early discontinuation were higher in the donepezil 23 mg/day group compared to the donepezil 10 mg/day group (18.6 vs 7.9%, respectively). Adverse events that contributed the most to the discontinuations were vomiting (2.9 vs 0.4%, respectively), nausea (1.9 vs 0.4%, respectively), diarrhea (1.7 vs 0.4%, respectively), and dizziness (1.1 and 0%, respectively). The most common adverse events with donepezil 23 mg/day compared to donepezil 10 mg/day were nausea (11.8 vs 3.4%, respectively), vomiting (9.2 vs 2.5%, respectively) and diarrhea (8.3 vs 5.3%, respectively). Serious adverse events occurred in 8.3% of patients receiving donepezil 23 mg/day and in 9.6% of patients receiving donepezil 10 mg/day. These included urinary tract infection (0.6 vs 0.4%, respectively), fall (0.6 vs 0.4%, respectively), pneumonia (0.3 vs 0.6%, respectively), syncope (0.2 vs 1.1%, respectively), aggression (0.2 vs 0.8%, respectively), and confusional state (0.1 vs 0.6%, respectively). Secondary: Not reported
Doody et al.[36] (2012) Donepezil 23 mg/day vs donepezil 10 mg/day Patients were	DB, MC Patients with moderate-to-severe Alzheimer's disease	N=not specified 24 weeks	Primary: Efficacy and safety Secondary: Not reported	Primary: At week 24, donepezil 23 mg/day provided significant cognitive benefits over 10 mg/day (P<0.01) on the SIB, with or without concomitant memantine. The higher dose showed no benefit on the global function, MMSE or ADL measures in either memantine subgroup. Rates of treatment-emergent adverse events were higher for donepezil 23 mg/day with memantine (80.7%) than 23 mg/day without memantine (69.7%) or 10 mg/day with/without memantine (66.7/62.0%); across all treatment groups, most events were mild/moderate in severity. Individual

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allowed to also take memantine.				rates of serious adverse events were low (<1.0%), regardless of concomitant memantine use. Secondary: Not reported
Raskind et al.[37] (2004) Galantamine 24 mg/day	OL Patients with mild-to-moderate Alzheimer's disease	N=194 36 months	Primary: ADAS-Cog, adverse events Secondary: Not reported	Primary: Patients treated continuously with galantamine for 36 months increased a mean of 10.2±0.9 points on the ADAS-Cog. This was a substantially smaller cognitive decline (approximately 50%) than that predicted for the placebo group. Patients discontinuing galantamine therapy before 36 months had declined at a similar rate before discontinuation as those completing 36 months of treatment. Almost 80% of patients who received galantamine for 36 months seemed to demonstrate cognitive benefits compared to those predicted for untreated patients. Secondary: Not reported
Rockwood et al.[38] (2008) Galantamine 24 mg/day	MC, OL Patients with Alzheimer's disease who had received galantamine treatment for up to 36 months	N=240 Up to 48 months	Primary: ADAS-Cog, DAD, adverse events Secondary: Not reported	Primary: Mean ADAS-Cog worsened from 22.6±8.6 at baseline to 31.3±13.1 at 48 months. DAD worsened from 73.4±18.1 at baseline to 36.1±29.0 at 48 months. Fifty one patients withdrew from the study. Secondary: Not reported
Wallin et al.[39] (2011) Galantamine 24 mg/day	MC, OL, PRO Patients with Alzheimer's disease and no previous cholinesterase	N=280 36 months	Primary: MMSE, ADAS-cog, IADL, CIBIC Secondary: Subgroup analysis	Primary: From baseline to 36 months, MMSE decreased from 23.3 to 21.74. The MMSE score was significantly better at two months (P<0.001) and at six months (P=0.006) compared to baseline, and was stable at 12 months (P=0.616) compared to baseline. The total mean decline in MMSE score from baseline after three years of treatment was 2.6

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	inhibitor therapy		by K-means cluster analysis	From baseline to 36 months, ADAS-cog increased from 16.85 to 19.39. The total change in ADAS-cog score after three years of treatment was 5.6 points above baseline values. The ADAS-cog scores at 6 months were not different from baseline (P=0.248), but deteriorated after that. Mean IADL scores demonstrated deteriorated at all time points compared to baseline (12.76 to 17.13). According to CIBIC scores at two months, 93% of patients remaining in the study were "improved or unchanged", at months six, 12, 24, and 36, 81, 69, 50 and 41% of the patients were "improved or unchanged", respectively. Secondary: Cluster analysis identified two response clusters. Cluster 1 included patients with low ability in ADAS-cog and IADL scores at baseline. These patients were older and less educated, but responded better at six months compared to cluster two patients. Cluster 2 patients included better ADAS-cog and IADL scores at baseline. Cluster 2 patients had a higher frequency of the APOE ε4 allele.
Brodaty et al.[40] (2006) Galantamine 2 to 50 mg/day	OL, OS, PRO Patients diagnosed with mild-to-moderately severe dementia	N=345 ITT N= 229 PP 6 month follow-up	Primary: MMSE, ADAS-Cog, CIBIC-Plus, IADL Secondary: Not reported	Primary: For the MMSE 65% of PP patients had an increased score at the three-month assessment as compared to baseline with an overall 92% response rate. 70% of PP patients had an increased score at the six-month assessment as compared to baseline with an overall 91% response rate. 44% of ITT patients had an increased score at the six-month assessment as compared to baseline (P values were not reported). For ADAS-Cog at 6 months, 86% of the PP patients and 33% of the ITT patients had a decrease in ADAS-Cog score. P value was not reported. For CIBIC-Plus at three months, 91% of PP patients were considered responders by their physicians; 28% were unchanged, 38% were minimally improved, 22% were much improved, 4% were very much

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				improved (P values not reported). For CIBIC-Plus at six months, 86% of PP patients were considered responders by their physicians; 20% were unchanged, 26% were minimally improved, 32% were much improved, 7% were very much improved. In the ITT patients, 54 % were classified as responders at six months (P values not reported). Most PP patients had no change in IADL scores at three and six months (P value not reported). Most PP patients had no change in behavior scores at three and six months (P value not reported). Secondary: Not reported
Cummings et al.[41] (2004) Galantamine 8 to 24 mg/day vs placebo	DB, PC, RCT 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
Scarpini et al.[42] (2011) <u>Phase 1</u> Galantamine 8 to 16 mg/day <u>Phase 2</u> Galantamine 16 mg/day	<u>Phase 1</u> MC, OL <u>Phase 2</u> DB, MC, RCT Mild to moderate Alzheimer's disease in patients ≥50 years of age	N=393 36 months	Primary: ADAS-cog/11 deterioration ≥4 points Secondary: CIBIC-plus, adverse events	<u>Phase1</u> Primary: Cognitive functions improved significantly on the ADAS-cog/11 scale with galantamine treatment at month seven relative to baseline (from 24.1 to 22.9, difference, -1.2; 95% CI, -2.3 to -0.1; P<0.01). Scores were similar to baseline values at the end of the OL phase at month 12 (mean score at baseline, 24.1; mean score at month 12, 24.7; 95% CI, -0.5 to 1.7, P=0.16). Secondary:

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vs placebo	(MMSE, 11 to 24)			CIBIC-plus score improved in 34.3%, was unchanged in 30.9%, and worsened in 34.9% of patients when compared to baseline. A total of 50.4% of patients reported adverse events, of which the most common was gastrointestinal disorders (21.3%), nervous system disorders (9.8%), and psychiatric disorders (19.7%). Serious adverse events were reported in 12.2%. <u>Phase 2</u> Primary: Patients receiving placebo were more likely to discontinue therapy prematurely compared to galantamine for any reason (HR, 1.76; 95% CI, 1.10 to 2.81; P=0.02) or lack of efficacy (HR, 1.80; 95% CI, 1.02 to 3.18; P=0.04). No significant difference was observed by ADAS-cog >4 between the groups (HR, 1.66; 95% CI, 0.78 to 3.54; P=0.19). Secondary: There were no significant differences between the treatment groups concerning mean values of the CIBIC-plus scale. A total of 34.1% of patients receiving galantamine and 27% of patients receiving placebo experienced adverse events. The most common adverse events were nervous system disorders (6.6%) and psychiatric disorders (5.3%). Serious adverse events were reported in 14.5% of galantamine-treated patients compared to 6.3% of patients in the placebo group.
Kavanagh et al.[43] (2011) Galantamine 16 to 24 mg/day vs placebo	OL, RCT Patients with mild-to-moderate Alzheimer's disease	N=3,523 (5 trials) 5 to 6 months	Primary: Changes from baseline in ADAS-Cog 11 at trial endpoint (two to five months after reaching maintenance doses) Secondary: Not reported	Primary: The proportion of patients who met criteria for "improved", "stable", or "non-rapid decline" at trial endpoint were 45.8, 59.5, and 87.6%, respectively with galantamine compared to 27.2, 37.1, and 67.7%, respectively with placebo. Changes in ADAS-Cog 11 scores with galantamine were -4.9, -4.7 and -2.9 points, respectively, for "improved", "stable" and "non-rapid decline" compared to -3.6, -3.4, and -1.2, respectively with placebo. Patients receiving galantamine who were reported to be "improved" or "stable" experienced improvement in ADAS-Cog 11 scores until 18

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				months after starting treatment, and attenuated deterioration thereafter. For galantamine-treated patients exhibiting "non-rapid decline", mean ADAS-Cog 11 score returned to baseline after approximately 12 months. Secondary: Not reported
Burns et al.[44] (2009) Galantamine 24 mg/day vs placebo	DB, MC, PC, RCT Patients 40 to 95 years of age with severe dementia of the Alzheimer type or probable Alzheimer's disease (MMSE, 5 to 12 points)	N=407 6 months	Primary: SIB, MDS-ADL, and adverse events Secondary: Not reported	Primary: In the completer analysis, the mean total SIB score of the galantamine group increased to 69.1 points at week 26. The mean SIB score in the placebo group decreased to 66.9. The between group least squares mean difference was 4.36 (95% CI, 1.3 to 7.5; P=0.006). In the completer analysis, the mean total MDS-ADL self-performance score worsened in both groups: scores at week 26 were 13.0 points in the galantamine group and 13.6 points in the placebo group. The between-group least squares mean difference was –0.41 points (95% CI, –1.3 to 0.5; P=0.383). In the LOCF analysis, the mean SIB score in the galantamine group increased to 69.3 points. In the placebo group, the mean SIB score decreased by 3.2 points. The between-group least squares mean difference was 5.02 points (95% CI, 2.17 to 7.86; P=0.0006). In the LOCF analysis, the mean total seven-item MDS-ADL self-performance score in the galantamine group worsened at endpoint to 13.1 points and to 14.0 points in the placebo group. Changes from baseline in the seven-item MDS-ADL self-performance score were 1.3 points and 1.7 points, respectively. The between-group least squares mean difference was –0.50 (95% CI, –1.39 to 0.39; P=0.394). Significant between-group differences were seen in the galantamine group for memory (P=0.006), praxis (P=0.010), and visuospatial ability (P=0.002). There were no significant differences in language (P=0.064) or attention (P=0.075). Scores for all eleven-item MDS-ADL self-performance subscales worsened in both treatment arms. The deterioration in the subscale score

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				for locomotion on unit was significantly less in the galantamine group (P=0.021). During the study, 88% of patients who received galantamine and 89% who received placebo had at least one adverse event. The most common adverse events in both treatment groups were urinary tract infections, vomiting, diarrhea, nausea, and falls. Secondary: Not reported
Raskind et al.[45] (2004) Galantamine 24 mg/day vs placebo	DB, PC, RCT Patients with mild-moderate Alzheimer's disease	N=194 36 months	Primary: ADAS-Cog, adverse events Secondary: Not reported	Primary: Patients treated continuously with galantamine for 36 months increased a mean of 10.2±0.9 points on the ADAS-Cog. This was a substantially smaller cognitive decline (approximately 50%) than that predicted for the placebo group. Patients discontinuing galantamine therapy before 36 months had declined at a similar rate before discontinuation as those completing 36 months of treatment. Almost 80% of patients who received galantamine for 36 months seemed to demonstrate cognitive benefits compared to those predicted for untreated patients. Secondary: Not reported
Wilcock et al.[46] (2000) Galantamine 24 mg/day vs galantamine 32 mg/day	DB Patients with mild-moderate Alzheimer's disease	N=653 6 months	Primary: ADAS-Cog, adverse events Secondary: Not reported	Primary: Both doses of galantamine were statistically better than placebo in the mean change in ADAS-Cog from baseline to endpoint (P<0.0001). Patients taking galantamine 24 mg had a -0.5 point mean change on the ADAS-Cog scale, while the 32 mg group had a -0.8 change. This compares to a +2.4 change for the placebo group. Statistical comparisons between the 24 mg group and the 32 mg group were not conducted. Discontinuations due to adverse events were 9, 14 and 22% in the placebo, 24 and 32 mg dose groups, respectively.

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vs placebo				Secondary: Not reported
Dunbar et al.[47] (2006) Galantamine IR 8 to 16 or 24 mg/day vs galantamine ER 8 to 16 or 24 mg/day vs placebo	Post hoc analysis, DB, MC, PC, RCT Patients with mild-to-moderate probable Alzheimer's disease	N=965 7 months	Primary: Nausea and vomiting Secondary: Not reported	Primary: Nausea reports were as follows: 16.9% of the galantamine ER group, 13.8% of galantamine IR group and 5.0% of placebo group. Vomiting reports were as follows: 6.6% of the galantamine ER groups, 8.6% of the galantamine IR group and 2.2% of the placebo group. During dose titration, the area under the curve of daily percentage of patients reporting nausea or vomiting was significantly higher in the galantamine IR group compared to placebo (320.9 vs 102.9; P=0.01) but for galantamine ER vs placebo and galantamine ER vs galantamine IR no significant differences were seen ([173.5 vs 102.9; P=NS], [320.9 vs 173.5; P=NS]). 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.[48] (2005) Galantamine IR 8 to 16 or 24 mg/day vs galantamine ER	AC, DB, MC, PC, PG, RCT Patients with mild-to-moderate probable Alzheimer's disease	N=971 6 months	Primary: ADAS-cog/11, CIBIC-Plus Secondary: ADCS-ADL, NPI, ADAS-cog/13, nonmemory ADAS-cog/ memory, ADAS-	Primary: Compared to placebo, galantamine was significantly more effective with improvement from baseline in ADAS-cog/11 scores (mean change, 1.3 and -1.4, respectively; P<0.001; 95% CI, –3.74 to –1.68; LOCF mean change, 1.2 and -1.3, respectively; P<0.001; 95% CI, –3.34 to –1.49). Galantamine also showed similar results when compared to placebo (OC mean change, –1.8 and 1.3, respectively; P<0.001; 95% CI, –4.17 to –2.08; LOCF mean change, –1.6 and 1.2, respectively; P<0.01; 95% CI, –3.70 to –1.86).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
8 to 16 or 24 mg/day vs placebo			Cog	Secondary: ADCS-ADL scores were significantly improved in the galantamine group vs placebo (P=0.003; 95% CI, 0.85 to 4.03; LOCF; P<0.001; 95% CI, 1.09 to 3.91). In galantamine groups vs placebo, NPI scores were not statistically significant but instead numerically significant (P=0.451; 95% CI, –2.77 to 1.23; LOCF; P=0.941; 95% CI, –1.85 to 1.82), (OC; P<0.205; 95% CI, –3.31 to 0.71; LOCF; P<0.102; 95% CI, –3.42 to 0.23). Statistical significance was found in cognition improvement from baseline for both galantamine groups compared to placebo based on ADAS-cog/13, non-memory ADAS-Cog, and memory ADAS-Cog scores.
Loy et al.[49] (2006) Galantamine 8 to 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 six months than three months (P values varied). When reported, ADCS-ADL, DAD and NPI scores for patients treated with galantamine were significantly improved over those in the placebo group (P values not reported). Secondary: Not reported
Herrmann et al.[50] (2011) Memantine 20 mg/day	OL Patients with moderate-to-severe Alzheimer's disease	N=31 3 months	Primary NPI-NH change in agitation and aggression subscale, CGI-C scale, caregiver impact, and effect on nursing burden	Primary: There was a significant decrease in the NPI-NH agitation/aggression subscale score with memantine (P=0.014). According to the CGI-C scores, 48% of patients were improved (much improved or minimally improved). A total of 52% of patients did not benefit from treatment (no change, minimally worse or much worse).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			measured by M-NCAS Secondary: Caregiver distress subscale of the NPI-NH, changes in psychotropic medications	There was a significant decrease in the M-NCAS total score (P=0.005), as well as decreases on the attitude (P=0.009) and strain (P=0.013) subscales with memantine therapy. Secondary: The NPI-NH subscale score decreased significantly with memantine therapy (P=0.009). Psychotropic medications were available in 28 patients, with 64.3% receiving at least one dose during the study. Lorazepam was the most commonly used psychotropic (P=0.046). Overall, seven patients decreased psychotropic medication use during the study, while three increased usage; Most remained the same for psychotropic usage.
Bakchine et al.[51] (2007) Memantine 20 mg/day vs placebo	DB, PC Patients with mild-to-moderate Alzheimer's disease	N=470 24 weeks	Primary: ADAS-COG and CIBIC-plus Secondary: Not reported	Primary: Patients in the memantine group showed a statistically significant improvement relative to placebo in ADAS-COG and CIBIC-plus at weeks 12 and 18. There was no significant difference between the groups at week 24. Secondary: Not reported
Reisberg et al.[52] (2003) Memantine 20 mg/day vs placebo	DB, PG Patients with moderate-to-severe Alzheimer's disease	N=252 28 weeks	Primary: CIBIC-Plus and ADCS-ADL Secondary: SIB	Primary: A significantly greater effect was observed in the memantine group compared to the placebo group on the ADCS-ADL (P=0.03). There was a significant difference in favor of memantine at week 28 on the CIBIC-Plus using the observed-cases analysis (mean score, 4.7 placebo vs 4.4, memantine; P=0.03), and a numerical difference at study endpoint in favor of memantine using the last-observed-carried-forward analysis (mean score, 4.8 placebo vs 4.5 memantine; P=0.06). Secondary: Memantine patients showed significantly less cognitive decline on the SIB total score compared to placebo-treated patients over the 28-week study period (P=0.002).

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Winblad et al.[53] (1999) Memantine 10 mg/day vs placebo	DB, PC Patients in Latvia with severe dementia, either Alzheimer's disease or vascular dementia	N=166 12 weeks	Primary: CGI-C and BGP Secondary: Safety	Primary: Significantly greater improvement was observed in the memantine group compared to the placebo group on the BGP and the CGI-C (P<0.016 and P<0.001, respectively). Separate analyses of the Alzheimer's disease population alone also yielded statistically significant results in favor of patients receiving memantine, by either the last-observed-carried-forward analysis or the observed-cases analysis on both outcome measures. At study endpoint, memantine patients showed significantly greater functional improvement compared to patients who received placebo, at study endpoint (P=0.012). Secondary: No significant differences in safety were found between the groups.
Winblad et al.[54] (2007) Memantine 20 mg/day vs placebo	MA Four studies: memantine as monotherapy, 2 studies of memantine vs placebo in patients already taking an acetylcholinesterase inhibitor; patients diagnosed with moderate-to-severe Alzheimer's disease	N=1,826 in subgroup with moderate-to-severe Alzheimer's disease 24 to 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 et al.[55] (2007) Memantine 20 mg/day vs	MA Patients diagnosed with moderate-to-severe Alzheimer's disease	N=1,826 24 to 28 weeks	Primary: ADAS-Cog, SIB, CIBIC-Pus, ADCS-ADL Secondary: Not reported	Primary: Significantly more patients in the placebo group (21%) had marked clinical worsening, as demonstrated by deteriorating scores, than in the memantine group (11%; P<0.001). Significantly more patients in the placebo group (28%) compared to the memantine group (18%) had documentation of worsening in any outcome

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				measure (P<0.001). Secondary: Not reported
McShane et al.[56] (2006) Memantine 10 to 30 mg/day vs placebo	MA (12 trials) Patients diagnosed with mild-to-moderate, moderate-to-severe and mild-to-moderate vascular dementia	N=3,731 (15 trials) Variable duration	Primary: CIBIC-Plus, SIB, ADAS-Cog, ADCS-ADL, NPI Secondary: Not reported	Primary: Significant improvement at six months was seen for patients with mild-to-moderate dementia treated with memantine on the ADAS-Cog scale (P=0.03); however, there was no significant difference seen for behavior and ADL scales. Significant improvement at six months was seen for patients with moderate-to-severe dementia treated with memantine for the following scales: CIBIC-Plus (P<0.00001), SIB (P<0.00001), ADCS-ADL (P=0.003) and NPI (P=0.004). Patients with vascular dementia treated with memantine had significant improvement in cognition scores and behavior scores but no significant change in global rating scales (ADAS-Cog; P=0.0002, NPI; P=0.03). Secondary: Not reported
Grossber et al.[57] (2013) Memantine extended-release 28 mg once daily vs placebo	DB, MC Outpatients with Alzheimer's disease (MMSE scores of 3 to 14)	N=677 24 week	Primary: Baseline-to-endpoint score change on the SIB and the endpoint score on the CIBIC-Plus. Secondary: Baseline-to-endpoint score change on the ADCS-ADL19; additional parameters included the	Primary: At 24 weeks memantine-treated patients significantly outperformed placebo-treated patients on the SIB (2.6; 95% CI, 1.0 to 4.2; P=0.001) and CIBIC-Plus (P=0.008). Secondary: At 24 weeks memantine-treated patients significantly outperformed placebo-treated patients on the NPI (P=0.005), and verbal fluency test (P=0.004); the effect did not achieve significance on ADCS-ADL19 (P=0.177). Adverse events with a frequency of >5.0 % that were more prevalent in the memantine group were headache (5.6 vs 5.1 %) and diarrhea (5.0 vs 3.9 %).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			baseline-to-endpoint score changes on the NPI and verbal fluency test	
Burns et al.[58] (2004) Rivastigmine	RETRO Patients with moderately severe Alzheimer's disease/dementia	N=2,126 3 trials, each 6 months	Primary: Effectiveness Secondary: Not reported	Primary: Mean ADAS-Cog score declined by 6.3 points in the placebo group and increased by 0.2 points in the rivastigmine group (P<0.001). Clinical benefits were also observed with the MMSE, the six-item PDS, and items of the BEHAV-AD assessed efficacy. Rivastigmine showed the same pattern of adverse events as in other studies, but the RR of dropping out due to adverse events was lower than in subjects with milder Alzheimer's disease. Secondary: Not reported
Dantoine et al.[59] (2006) Rivastigmine 3 to 12 mg/day Addition of memantine 5 to 20 mg/day was allowed for non-responders of rivastigmine at the end of week 16.	MC, OL Patients at least 50 years of age with probable Alzheimer's disease according to criteria of DSM-IV, baseline scores of <18 for MMSE or scores of >4 on GDS, previously treated for at least 6 months prior with donepezil 5 to 10 mg/day or galantamine 16 to 24 mg/day and considered not	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)	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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	stabilized, current stabilized medications allowed	Total 28 weeks		For the 82.6% who worsened from baseline at the end of Phase 1, 81.4% improved or had no change at the end of Phase 2 with the addition of memantine on the CGI-C. At the end of Phase 1, MMSE and NPI showed significant improvements (P<0.001 and P<0.05, respectively) while there was no change from baseline for Ten-point Clock-drawing Test and D-KEFS verbal fluency test scores and the Mini-Zarit interview. At the end of Phase 2, D-KEFS verbal fluency test, Mini-Zarit, and especially MMSE scores showed significant improvement (P<0.05, P<0.001 and P<0.001, respectively).
Olin et al.[60] (2010) Rivastigmine 6 to 12 mg/day and memantine 20 mg/day	MC, OL, PRO Patients ≥50 years of age with moderate-to-severe Alzheimer's disease (MMSE ≥10 to ≤20)	N=116 26 weeks	Primary: Safety and tolerability Secondary: ADCS-CGIC, ADCS-ADL measured	Primary: Nausea and vomiting occurred in 26.7 and 10.3% of patients, respectively. Most cases were mild with few severe cases reported (2.6 and 2.6%, respectively). At least one treatment-emergent adverse event was experienced by 81.9% of patients. The most common adverse events were nausea (26.7%), dizziness (11.2%), vomiting (10.3%), and diarrhea (10.3%). No patients exhibited clinically significant ECG abnormalities. Secondary: At week 26, 59% of patients experienced no decline in MMSE total score from baseline. The mean change from baseline in MMSE total score was 0.7. At week 26, there was no change in global ADCS-CGIC scores. Patient and caregiver assessed mental/cognitive state, behavior and functioning severity scores were maintained to a similar extent throughout the study. The mean overall rating on the ADCS-CGIC was 4.0. At week 26, 64.5% of patients were considered unchanged or improved.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The mean ADAS-ADL scores significantly declined by -2.9. At week 26, cognition, behavior and global functioning were unchanged or improved in 63.2, 71.1 and 77.6% of patients respectively.
Gauthier et al.[61] (2010) Rivastigmine 3 to 12 mg/day	MC, OL, OS, PRO Patients with mild-moderate Alzheimer's disease	N=3,800 12 months	Primary: Physician-assessed abbreviated CGI-C, MMSE, psychotropic medication use Secondary: Not reported	Primary: At six months, the proportion of patients who were reported as being improved vs no change vs deteriorating were 46.4 vs 44.9 vs 8.8% for attention; 42.8 vs 50.0 vs 7.2% for apathy; 41.1 vs 49.5 vs 9.4% for anxiety; 33.8 vs 68.4 vs 7.7% for agitation; 35.1 vs 54.8 vs 10.1% for irritability; and 30.8 vs 63.8 vs 5.4% for sleep disturbance. At 12 months, the proportion of patients who were reported as being improved vs no change vs deteriorating were 47.9 vs 41.0 vs 11.1 for attention; 44.1 vs 46.7 vs 9.2% for apathy; 41.8 vs 47.3 vs 10.9% for anxiety; 33.5 vs 57.6 vs 8.9% for agitation; 33.8 vs 56.4 vs 9.8% for irritability; and 29.7 vs 64.7 vs 5.6% for sleep disturbance. Overall, CGI-C at six and 12 months demonstrated a larger percentage of patients with improvement vs deterioration. At six months, 54% of patients overall demonstrated no change. At 12 months, 52% of patients overall demonstrated no change. MMSE scores were 20.8 at baseline, 21.5 after three months, 21.3 after six months, and 21.3 after 12 months. At baseline, 61.3% of patients were not taking a psychotropic medication. At six months, the proportion of patients not taking any psychotropic medications increased to 70.8%; at 12 months, it was 84.7%.
Birks et al.[62] (2000) Rivastigmine 6 to 12 mg/day vs placebo	MA (8 trials) Patients diagnosed with Alzheimer's disease	N=3,660 12 to 52 weeks	Primary: ADAS-Cog, ADL, adverse events Secondary: Not reported	Primary: Statistically significant differences were seen in patients treated with rivastigmine at doses of 6 to 12 mg/day as compared to placebo for the following outcomes: ADAS-Cog (WMD, -2.09; 95% CI, –2.65 to –1.54) and ADL (WMD, -2.15; 95% CI, –3.16 to –1.13). At 26 weeks, 55% of patient had severe dementia in the rivastigmine group as compared to 59% in the placebo group (OR, 0.78; 95% CI, 0.64 to 0.94).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Adverse events (nausea, vomiting, diarrhea, anorexia, headache, syncope, abdominal pain and dizziness) were reported significantly more frequently in the rivastigmine group than with placebo. Secondary: Not reported
Birks et al.[63] (2009) Rivastigmine vs placebo	MA Patients diagnosed with probable Alzheimer's disease	N=4,775 (9 trials) Variable duration	Primary: Cognitive function, global impression, activities of daily living, behavioral disturbance, withdrawal rates, and incidence of adverse effects Secondary: Not reported	Primary: <u>Cognitive function</u> The meta-analysis, using WMD, demonstrated benefit on cognitive function as measured by ADAS-Cog test scores for rivastigmine compared to placebo as follows: rivastigmine 1 to 4 mg/day at 18 weeks (WMD, -1.07; 95% CI, -1.66 to -0.48; P=0.0004) and 26 weeks (WMD, -0.84; 95% CI, -1.48 to -0.19; P=0.01); rivastigmine 6 to 12 mg/day at 12 weeks (WMD, -1.49; 95% CI, -1.96 to -1.01; P<0.00001), 18 weeks (WMD, -1.79; 95% CI, -2.30 to -1.29; P<0.00001) and 26 weeks (WMD, -1.99; 95% CI, -2.49 to -1.50; P<0.00001). An additional analysis of ADAS-Cog dichotomized into those showing less than four points improvement and those showing four or more points improvement at 26 weeks shows benefit for cognitive function for the 6 to 12 mg daily of rivastigmine compared to placebo (83% did not show four points improvement compared to 89%; OR, 0.6; 95% CI, 0.4 to 0.8). There was no difference for the 1 to 4 mg/day dose compared to placebo (88% did not show four points improvement compared to 90%; OR, 0.84; 95% CI, 0.60 to 1.19). MMSE shows similar results in favor of rivastigmine at 26 weeks compared to placebo as follows: rivastigmine 1 to 4 mg/day at 26 weeks (WMD, 0.43; 95% CI, 0.08 to 0.78; P=0.02) and rivastigmine 6 to 12 mg/day at 26 weeks (WMD, 0.82; 95% CI, 0.56 to 1.08; P<0.00001). One study used the SIB, which shows benefit associated with higher dose rivastigmine compared to placebo at 26 weeks (WMD, 4.53; 95% CI, 0.47 to 8.59; P=0.03).

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				Global assessment Using the CIBIC-Plus scale or the ADCS-CGIC scale, there were benefits associated with rivastigmine compared to placebo as follows: rivastigmine 6 to 12 mg/day at 12 weeks (OR, 0.74; 95% CI, 0.60 to 0.92; P=0.008), 18 weeks (OR, 0.79; 95% CI, 0.64 to 0.98; P=0.03) and at 26 weeks (OR, 0.66; 95% CI, 0.55 to 0.79; P<0.00001); rivastigmine 1 to 4 mg/day at 26 weeks (OR, 0.71; 95% CI, 0.55 to 0.93; P=0.01). Using GDS, there were benefits associated with rivastigmine 6 to 12 mg/day compared to placebo (55% showed the worse condition compared to 59%; OR, 0.78; 95% CI, 0.64 to 0.94; P=0.01) but not with 1 to 4 mg daily rivastigmine compared to placebo. ADL The PDS showed an improvement associated with rivastigmine compared to placebo as follows: rivastigmine 6 to 12 mg/day at 12 weeks (WMD, 1.08; 95% CI, 0.19 to 1.98; P=0.02), 18 weeks (WMD, 1.90; 95% CI, 0.93 to 2.88; P=0.0001), and 26 weeks (WMD, 2.15; 95% CI, 1.13 to 3.16; P<0.0001). One study assessing ADL using the ADCS-ADL scale and showed benefit for rivastigmine 6 to 12 mg/day at 24 weeks (WMD, 1.80; 95% CI, 0.20 to 3.40; P=0.03). Behavioral disturbance There was no difference between rivastigmine and placebo in behavioral disturbance found in two studies using the neuropsychiatric instrument (NPI-10, and NPI-12). Withdrawals before the end of treatment There were no significant differences in withdrawal rates with rivastigmine 1 to 4 mg/day and placebo at 12, 18 and 26 weeks. There were significant differences in withdrawal rates for the higher dose group in favor of placebo as follows: rivastigmine 6 to 12 mg/day at 12 weeks (OR, 2.60; 95% CI, 1.19 to 5.68; P=0.02), 18 weeks (OR, 4.02; 95% CI, 1.31 to 12.32; P=0.01), and 26 weeks (OR, 2.19; 95% CI, 1.83 to 2.63; P<0.00001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Adverse events There were no significant differences in the numbers of patients with at least one adverse event between the lower dose rivastigmine (1 to 4 mg/day) and placebo groups. There were significant differences between the higher dose rivastigmine (6 to 12 mg/day) and placebo groups in favor of placebo by the end of the titration period (OR, 2.96; 95% CI, 2.39 to 3.68; P<0.00001) and by 26 weeks (OR, 2.49; 95% CI, 2.05 to 3.02; P<0.00001). There were no significant differences in the numbers of patients with at least one severe adverse event between the lower dose rivastigmine (1 to 4 mg/day) and placebo groups. There were significant differences between the higher dose rivastigmine (6 to 12 mg daily) and placebo groups in favor of the placebo group for the titration period (OR, 1.88; 95% CI, 1.39 to 2.55; P<0.0001). There were significant differences, in favor of placebo, for the rivastigmine 6 to 12 mg/day group by the end of the titration period, and by 26 weeks for the number of patients suffering nausea, vomiting, diarrhea, anorexia, headache, syncope, abdominal pain and dizziness. There were significant differences in favor of placebo, for the rivastigmine 1 to 4 mg/day group by the end of the titration period and by 26 weeks for the number of patients suffering nausea, vomiting, diarrhea, and anorexia. Secondary: Not reported
Rosler et al.[64] (1999) Rivastigmine 1 to 4 mg/day vs rivastigmine 6 to 12 mg/day	DB, MC, PC, RCT Patients 50 to 85 years of age and not able to bear children, all patients met criteria for Alzheimer's type dementia as described in the DSM-IV and	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	Primary: Significant improvement in cognitive function assessed by the ADAS-Cog was observed with the higher dose group by ≥4 points compared to placebo (P<0.05). At week 26, significantly more patients in both rivastigmine groups had improved in global function as assessed by the CIBIC compared to those in the placebo group (P<0.05). Mean scores on the PDS improved from baseline in the higher dose group but fell in the placebo group (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	criteria for probable Alzheimer's disease		tolerability	At week 26, mean scores in the MMSE and the GDS significantly improved in patients receiving rivastigmine 6 to 12 mg/day (P<0.05). Secondary: Discontinuation rates for any reason were significantly higher in the higher dose group than in the lower dose or placebo group (33% vs 14%). Adverse events related to treatment including nausea, vomiting, diarrhea, abdominal pain and anorexia, were generally mild and occurred most frequently during the dose escalation phase (23% in higher dose group, 7% in lower dose group and 7% in placebo group).
Articus et al.[65] (2011) Rivastigmine patch 9.5 mg/24 hours	MC, OL Patients with Alzheimer's disease	N=208 24 weeks	Primary: Proportion of patients treated with rivastigmine for ≥8 weeks at week 24 Secondary: Tolerability, week 24 MMSE, ADCS-CGIC, ADCS-ADL, ADCPQ, Zarit Burden Interview Score	Primary: In the ITT population, 80.8% of patients (95% CI, 75.0 to 86.5) were treated for at least eight weeks with rivastigmine. A total of 74.2% of patients (95% CI, 67.8 to 80.5) were treated for at least eight weeks and completed the study. A total of 74.2% of patients treated rivastigmine patch were able to reach and maintain the maximum dose for at least eight weeks. The most common adverse events being nausea (10.1%), erythema (8.7%), pruritus (8.2%), and vomiting (7.2%). Secondary: The most common adverse events were nausea (10.1%), erythema (8.7%), pruritus (8.2%), vomiting (7.2%), diarrhea (4.3%) and agitation (4.3%). At week 24, improvements were seen on: MMSE (1.3), and ADCS-ADL (1.3). At week 24, improvements in ADCS-CGIC were demonstrated in 34.6% of patients as assessed by patients, and in 29.7% of patients as assessed by the caregiver. ADCPQ scores improved 18.5 points, and Zarit Burden Interview Score improved slightly at each visit until week 24 (-0.4).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Grossberg et al.[66] (2009) Rivastigmine patch 9.5 mg/24 hours to 17.4 mg/24 hours	OL Patients 50 to 85 years of age with Alzheimer's disease (MMSE scores 10 to 20)	N=870 28 weeks (weeks 25 to 52 of open-label extension)	Primary: Safety and tolerability Secondary: ADAS-cog	Primary: During the first four weeks of the open-label extension, patients formerly randomized to rivastigmine treatment (capsule or patch) reported fewer adverse events than those formerly randomized to placebo (≤15.2 vs 28.2%). This prior exposure effect was noted for nausea (≤2.5 vs 8.5%) and vomiting (≤1.9 vs 6.0%). A total of 57.6% of patients reported adverse events during the OL extension (weeks 25 to 52), with nausea and vomiting being reported most frequently (15.7 and 14.3%, respectively). During the OL extension, over 90% of all patients experienced ''no, slight, or mild'' skin irritation as their most severe application-site reaction. The symptoms that were most commonly reported as moderate or severe were erythema and pruritus (7.7 and 5.6%, respectively). Serious adverse events occurred in 1.0% of patients during the first four weeks of the OL extension phase (weeks 25 to 28) and 9.4% of patients during the full open-label extension phase (weeks 25 to 52). The most common serious adverse events were gastrointestinal disorders (2.0%), infections and infestations (2.0%), cardiac disorders (1.7%), and nervous system disorders (1.5%). Eight deaths occurred during the OL extension phase and a further two occurred during the 30-day follow-up period. The causes of death were most commonly cardiac disorders (n=5) and nervous system disorders (n=3). None were considered treatment related. Secondary: Patients previously randomized to placebo who were switched to the 9.5 mg/24 hour rivastigmine patch during the OL extension experienced a 1.3-point increase in their ADAS-cog scores during weeks 24 to 40. There was no overall change in ADAS-cog score at week 40 compared to baseline (95% CI, -1.4 to 0.6). The increase in ADAS-cog score was not sustained beyond week 40. Patients receiving rivastigmine treatment for the entire study (weeks 0 to

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				52) showed a deterioration of 0.3 points (95% CI, -0.4 to 0.9) on the ADAS-cog at week 52. Those receiving placebo for weeks 0 to 24, followed by the patch, showed a deterioration of 0.9 points [95% CI, -0.4 to 2.1).
Gauthier et al.[67] (2013) Rivastigmine transdermal patch 4.6 mg/24 hours or 9.5 mg/24 hours, once daily	OS Patients with Alzheimer's disease with MMSE score of 10 to 26 and GDS score of 4 to 6	N=1,204 18 months	Primary: Change in MMSE from baseline to 18 months Secondary: Change in MMSE at six and 12 months and change in GDS, assessment of patient ability, overall patient assessment rating, caregiver-reported compliance and treatment satisfaction at six, 12, and 18 months	Primary: Over 18 months of treatment there were no clinically significant changes in MMSE. Secondary: Over 18 months of treatment there were no clinically significant changes in GDS. The majority of patients showed improvement or no change in GDS, assessment of patient ability and overall patient assessment rating over 18 months. The proportion with reported improvement in GDS, assessment of patient ability and overall patient assessment rating was higher than the proportion that deteriorated. Compliance improved from baseline to 18 months and for 88.2% of patients caregivers preferred the transdermal patch to oral medications.
Sadowsky et al.[68] (2010) US13 and US18 Rivastigmine capsules 3 to 12 mg/day US38 Rivastigmine patch 4.6 mg/24 hours for 5 weeks, then rivastigmine patch 9.5 mg/24 hours	US13 and US18 PRO, MC, OL US38 RCT, MC, OL Patients ≥49 years of age with a diagnosis of dementia of the Alzheimer type (MMSE ≥8 to ≤26 or MMSE ≥10 to ≤24) who showed a	N=592 25 to 26 weeks	Primary: Safety and tolerability	Primary: In US13 and US18, 67.7% of patients completed the studies and 32.3% of patients withdrew due to adverse events (59.8%), unsatisfactory treatment effect (15.9%), withdrawal of consent (15%), and loss to follow-up (6.5%). The remaining 2.7% of patients discontinued due to protocol deviation, administrative problem, or death. In US13 and US18, the most frequently reported adverse events (AEs) were nausea (32.9%), vomiting (24.1%), dizziness (11.8%), weight loss (9.1%) agitation (7.9%), fall (7.9%) and confused state (7.9%). Serious AE's were reported in 6% of patients and included pneumonia (1.8%), syncope (1.2%), dehydration (1.2%) and vomiting (1.2%). In US38, 67.4% of patients completed the study. The primary reasons for

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
for 20 weeks	poor response to donepezil			not completing the study were adverse events (44.7%), withdrawal of consent (29.4%), unsatisfactory treatment effect (10.6%), protocol deviation (7.1%), and loss to follow-up (3.5%). The remaining 4.7% of patients discontinued due to administrative problems, abnormal test procedure, or death. In US38, 70.5% of patients reported at least 1 AE. More patients in the immediate-switch group (73.3%) experienced at least one AE during the study than in the delayed-switch group (67.7%). The most common adverse events were application site reaction (15.3%), and agitation (6.9%). The most common serious AEs reported were syncope (1.1%), dehydration (0.8%) and pneumonia (0.4%). Discontinuation due to AE (14.6%) was the most common reason for patients not completing the extension phase in both immediate- and delayed-switch groups; the differences between the groups were NS. Discontinuations occurred for the following reasons: application site reaction (4.2%), disease progression (2.3%), and agitation (1.5%). Discontinuation due to gastrointestinal AEs was lower for the rivastigmine patch compared to the capsules.
Cummings et al.[69] (2012) 10 cm^2 rivastigmine patch (9.5 mg/24 hours) vs 15 cm^2 rivastigmine patch (13.3 mg/24 hours)	DB, PG. RCT Patients 50 to 85 years of age with MMSE scores of 10 to 24 diagnosed with Alzheimer's disease, all patients were required to be living with someone or to be in daily contact with a caregiver	N=567 48 weeks	Primary: ADCS-IADL scale and ADAS-cog Secondary: Time to functional decline on the ADCS-IADL, change in the Trail Making Test parts A and B, and change in the NPI-10, and the NPI-caregiver distress scale.	Primary: The 13.3 mg/24 hours patch was statistically superior to the 9.5 mg/24 hours patch on the ADCS-IADL scale from week 16 (P=0.025) onwards including week 48 (P = 0.002), and ADAS-cog at week 24 (P= 0.027), but not at week 48 (P = 0.227). Secondary: Functional decline on the ADCS-IADL tended to occur later in the 13.3 mg/24 h patch group than in the 9.5 mg/24 hours patch group, but the observed difference did not reach significance. Proportion of patients with functional decline was 77.0% in the 13.3 mg/24 hours patch group compared to 81.2% with the 9.5 mg/24 hours patch Group. The difference was not statistically significant. Patients in the 13.3 mg/24 hours patch group had smaller increases in time to complete the Trail Making Test parts A at weeks 24 and 48 compared to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				those in the 9.5 mg/24 hours patch group, but the observed difference did not reach significance. Differences were not significantly different in changes in the change in the 10-item (NPI-10), and the NPI-caregiver distress scale. The most frequently reported adverse events by primary system organ class were gastrointestinal disorders (29.3 vs. 19.1%, 13.3 and 9.5 mg/24 hours patch, respectively), psychiatric disorders (25.4 vs. 21.6%, respectively) and nervous system disorders (21.4 vs. 18.4%, respectively). Skin and subcutaneous tissue disorders were less frequently observed with the 13.3 mg/24 hours than the 9.5 mg/24 hours patch (2.1 vs 6%).
Cummings et al.[70] (2010) Rivastigmine patch 9.5 mg/24 hours vs rivastigmine patch 17.4 mg/24 hours vs placebo	DB, PC, PRO, RCT Patients 50 to 85 years of age with mild-to-moderate Alzheimer's disease	N=1,195 24 to 52 weeks	Primary: Tolerability at 24 weeks Secondary: Patients skin condition at the application site at 28 weeks	Primary: No serious skin reactions were reported in either the 24 or 28 week phases of the study. During the 24 week period, 574 patients wearing an active patch and 579 patients wearing a placebo patch underwent at least one assessment of application-site skin condition. Of patients on the 9.5 mg/24 hour patch, erythema and pruritus were the most commonly reported reactions (moderate in 7.6% of patients and severe in 6.7% of patients). A total of 89.6% of patients in the patch group had "no, slight, or mild" signs and symptoms for their most severe application site reaction. Secondary: A total of 870 patients entered the 28 week phase of the study and received rivastigmine 9.5 mg/24 hours patch. Overall, the skin tolerability profile was similar to the DB phase. A total of 91.5% of patients experienced "no, slight, or mild" symptoms as their most severe application site reaction, with erythema and pruritus being the most common finding. A total of 3.7% of patients discontinued treatment due to skin reactions during the open-label extension, and there was no increase in the severity of skin reaction noted.
Molinuevo et al.[71] (2012)	MC, OS, PRO Patients with mild-	N=649 6 months	Primary: Adherence rates	Primary: At baseline, 0.6% of patients were taking ≥80% of their medication as prescribed. At three and six months, 77 and 88.1%, respectively, were

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Rivastigmine patch 9.5 mg/24 hours vs rivastigmine 3 to 12 mg/day	to-moderate Alzheimer's disease		Secondary: Strategies followed by a physician to improve adherence and reasons for nonadherence reported by patients	noted to be taking more than 80% of their medication as prescribed (P<0.0001 vs baseline). The proportion of adherent patients at three months was 73.6% and at six months was 85.9% (P<0.0001). Secondary: Modification of Alzheimer's disease treatment was the only intervention that substantially improved adherence at three months (P<0.0001). At the six month visit, psychoeducation was the only effective strategy that reached statistical significance (P<0.0001). The most common reasons for nonadherence include forgetfulness (56.4%), avoidance of adverse events (30.7%), and refusal of treatment (25.3%).
Boada et al.[72] (2013) Rivastigmine transdermal patch vs rivastigmine capsules	OL Patients treated with rivastigmine	N=1,078 Duration not specified	Primary: Patient satisfaction (Treatment Satisfaction with Medicines and the Morisky-Green questionnaires) Secondary: Not reported	Primary: Satisfaction reported was greater with transdermal than oral rivastigmine: mean+standard deviation of the total Treatment Satisfaction with Medicines score, 72.5+14.1 vs 65.2+12.5; P<0.001. The proportion of adherent patients was greater with transdermal than with oral rivastigmine (65.0 vs 41.4%; P<0.001). Satisfaction, in turn, was significantly greater in adherent cases than in nonadherent cases. Secondary: Not reported
Blesa González et al.[73] (2011) Rivastigmine 6 to 12 mg/day (RO) vs rivastigmine patch titrated to	MC, OL, RCT Patients ≥60 years of age with mild-to-moderate Alzheimer's disease who were previously treated with oral rivastigmine	N=142 3 months	Primary: Gastrointestinal adverse events Secondary: Overall tolerance, local tolerance for those patients on patches, satisfaction level, and cognitive state	Primary: Gastrointestinal adverse events were reported in <5% of patients receiving patches (4.7% in RPT and 4.3% in RP) vs 6.1% in RO patients. No statistical significance was reached (P=0.8667). Gastrointestinal adverse events were noted in 11 cases, two in RPT patients, six in RP patients, and three in the RO patients (P=0.3067). Secondary: Overall tolerability did not reveal any significant differences among the groups (P=0.8239).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
9.5 mg/24 hours (RPT) vs rivastigmine patch 9.5 mg/24 hours (RP)			by MMSE	Local tolerability revealed skin or subcutaneous tissue adverse events reported in 11.6% of patients in the RPT group vs 17% of patients in the RP group (P=0.4055). All skin adverse events were reported as slight or moderate intensity. RP was defined by 72% of patients as very easy to use, while RO was considered very easy to use by 30% of patients (P=0.0005). In RP patients, 67% considered it very easy to follow compared to 19% of RO patients (<0.0001). A total of 72% of RP patients confirmed the treatment never interfered with their daily lives vs 40% of the RO group (P=0.0085). Overall satisfaction comparisons revealed that in RP patients, 60% were very satisfied vs 14% in RO patients (P<0.0001). MMSE did not demonstrate significant differences among treatment groups when compared at one and three month visits.
Winblad et al.[74] (2007) Rivastigmine patch 9.5 mg/24 hours vs rivastigmine patch 17.4 mg/24 hours vs rivastigmine 12 mg/day vs placebo	DD, PC, RCT Patients 50 to 85 years of age with MMSE scores of 10 to 20 diagnosed with Alzheimer's disease, all patients were required to be living with someone or to be in daily contact with a caregiver	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 to 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).
Winblad, Kawata et al[75] (2007)	DB, DD, PC ACs included	N=1,059 24 week	Primary: ADCPQ	Primary: At 8 weeks, general preference was seen for the patch: 68% of caregivers preferred the patch over capsule form (P<0.0001).

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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	different size rivastigmine patches and rivastigmine capsules		Secondary: Not reported	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 et al.[76] (2007) Rivastigmine patch 9.5 mg/24 hours vs rivastigmine patch 17.4 mg/24 hours vs rivastigmine 12 mg/day vs	DB, DD, MC, PG Women or men 50 to 85 years of age with a diagnosis of dementia of the Alzheimer's type according to the DSM-IV, and probable Alzheimer's disease	N=1,195 24 weeks	Primary: ADAS-Cog, ADCS-CGIC Secondary: ADCS-ADL scale; NPI for behavior and psychiatric symptoms; MMSE for cognition; Ten Point Clock-drawing Test for assessment of visuospatial and executive functions; Trail Making Test Part	Primary: Patients receiving rivastigmine patches or capsules showed significant benefits compared to placebo at week 24 on the ADAS-Cog subscale (P<0.05 vs placebo for all rivastigmine groups). Treatment differences on the ADCS-CGIC were statistically significant for the 10 cm^2 patch and capsule group (all P<0.05 vs placebo). The 20 cm^2 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo			A for assessment of attention, visual tracking and motor processing speed	different from those in the placebo groups (all P>0.05).
Blesa et al.[77] (2007) Rivastigmine patch 9.5 mg/24 hours vs rivastigmine patch 17.4 mg/24 hours vs rivastigmine 12 mg/day vs placebo	DB, DD, PC ACs included different size rivastigmine patches and rivastigmine capsules, caregiver preference based on data generated during the IDEAL trial (Winblad et al)	N=1,059 24 week	Primary: ADCPQ Secondary: Not reported	Primary: At 8 weeks, general preference was seen for the patch: 68% of caregivers preferred the patch over capsule form (P<0.0001). 70% of caregivers preferred the patch due to ease of schedule (P<0.0001). 55% of caregivers preferred the patch due to ease of use (P=0.0008). At 24 weeks, general preference was seen for the patch: 72% of caregivers preferred the patch over capsule form (P<0.0001). 74% of caregivers preferred the patch due to ease of schedule (P<0.0001). 64% of caregivers preferred the patch due to ease of use (P<0.0001). Caregivers preferred the patch over capsule dosage form, regardless of size of patch (P<0.0001). At eight weeks, caregivers indicated greater satisfaction overall (P<0.0001), greater satisfaction with administration (P<0.0001), less interference with daily life with the patch than the capsule (P<0.01). Secondary: Not reported
Farlow et al.[78] (2011) Rivastigmine patch 9.5 mg/24 hours vs rivastigmine patch 17.4 mg/24 hours vs rivastigmine 12	RETRO Patients with mild-to-severe Alzheimer's disease	N=1,050 24 weeks	Primary: ADAS-cog, ADCS-CGIC, and ADCS-ADL Secondary: Not reported	Primary: In patients with moderate disease, there was a significant improvement on ADAS-cog scores with the rivastigmine 17.4 mg/24 hour patch (P=0.0009) and rivastigmine capsule (P=0.0128). For patients with moderately severe disease, there was a significant improvement in ADAS-cog scores with the rivastigmine 17.4 mg/24 hour patch (P=0.006), rivastigmine 9.5 mg/24 hour patch (P=0.0163), and rivastigmine capsule (P=0.0071) compared to placebo. For patients with severe disease, there was a significant improvement on ADCS-CGIC scores with the rivastigmine 9.5 mg/24 hour patch (P=0.037) and rivastigmine capsule (P=0.0073) compared to placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/day vs placebo				For patients with moderately severe disease, there was a significant improvement on ADCS-CGIC scores with the rivastigmine 17.4 mg/24 hour patch (P=0.043) and rivastigmine 9.5 mg/24 hour patch (P=0.0116) compared to placebo. Significant improvement on ADCS-CGIC scores were seen with the rivastigmine 17.4 mg/24 hour patch in patients with moderate disease (P=0.03) and mild to moderate disease (P=0.0455) compared to placebo. For patients with moderately severe disease, there was a significant improvement on ADCS-ADL scores with the rivastigmine 17.4 mg/24 hour patch (P=0.0211) compared to placebo. For patients with moderate disease, there was a significant improvement on ADCS-ADL scores with the rivastigmine 17.4 mg/24 hour patch (P=0.0194) and rivastigmine capsule (P=0.0077) compared to placebo. There was no significant difference in ADCS-ADL scores among the treatment groups in patients with severe AD.
Choi et al.[79] (2011) Rivastigmine patch 4.6 mg/24 hours for 4 weeks, then rivastigmine patch 9.5 mg/24 hours for 4 weeks, then rivastigmine patch 9.5 mg/24 hours and memantine 5 mg/day titrated to 20 mg/day vs rivastigmine patch	MC, OL, RCT Patients with mild-to-moderate Alzheimer's disease	N=172 24 weeks	Primary: Tolerability Secondary: Efficacy as measured by CMAI-K, ADAS-cog, K-MMSE, FAB, CGA-NPI, ADCS-ADL and CDR-SB scores	Primary: The incidence of adverse events (53.4 vs 50.6%) and discontinuation due to adverse events (6.8 vs 4.8%) was not different between patients with and without memantine, respectively. The most common adverse events were skin irritation in both treatment groups (42 vs 34.9%; P=0.71), but discontinuation was rare (4.5 vs 2.4%; P=0.74). Secondary: CMAI-K scores favored rivastigmine monotherapy vs combination therapy at the end of treatment (P=0.01). Changes in other efficacy measures (ADAS-cog, K-MMSE, FAB, CGA-NPI, ADCS-ADL and CDR-SB) were not significantly different.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
9.5 mg/24 hours				
Farlow et al.[80] (2010) Rivastigmine patch 9.5 mg/24 hours and memantine vs rivastigmine patch 9.5 mg/24 hours	OL, RCT Patients ≥50 years of age with mild-to-moderate Alzheimer's disease who had been receiving donepezil for at least 6 months and at a stable dose of 5-10 mg/day for a minimum of 3 months	N=261 25 weeks	Primary: Safety and tolerability of rivastigmine transdermal patch, with or without concomitant memantine Secondary: Changes in cognition, global functioning and activities of daily living measured by MMSE and ADCS-ADL using the CGIC	Primary: The incidences of adverse events (73.3 vs 67.5%) and serious adverse events (10.4 vs 7.1%) were both slightly higher in patients receiving concomitant memantine, but the differences were NS (95% CIs, -5.2 to 16.9 and -3.6 to 10.1 for adverse events and serious adverse events, respectively). The most frequent adverse events in the combination therapy group and the rivastigmine monotherapy group were application site reactions (17.5 vs 13.5%, respectively) and agitation (5.9 vs 7.9%, respectively). Secondary: Concomitant memantine was associated with no significant changes in efficacy, as assessed by CGIC and MMSE scores. Global functioning remained unchanged or improved (CGIC rating ≤4) in 57.7 and 67.2% of patients with memantine and patients without memantine, respectively (P=0.604). ADCS-ADL scores deteriorated from baseline in both groups, with significant worsening in patients receiving memantine compared to those not receiving memantine (mean change from baseline rivastigmine and memantine vs rivastigmine monotherapy: -5.3 vs -2.0; P=0.043).
Harry et al[81] (2005) Donepezil with doses ranging from 5 to 10 mg/day or galantamine with doses ranging from 8 to 36 mg/day vs	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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				
Wilcock et al.[82] (2003) Donepezil 10 mg/day vs galantamine 24 mg/day	MC, PG, RCT Patients with Alzheimer's disease	N=182 52 weeks	Primary: BrADL Secondary: MMSE, ADAS-Cog, NPI	Primary: BrADL total score showed no significant difference between treatment groups in mean change from baseline to week 52. Secondary: Galantamine patients' scores on the MMSE at week 52 did not differ significantly from baseline, whereas donepezil patients' scores deteriorated significantly from baseline (P<0.0005).The between group difference in MMSE change did not reach statistical significance. In the ADAS-Cog analysis, between group differences for the total population were NS, whereas galantamine treated patients with MMSE scores of 12 to 18 demonstrated an increase (worsening) in the ADAS-Cog score of 1.61+/-0.80 vs baseline, compared to an increase of 4.08+/-0.84 for patients treated with donepezil. More caregivers of patients receiving galantamine reported reductions in burden compared to donepezil. Changes from baseline in NPI were similar for both treatments.
Jones et al.[83] (2004) Donepezil 10 mg/day vs galantamine 12 mg twice daily	OL, RCT Patients with Alzheimer's disease	N=120 12 weeks	Primary: Ease of use and tolerability, ADAS-Cog, effects on cognition and activities of daily living Secondary: Not reported	Primary: Physicians and caregivers reported statistically significant greater satisfaction/ ease of use with donepezil compared to galantamine at weeks four and 12. Significantly greater improvements in cognition were observed for donepezil vs galantamine on the ADAS-Cog at week 12 and at endpoint. Activities of daily living improved significantly in the donepezil group compared to the galantamine group at weeks four and 12 (P<0.05). Forty-six percent of galantamine patients reported gastrointestinal adverse events vs 25% of donepezil patients. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Modrego et al.[84] (2010) Donepezil 10 mg/day vs memantine 20 mg/day	PG, RCT, SB Patients with mild-to-moderate Alzheimer's disease	N=63 6 months	Primary: ADAS-cog, NPI, DAD, changes in N-acetylaspartate metabolite levels Secondary: Not reported	Primary: There were no significant differences in the clinical scales with donepezil and memantine (donepezil: ADAS-cog, -0.12; P=NS, NPI, -0.04; P=NS, DAD, 6.67; P=0.014) (memantine: ADAS-cog, -1.37; P=NS, NPI, 1.25;P=NS, DAD, 4.46; P=NS). More patients worsened than improved on either drug. Daily living activities decreased by 4.4% in the memantine group and 6.6% in the donepezil group (P=0.6). At baseline, N-acetylaspartate/Cr ratio in the PCG correlated significantly with the ADAS-cog (P=0.02) and MEC (P=0.02). The N-acetylaspartate/Cr ratio correlated with the baseline ADAS-cog (P=0.02) in the left temporal lobe. At week 24, the PCG was the only area where the correlation was significant. The patients who improved in the ADAS-cog showed increases in the N-acetylaspartate/Cr ratios (P=0.004). None of the baseline metabolite levels predicted response to treatment in any of the examined areas. Secondary: Not reported
Wilkinson et al.[85] (2002) Donepezil 10 mg/day vs rivastigmine 6 mg twice daily	OL, RCT Patients with mild-to-moderate Alzheimer's disease	N=111 12 weeks	Primary: ADAS-Cog, tolerability Secondary: Not reported	Primary: More patients taking donepezil completed the study (89.3%) compared to the rivastigmine group (69.1%; P=0.009). 10.7% of the donepezil group and 21.8% of the rivastigmine group discontinued treatment due to adverse events. 87.5% of the donepezil patients and 47.3% of the rivastigmine patients remained on the maximum approved dose of each drug at the last study visit. Both groups showed comparable improvements in ADAS-Cog administered at weeks four and 12.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Van Puyvelde et al.[86] (2011) Galantamine vs donepezil or rivastigmine (safety control group)	MC, OS, PRO Patients with mild-to-moderate Alzheimer's disease	N=128 6 months	Primary: Safety, patients and caregiver satisfaction, global impression as reported by the physician Secondary; Not reported	Primary: Adverse events were similar among both treatment groups (galantamine, 34%; SCG, 34.4%). The incidence of serious (12 events) and severe (15 events) adverse events with galantamine was similar to the SCG group (serious: galantamine 9.3% vs safety control group 9.7%); severe: galantamine 11.3% vs safety control group 12.9%. A total of 84.5% of patients treated with galantamine continued their treatment after six months. Patients receiving galantamine reported their condition as improved (49%), unchanged (47%) and worsened (4%). Caregivers rated global evaluation as better (37%), unchanged (41%) and worse (22%) with galantamine. Physicians rated global clinical impression of change as better (46%), unchanged (34%) and worse (20%) with galantamine. Measurements of cognition and behavior remained stable. The appreciation of physicians and caregivers corresponded well (P<0.001). Secondary: Not reported
Tariot et al.[87] (2004) Memantine 20 mg/day vs donepezil	DB, MC, PC, RCT Patients with moderate-to-severe Alzheimer's disease who received stable doses of donepezil	N=404 24 weeks	Primary: SIB, ADCS-ADL, CIBIC-Plus, BGP Secondary: Not reported	Primary: A significantly greater therapeutic effect was observed in the memantine group than in the placebo group on the ADCS-ADL, SIB and CIBIC-Plus. Patients receiving memantine in combination with donepezil demonstrated significantly less decline in ADCS-ADL scores compared to patients receiving donepezil-placebo over the 24-week study period (P=0.02). Patients receiving memantine showed significantly less cognitive decline in SIB scores compared to patients receiving placebo. Therapy with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				memantine-donepezil resulted in sustained cognitive performance above baseline compared to the progressive decline seen with the donepezil-placebo treatment. The change in total mean scores favored memantine vs placebo for the CIBIC-Plus (possible score range was 1-7), 4.41 vs 4.66, respectively (P=0.03). Treatment discontinuations due to adverse events for memantine vs placebo were 7.4% of the patients compared to 12.4%. Secondary: Not reported
Bullock et al.[88] (2005) Rivastigmine 3 to 12 mg/day vs donepezil 5 to 10 mg/day	DB, MC, RCT Patients 50 to 85 years of age with moderate to moderately-severe Alzheimer's disease (MMSE score 10-20)	N=994 24 months	Primary: SIB Secondary: GDS, ADCS-ADL, MMSE, NPI	Primary: Donepezil-treated patients declined 9.91 points from baseline on the SIB as compared to rivastigmine-treated patients, who declined by 9.30 points (P=NS). Secondary: Rivastigmine was more effective than donepezil on the ADCS–ADL, on which there was a between-treatment difference of 2.1 points after two years (P=0.007), and greater efficacy on the GDS (P=0.049). There were no significant differences in MMSE and NPI between the treatment groups. More patients receiving rivastigmine reported 'any adverse event' compared to those receiving donepezil during the titration phase (82.0 and 64.7%, respectively). Adverse events were higher with rivastigmine during the titration phase and included nausea (32.9 vs 15.2%) and vomiting (27.9 vs 5.8%). In the maintenance phase, adverse event rates in the two groups were similar (78.7% for the rivastigmine group and 76.9% for the donepezil group). Premature discontinuations due to adverse events were higher in the rivastigmine group during the titration phase (14.1 vs 7.0% for donepezil) but similar in the maintenance phase (17.9 vs 14.1% for donepezil).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Mossello et al.[89] (2004) Donepezil 5 to 10 mg/day vs galantamine 16 to 24 mg/day vs rivastigmine 6 to 12 mg/day	OL, OS Patients with mild-to-moderate Alzheimer's disease	N=407 9 months	Primary: MMSE, ADL and IADL Secondary: Not reported	Primary: There were no differences amongst the three groups in regards to any of the outcome measures (galantamine was not included in the MMSE comparison due to the small number of treated patients). Discontinuation due to adverse effects was lower in those patients on donepezil (3%) vs rivastigmine (17%; P=0.01) and vs galantamine (21%; P=0.01). Secondary: Not reported
Aguglia et al.[90] (2004) Donepezil vs galantamine vs rivastigmine	OL Patients with Alzheimer's disease	N=242 6 months	Primary: MMSE, ADAS-Cog, ADL and IADL Secondary: Not reported	Primary: There were no statistical differences on changes in the MMSE, ADAS-Cog, ADL or IADL measures amongst the three groups. There were no differences on changes in the IADL measure among the three groups. 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.[91] (2005) Donepezil vs	OL, PRO Patients with mild-to-moderate Alzheimer's disease	N=147 6 months	Primary: MMSE Secondary: Not reported	Primary: All three treatment groups had better MMSE scores compared to control (donepezil; P<0.001, galantamine; P<0.01, and rivastigmine; P<0.03). There were no statistical differences between the groups on measures of cognitive decline (via MMSE).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
galantamine vs rivastigmine vs historical controls				Secondary: Not reported
Rodda et al.[92] (2009) Donepezil 5 to 10 mg/day vs galantamine 8 to 24 mg/day vs rivastigmine 9 to 17.4 mg/day	RETRO Patients with Alzheimer's disease being treated with donepezil, rivastigmine or galantamine monotherapy	N=6,110 12 to 170 weeks	Primary: NPI Secondary: Not reported	Primary: Three of the 14 studies reviewed reported statistically significant improvement in overall NPI score or in the agitation/aggression item of the NPI only. One study demonstrated a significant difference in NPI score between groups randomized to either continuation or discontinuation of donepezil (placebo following an initial OL treatment phase. Of these four positive studies, two specified a minimum level of behavioral disturbance at baseline and used behavioral scores as a primary outcome. Secondary: Not reported
Howard et al.[93] (2012) Donepezil 10 mg/day vs memantine 20 mg/day vs	DB, MC, RCT Community-based patients with moderate-to-severe Alzheimer's disease who were taking donepezil 10 mg/day for ≥3 months	N=295 52 weeks	Primary: Standardized Mini-Mental State Examination and BADLS scores Secondary: NPI, caregiver health status assessed by General Health Questionnaire 12	Primary: Mean donepezil vs placebo Standardized Mini-Mental State Examination scores were higher with donepezil (better cognitive function) by an average of 1.9 points (95% CI, 1.3 to 2.5; P<0.001) and BADLS scores were lower (less functional impairment) by 3.0 points (95% CI, 1.3 to 2.5; P<0.001). Both outcomes demonstrated significant heterogeneity in treatment efficacy over tome (P=0.002 and P=0.004, respectively), with less benefit apparent at the six week assessment than at later time points. From six weeks onward, differences were roughly parallel. Mean donepezil+memantine vs placebo+memantine Standardized Mini-Mental State Examination scores were higher with donepezil by an

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
donepezil 10 mg/day and memantine 20 mg/day vs placebo				average of 1.2 points (95% CI, 0.6 to 1.8; P<0.001) and BADLS scores were lower by 1.8 points (95% CI, 0.3 to 2.8; P<0.001). Both outcomes were smaller than the minimum clinically important difference. Interactions of memantine therapy with visit were NS. Both donepezil and memantine demonstrated benefits on both Standardized Mini-Mental State Examination and BADLS larger in the absence of other agents alone, though statistically insignificant (P=0.14 and P=0.09, respectively). No significant benefits were seen adding memantine to donepezil on Standardized Mini-Mental State Examination scores (0.8 points higher with memantine and placebo; 95% CI, -0.1 to 1.6; P=0.07) or BADLS scores (0.5 points lower with memantine than placebo; 95% CI, 2.2 to 1.2; P=0.57). Secondary: NPI scores were lower for patients on memantine compared to placebo, indicating fewer behavioral and psychological symptoms by 4.0 points (99% CI, 0.6 to 7.4; P=0.002). No observable NPI differences noted with continuation, as compared to discontinuation of donepezil therapy (2.3 points lower with continuation; 95% CI, -1.1 to 5.7; P=0.08). Donepezil+memantine vs donepezil demonstrated a lower NPI score by 5.1 points (99% CI, 0.3 to 9.8; P=0.006). Continuation of donepezil and donepezil+memantine compared to the placebo and memantine + placebo demonstrated larger average decreases (indicating fewer psychological symptoms) across trial visits in General Health Questionnaire 12 scores for caregiver health status. There was a 0.5 point larger decrease with continuation vs discontinuation of donepezil (99% CI, -0.01 to 1.0; P=0.01) and 0.5 point larger decrease with memantine vs placebo (95% CI, -0.1 to 0.9; P=0.03), though significance was not reached to allow for multiple secondary outcomes.
Porsteinsson et al.[94] (2008)	PC, R Patients with probable	N=433 24 weeks	Primary: ADAS-cog, CIBIC-Plus	Primary: No significant difference in ADAS-cog and CIBIC-Plus was found between memantine and placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Memantine 20 mg/day plus cholinesterase inhibitor vs cholinesterase inhibitor plus placebo	Alzheimer's disease, MMSE scores between 10 to 22, concurrently taking a cholinesterase inhibitor		Secondary: ADCS-ADL, NPI, MMSE	Secondary: No significant difference in ADCS-ADL, NPI or MMSE was found between memantine and placebo.
Cumming et al.[95] (2006) Memantine 20 mg/day plus donepezil vs donepezil	DB, PC, PG, PRO Patients with moderate-to-severe Alzheimer's disease who received stable doses of donepezil	N=404 24 weeks	Primary: NPI Secondary: Not reported	Primary: NPI scores significantly favored the memantine group at 12 weeks and at 24 weeks. At week 12, NPI scores increased (worsening behavior) 1.7 points in the placebo group and decreased 2.5 points in the memantine group (P<0.001). At week 24, NPI scores increased 3.7 points (worsening behavior) in the placebo groups and the memantine group returned to baseline (P=0.002). Fewer patients developed delusions in the memantine treatment group than the placebo group (P=0.011). Secondary: Not reported
Maidment et al[96] Memantine 20 mg daily vs placebo or memantine 20 mg daily in combination with a	MA Patients with probable Alzheimer's disease	N=1,750 Duration varied	Primary: NPI Secondary: Not reported	Primary: Compared to the placebo group patients receiving memantine improved by 1.99 on the NPI scale (95% CI, -0.08 to -3.91; P=0.041). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
cholinesterase inhibitor (doses varied) vs placebo in combination with a cholinesterase inhibitor (doses varied)				
Wilkinson et al.[97] (2009) Cholinesterase inhibitors (donepezil 5 or 10 mg/day) vs placebo	MA Patients with mild-to-moderate Alzheimer's disease	N=906 (3 trials) 24 weeks	Primary: MMSE Secondary: Not reported	Primary: A significantly greater percentage of placebo patients than donepezil-treated patients met the specified criteria for all three definitions of clinical worsening. The OR for clinical worsening were significantly reduced for donepezil-treated patients compared to placebo patients (P<0.0001 for all definitions). Among patients meeting criteria for clinical worsening, mean declines in MMSE scores were greater for placebo than donepezil-treated patients. This outcome was also apparent when milder (MMSE, 18 to 26) and more moderate (MMSE, 10 to 17) subgroups were analyzed separately. Secondary: Not reported
Feldman et al.[98] (2009) Cholinesterase inhibitors	OS, PRO Alzheimer's disease patients with and without cerebrovascular disease	N=548 7 years	Primary: Time to nursing home placement Secondary: Identify factors noted to reduce risk of NHP, including measurement of DAD and MMSE	Primary: The overall median time to permanent institutional admission was 42.4 months (95% CI, 38.0 to 48.0 months). Secondary: Factors noted to reduce the risk of being admitted to a nursing home included higher baseline DAD and MMSE scores, Alzheimer's disease diagnosis, living with caregiver, country, and treatment duration (P<0.05). Each year of treatment demonstrated a reduced risk of nursing home admission (galantamine, -31%, other cholinesterase inhibitors , -29%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Trinh et al.[99] (2003) Cholinesterase inhibitors vs placebo	MA Trials included outpatients with mild or moderate Alzheimer's disease who were treated for at least one month with a cholinesterase inhibitor	29 trials Duration varied	Primary: NPI, ADAS-noncog, ADL and IADL Secondary: Not reported	Primary: Cholinesterase inhibitors improved the NPI statistically better than placebo (95% CI, 0.87 to 2.57). Cholinesterase inhibitors improved the ADAS-noncog measure numerically but not statistically compared to placebo (95% CI, 0.0 to 0.05). Cholinesterase inhibitors improved ADL numerically but not significantly better than placebo (95% CI, 0.0 to 0.19). Cholinesterase inhibitors improved IADL statistically compared to placebo (95% CI, 0.01 to 0.17). Secondary: Not reported
Lanctot et al.[100] (2003) Cholinesterase inhibitors 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 one additional patient to benefit was 7 (95% CI, 6 to 9) for stabilization or better, 12 (95% CI, 9 to 16) for minimal improvement or better and 42 (95% CI, 26 to 114) for marked improvement. The number needed to treat for one additional patient to experience an adverse event was 12 (95% CI, 10 to 18). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Birks et al.[101] (2006) Cholinesterase inhibitors vs placebo	MA Patients diagnosed with mild, moderate or severe dementia due to Alzheimer's disease	N=7,298 Minimum 6 months	Primary: CIBIC-Plus, GBS, GDS, ADAS-Cog, MMSE, SIB, NPI, ADL scored by PDS and DAD Secondary: Withdrawals prior to six months, adverse events	Cholinesterase inhibitor vs placebo (12 trials) Primary: Significant benefit was seen in CIBIC-Plus for patients treated with a cholinesterase inhibitor over placebo; more patients were scored as "showed improvement" than "showed decline/no change" (OR, 1.56; 95% CI, 1.32 to 1.85; P<0.00001): eight studies. No significant difference was seen in GBS between the cholinesterase inhibitor and placebo groups at one year (P value not reported): one trial. Significant improvement in ADAS-Cog was found for patients treated with donepezil, galantamine, or rivastigmine over placebo (WMD, –2.66; 95% CI, –3.02 to –2.31; P<0.00001): 10 studies. Significant benefit was seen in MMSE for patients treated with a cholinesterase inhibitor over placebo (WMD, 1.37; 95% CI, 1.13 to 1.61; P<0.00001): nine studies. Significant benefit was seen in ADL-PDS and DAD for patients treated with a cholinesterase inhibitor over placebo (WMD, 2.40; 95% CI, 1.55 to 3.37; P<0.00001 for PDS; and WMD, 4.39; 95% CI, 1.96 to 6.81; P=0.0004 for DAD). Significant benefit was seen in NPI for patients treated with a cholinesterase inhibitor over placebo (WMD, –2.44; 95% CI, –4.12 to –0.76; P=0.004). Secondary: Significantly more patients treated with a cholinesterase inhibitor (29%) withdrew prior to six months than those in the placebo groups (18%; P<0.00001). Adverse events that occurred significantly more frequently in the cholinesterase inhibitor group than the placebo group, from pooled data from at least 6 trials included: abdominal pain, anorexia, dizziness, diarrhea, headache (P<0.0001), insomnia (P=0.007), nausea, vomiting (P<0.00001 unless noted).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Donepezil vs rivastigmine (one trial) Primary: There was no statistically significant difference between the treatment groups for cognitive function, ADL scales, behavior disturbances and global assessment (P values not reported). Secondary: Significantly fewer patients in the donepezil group withdrew from treatment after 2 years than in the rivastigmine group (OR, 0.64; 95% CI, 0.50 to 0.83; P=0.0006). Adverse events that occurred significantly more frequently at 12-16 weeks of treatment in the rivastigmine group than in the donepezil group included: nausea (P<0.00001), vomiting (P<0.00001), falls (P=0.01), hypertension (P=0.01), anorexia (P=0.0005) and weight loss (P=0.001), and after 16 weeks to 2 years of treatment: nausea (P=0.0002), vomiting (P<0.00001) and anorexia (P=0.02). No significant difference between treatment groups for serious adverse events was noted (P value not reported).
Hansen et al.[102] (2008) Cholinesterase inhibitors	MA Patients with Alzheimer's disease	26 trials Variable duration	Primary: Cognition (ADAS-cog), function, behavior (NPI), global assessment of change (CIBIC+ and CGI-C) Secondary: Not reported	Primary: <u>Cognition (14 studies)</u> The pooled WMD in change between active treatment and placebo was -2.67 (95% CI -3.28 to -2.06) for donepezil, -2.76 (95% CI -3.17 to -2.34) for galantamine, and -3.01 (95% CI -3.80 to -2.21) for rivastigmine. <u>Function (14 studies)</u> The pooled standardized mean difference between active treatment and placebo was 0.31 (95% CI, 0.21 to 0.40) for donepezil, 0.27 (95% CI, 0.18 to 0.36) for galantamine, and 0.26 (95% CI, 0.11 to 0.40) for rivastigmine. <u>Behavior (seven studies)</u> The pooled WMD in NPI score between active treatment and placebo was -4.3 (95% CI, -5.95 to -2.65) for donepezil and -1.44 (95% CI, -2.39 to -0.48) for galantamine.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Global assessment of change (nine studies) The pooled RR of responding for active treatment compared to placebo was 1.88 (95% CI, 1.50 to 2.34) for donepezil, 1.15 (95% CI, 0.96 to 1.39) for galantamine, and 1.64 (95% CI, 1.29 to 2.09) for rivastigmine. Secondary: Not reported
Kim et al.[103] (2011) Cholinesterase inhibitors	MA Cognitively impaired older adults	54 trials Variable duration	Primary: Falls, syncope, fracture and accidental injury reported Secondary: Not reported	Primary: Cholinesterase inhibitors usage was associated with the greatest risk of syncope compared to placebo (OR, 1.53; 95% CI, 1.02 to 2.30), but not with any other events: falls (OR, 0.88; 95% CI, 0.74 to 1.04); fracture (OR, 1.39; 95% CI, 0.75 to 2.56); accidental injury (OR, 1.13; 95% CI, 0.87 to 1.45). Memantine was associated with fewer fractures (OR, 0.21; 95% CI, 0.05 to 0.85), but not with other events: falls (OR, 0.92; 95% CI, 0.72 to 1.18), syncope (OR, 1.04; 95% CI, 0.35 to 3.04); accidental injury (OR, 0.80; 95% CI, 0.56 to 1.12). There were no differential effects noted according to type and severity of cognitive impairment, residential status, or length of follow-up.
Parkinson's Disease				
Emre et al.[104] (2004) Rivastigmine 3 to 12 mg/day; average dose 8.6 mg/day vs placebo	DB, MC, PC, RCT Patients at least 50 years of age with mild-to-moderate dementia developed 2 years after the diagnosis of Parkinson's disease	N=541 Dose titration over the first 16 weeks with a subsequent assessment period of 8 weeks Total of 24 weeks	Primary: ADAS-Cog, ADCS-CGIC Secondary: ADCS-ADL, NPI-10, MMSE, CDR power of attention tests, D-KEFS verbal fluency test, Ten Point Clock-drawing Test	Primary: Patients who were receiving rivastigmine had significant improvement of 2.1 points in the 70-point ADAS-Cog scores vs worsening of 0.7 point in the placebo group from baseline (P<0.001). 19.8% of patients in the rivastigmine group and 14.5% in the placebo group clinically improved in the ADCS-CGIC scores. 13% of patients in the rivastigmine group and 23.1% in the placebo group clinically worsened in the ADCS-CGIC scores (P=0.007). Secondary: All secondary outcomes were significantly better in the rivastigmine group compared to placebo, as reflected by the changes in the ADCS-ADL score (P=0.02), NPI-10 (P=0.02), MMSE (P=0.03), CDR power of attention tests (P=0.009), D-KEFS verbal fluency test (P<0.001) and the Ten Point

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Clock- drawing Test (P=0.02).
Wesnes et al.[105] (2005) Rivastigmine 3 to 12 mg/day, average dose 8.6 mg/day vs placebo	DB, MC, PC, RCT Patients at least 50 years old with Parkinson's disease	N=487 24 weeks	Primary: Power of attention, continuity of attention, cognitive reaction time, reaction time variability Secondary: Not reported	Primary: At week 16, there was no statistical significance from baseline scores between rivastigmine and placebo for power of attention (P=0.11) but there was a significance at week 24 (P<0.01). By week 16, there was a significant improvement with continuity of attention (P=0.001) compared to placebo and this parameter continued to improve at week 24 (P=0.0001). Cognitive reaction time showed significant improvement by the end of week 24 (P<0.001) vs week 16 (P=0.064) but declined with placebo. Reaction time variability continued to show improvement over placebo from week 16 (P<0.05) to week 24 (P<0.001). Secondary: Not reported
Schmitt et al.[106] (2010) Rivastigmine 3 to 12 mg/day vs placebo	DB, MC, PC, RCT Patients with Parkinson's disease dementia	N=541 24 weeks	Primary: Executive function as assessed by D-KEFS measures Secondary: Not reported	Primary: Rivastigmine was associated with significantly more correct responses, fewer set loss errors, and more total responses made (within time available), compared to placebo (all P<0.05). There was no significant difference in total repetition errors (P=0.57). Rivastigmine was associated with a significantly higher Card Sorting recognition description score than placebo (P=0.03). Word reading errors, word comprehension, and sort recognition errors were NS. There were significantly more correct substitutions on the Symbol Digit Modalities Test compared to placebo (P=0.02). Rivastigmine was associated with significantly fewer self-corrected errors on the Color-Word Interference inhibition/switching subtest compared to placebo (P=0.049). Treatment differences in numbers of correct responses were near statistical significance (P=0.050). Other treatment differences in this battery of executive function tests were not statistically significant. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Olin et al.[107] (2010) Rivastigmine 3 to 12 mg/day vs placebo	DB, MC, PC, RCT Patients ≥50 years of age with Parkinson's disease dementia	N=541 24 weeks	Primary: Tolerability and efficacy as measured by ADCS-ADL Secondary: Not reported	Primary: A total of 75.8% of patients completed the study (rivastigmine, 72.7% vs placebo, 82.1%). The primary reasons for discontinuation were adverse events (17.1% for rivastigmine vs 7.8% for placebo) and withdrawal of consent (5.8% rivastigmine vs 1.1% placebo). At 24 weeks, rivastigmine was associated with significantly less deterioration compared to placebo based on ADCS-ADL total scores (-1.1 vs -3.6, respectively; P=0.023). Similar improvement were seen with rivastigmine compared to placebo on the basic ADCS-ADL subscale (-0.5 vs -1.7, respectively; P=0.025), and on high level function ADLs (0.1 vs -1.0; P=0.017). No other measures were significantly different among the treatment groups. Secondary: Not reported
Maidment et al.[108] (2006) Rivastigmine 3 to 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 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).

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

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

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

Additional Evidence

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

Stable Therapy
The cholinesterase inhibitors exhibit similar pharmacologic properties, and evidence from comparative studies support a switch strategy when patients are intolerant to one drug or when a therapeutic dose cannot be reached.[109] Gauthier et al. reported that when switched from donepezil to rivastigmine, approximately 50% of those who had adverse events or a lack of efficacy with donepezil tolerated or responded well to rivastigmine.[110] Wilkinson et al. found no difference in tolerability when patients were switched from donepezil to galantamine using either a four-day washout period or a seven-day washout period.[111] Sadowsky et al. evaluated immediate switch (no washout) or delayed switch (seven-day washout) from oral donepezil to transdermal rivastigmine following a four-week treatment period with donepezil.[112] The authors found that the rates of discontinuation due to any reason or adverse events were similar between the treatment groups. They concluded that both switch strategies were safe and well tolerated. Sakka et al. evaluated patients with moderate-to-severe Alzheimer's disease who were switched to donepezil after experiencing a treatment failure or intolerance with memantine.[113] The authors concluded that donepezil was effective and well tolerated in patients who discontinued memantine monotherapy, including those patients with previous exposure to cholinesterase inhibitors. A post-hoc analysis of five-month trial data with galantamine demonstrated that patients had similar efficacy outcomes, whether or not they had received prior anticholinesterase therapy, suggesting that a previous failure did not predict response to galantamine.[114]

Impact on Physician Visits
Fillenbaum et al. evaluated the frequency of outpatient visits for patients with Alzheimer's disease.[115] Outpatient visit ranged from 81 to 95% and was not related to the stage of dementia or institutional status. Leibson et al. demonstrated that the onset of Alzheimer's disease is not associated with greater use of acute care services, nor is the high use of nursing home care offset by fewer emergency room or hospital encounters.[116] Clark et al. evaluated a telephone intervention program where healthcare professionals work with patients and caregivers to determine resources within the family of an Alzheimer's patient.[117] Alzheimer's patients in the program felt less embarrassed and isolated because of their memory problems and reported less problems coping with their disease. Intervention patients with more severe impairment had fewer physician visits, were less likely to have an emergency room visit or hospital admission, and had decreased depression and strain. Wimo et al. demonstrated that the use of memantine in patients with moderate-to-severe Alzheimer's disease was associated with less total caregiver time compared to placebo.[118] There were also fewer patients institutionalized at week 28 in the memantine group compared to placebo.

IX. Cost

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

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

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

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

Rx=prescription

Table 8. Relative Cost of the Alzheimer's Agents

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

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

X. Conclusions

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

There are several guidelines which discuss the role of these agents in the management of Alzheimer's disease.[14-18] The primary goal of treatment is to delay the progression of symptoms and preserve functional ability.[16] The use of a cholinesterase inhibitor may lead to modest improvements in some patients; therefore, it is appropriate to offer a trial of one of these agents for patients with mild-to-moderate disease.[15-16] Memantine can be considered for the treatment of patients with moderate-to-severe disease and it may be prescribed as monotherapy or in combination with a cholinesterase inhibitor.[16] Guidelines do not give preference to one agent over another. Clinicians should base the treatment decision on tolerability, adverse events and ease of use.[15]

Numerous clinical trials have evaluated the efficacy and safety of the cholinesterase inhibitors and memantine. Several outcomes have been assessed (using more than 40 different instruments), including cognition, global function, behavior and quality of life. There is consistent evidence from well-designed studies that donepezil, galantamine, rivastigmine and memantine positively affect cognition and global function, although the improvements are modest. The findings are less consistent for other outcomes, including behavior and quality of life. In most cases, the duration of these clinical trials were less than one year. Thus, there is insufficient evidence to determine the optimal duration of therapy.[15-16] There are relatively few studies that directly compare the efficacy and safety of the Alzheimer's agents. Most of the trials have compared active treatment to placebo or no treatment. The studies also differ with regards to design, patient population and treatment duration, which make it difficult to compare the results.

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

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

XI. Recommendations

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

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Antidepressants
AHFS Class 281604
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I. Overview

The antidepressants are approved to treat a variety of mental disorders, including anxiety disorders, depressive disorders, eating disorders (bulimia nervosa) and premenstrual dysphoric disorder.[1-35] Anxiety disorders include agoraphobia, anxiety disorder due to another medical condition, generalized anxiety disorder, other specified anxiety disorder, panic disorder, selective mutism, separation anxiety disorder, social anxiety disorder or social phobia, specific phobia, substance/medication induced anxiety disorder and unspecified anxiety disorder.[36,37] Some of the antidepressants are also approved to treat nonpsychiatric conditions, such as chronic musculoskeletal pain, diabetic peripheral neuropathy, fibromyalgia, insomnia, moderate to severe vasomotor symptoms associated with menopause, nocturnal enuresis and tobacco abuse.[1-35]

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

Monoamine oxidase is an enzyme that is distributed in various tissues throughout the body. This enzyme is responsible for the catabolism of monoamines ingested in food, as well as for the inactivation of neurotransmitters (e.g., serotonin, norepinephrine and dopamine).[1-3] MAOIs increase the concentration of these neurotransmitters, which leads to their antidepressant activity. There are two types of monoamine oxidase, including MAO-A and MAO-B. The MAOIs differ with regards to selectivity for MAO receptor type and reversibility.[4-7] The SNRIs are potent inhibitors of neuronal norepinephrine and serotonin reuptake.[8-11] The SSRIs inhibit the neuronal uptake of serotonin and have minimal effects on norepinephrine or dopamine neuronal uptake.[12-21] The clinical efficacy of the SNRIs and SSRIs is thought to be related to the potentiation of neurotransmitter activity in the central nervous system. The exact mechanism of action of the serotonin modulators is unknown. Nefazodone inhibits neuronal uptake of serotonin and norepinephrine, and is a direct antagonist of serotonin ($5\text{-}HT_2$) receptors. Nefazodone and trazodone also block $alpha_1$-adrenergic receptors, which may be associated with postural hypotension.[1-3,22] Trazodone is thought to selectively inhibit serotonin uptake at the presynaptic neuronal membrane.[1-3] Vilazodone is a selective serotonin reuptake inhibitor and partial serotonin $5\text{-}HT_{1A}$ receptor agonist.[23] Vortioxetine exhibits various serotonergic activities including the inhibition of the reuptake of serotonin, antagonistic effects at the $5\text{-}HT_3$, $5\text{-}HT_7$ and $5\text{-}HT_{1D}$ receptors, inhibition of the serotonin transporter, agonistic effects at $5\text{-}HT_{1A}$ receptors and partial agonistic effects at $5\text{-}HT_{1B}$ receptors.[24] The TCAs interact with a wide variety of central nervous system receptor types, and as a result, cause many undesirable side effects. Clinically, they inhibit the reuptake of norepinephrine (secondary amines) and serotonin (tertiary amines) at the presynaptic neuron.[1-3,25-29] The miscellaneous antidepressants include bupropion and mirtazapine. Bupropion is a relatively weak inhibitor of the neuronal uptake of norepinephrine and dopamine; it does not inhibit monoamine oxidase or the reuptake of serotonin.[30-33] Mirtazapine is a tetracyclic compound, but is unrelated to the TCAs. It acts as an antagonist at central $alpha_2$-adrenergic receptors, which is thought to result in an increase in central noradrenergic and serotonergic activity.[34-35] Mirtazapine is also a potent antagonist of histamine receptors and is a moderate peripheral $alpha_1$-adrenergic receptor antagonist, which results in sedation and orthostatic hypotension.

Since the last review, a generic has become available for Cymbalta® (duloxetine). New formulations of desvenlafaxine extended-release have been approved as Desvenlafaxine ER® and Khedezla®, and a new formulation consisting of 450 mg of bupropion extended-release has been approved as Forfivo XL®. In addition, three new agents have become available, including Brintellix® (vortioxetine), Brisdelle® (paroxetine mesylate capsule) and Fetzima® (levomilnacipran).

The antidepressants that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. The majority of the products are available in a generic formulation, and there is at least one generic product available in each antidepressant subclass. This class was last reviewed in August 2012.

Table 1. Antidepressants Included in this Review

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

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
	tablet		

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

II. Evidence-Based Medicine and Current Treatment Guidelines

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

Table 2. Treatment Guidelines Using the Antidepressants

Clinical Guideline	Recommendation(s)
American Psychiatric Association: **Practice Guideline for the Treatment of Patients with Major Depressive Disorder, Third Edition (2010)**[38]	Acute phase • Pharmacotherapy: o An antidepressant medication is recommended as an initial treatment choice for patients with mild to moderate major depressive disorder (MDD) and definitely should be provided for those with severe MDD. o Due to the fact that the effectiveness of antidepressant medications is generally comparable between classes and within classes of medications, the initial selection of an antidepressant medication will largely be based on the anticipated side effects; the safety or tolerability of these side effects; pharmacological properties of the medication and additional factors such as medication response in prior episodes, cost and patient preference. o For the majority of patients, a selective serotonin reuptake inhibitor (SSRI), serotonin norepinephrine reuptake inhibitor (SNRI), bupropion or mirtazapine is optimal. o In general, the use of nonselective monoamine oxidase inhibitors (MAOIs) should be restricted to patients who do not respond to other treatments. o During the acute phase of treatment, patients should be carefully and systematically monitored on a regular basis to assess their response to pharmacotherapy. o If side effects do occur, an initial strategy is to lower the dose of the antidepressants or to change to an antidepressant that is not associated with those side effects. • Assessing the adequacy of treatment response: o It is important to establish that treatment has been administered for a sufficient duration and at a sufficient frequency or, in the case of medication, dose. o Generally, four to eight weeks of treatment are needed before concluding that a patient is partially responsive or unresponsive to a specific intervention. • Strategies to address non-response: o For individuals who have not responded fully to treatment, the acute phase of treatment should not be concluded prematurely, as an incomplete response to treatment is often associated with poor functional outcomes. o If at least a moderate improvement in symptoms is not observed within four to eight weeks of treatment initiation, the diagnosis should be reappraised, side effects assessed, complicating co-occurring conditions and psychosocial factors reviewed and the treatment plan adjusted. o It is important to assess the quality of the therapeutic alliance and treatment adherence. o If medications are prescribed, the psychiatrist should determine

Clinical Guideline	Recommendation(s)
	whether pharmacokinetic or pharmacodynamic factors suggest a need to adjust medication dose. o After an additional four to eight weeks of treatment, if the patient continues to show minimal or no improvement in symptoms, the psychiatrist should conduct another thorough review of possible contributory factors and make additional changes in the treatment plan. o There are a number of strategies available when a change in treatment seems necessary. ▪ For patients treated with an antidepressant, optimizing the medication dose is a reasonable first step if the side effect burden is tolerable and the upper limit of a medication dose has not been reached. ▪ In patients who have shown minimal improvement or experienced significant medication side effects, other options include augmenting the antidepressant with a depression-focused psychotherapy or with other agents or with changing to another non-MAOI antidepressant. ▪ Patients may be changed to an antidepressant from the same pharmacological class or to one from a different class. ▪ Patients who have not responded to an SSRI, may respond to SNRI. ▪ Augmentation of antidepressant medications can utilize another non-MAOI antidepressant, generally from a different pharmacological class, or a non-antidepressant medication, such as lithium, thyroid hormone or a second generation antipsychotic. <u>Continuation phase</u> • During the continuation phase of treatment, the patient should be carefully monitored for signs of possible relapse. • Systematic assessment of symptoms, side effects, adherence and functional status is essential and may be facilitated through the use of clinician- and/or patient-administered rating scales. • To reduce the risk of relapse, patients who have been treated successfully with antidepressant medications in the acute phase should continue treatment with these agents for four to nine months. • In general, the dose used in the acute phase should be used in the continuation phase. • To prevent a relapse of depression in the continuation phase, depression-focused psychotherapy is recommended, with the best evidence available for cognitive behavioral therapy (CBT). <u>Maintenance phase</u> • In order to reduce the risk of a recurrent depressive episode, patients who have had three or more prior MDD episodes or who have chronic MDD should proceed to the maintenance phase of treatment after completing the continuation phase. • Maintenance therapy should also be considered for patients with additional risk factors for recurrence. • Additional considerations that may play a role in the decision to use maintenance therapy include patient preference, the type of treatment received, the presence of side effects during continuation therapy, the probability of recurrence, the frequency and severity of prior depressive episodes, the persistence of depressive symptoms after recovery and the presence of co-occurring disorders. Such factors also contribute to decisions about the duration of the maintenance phase.

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

National Institute for Health and Clinical Excellence: **Treatment and Management of Depression in Adults (Update) (2009)**[39]	<u>Persistent subthreshold depressive symptoms or mild to moderate depression</u>
	• Do not use antidepressants routinely to treat persistent subthreshold depressive symptoms or mild depression.
	• Consider antidepressants for the following people:
	  o A past history of moderate or severe depression.
	  o Initial presentation of subthreshold depressive symptoms that have been present for a long period (typically at least two years).
	  o Subthreshold depressive symptoms or mild depression that persist(s) after other interventions.
	
	<u>Persistent subthreshold depressive symptoms or mild to moderate depression with inadequate response to initial interventions, and moderate and severe depression</u>
	• For patients with persistent subthreshold depressive symptoms or mild to moderate depression who have not benefited from a low-intensity psychosocial intervention, discuss the relative merits of different interventions with the person and provide:
	  o An antidepressant (normally an SSRI) or a high intensity psychosocial intervention.
	• For people with moderate or severe depression, provide a combination of an antidepressant medication and a high intensity psychological intervention.
	• The choice of intervention should be influenced by the duration of the episodes of depression and the trajectory of symptoms, previous course of depression and response to treatment, likelihood of adherence to treatment and any potential adverse effects and the patient's treatment preference and priorities.
	
	<u>Antidepressant drugs</u>
	• Choice of antidepressant:
	  o Discuss the choice of antidepressant with the patient, including any

Clinical Guideline	Recommendation(s)
	anticipated adverse events and potential drug interactions, and their perception of the efficacy and tolerability of any antidepressant they have previously taken. o When an antidepressant is used, it should normally be an SSRI in a generic form. The SSRIs are equally effective as other antidepressants and have a favorable risk-benefit ratio. Fluoxetine, fluvoxamine and paroxetine are associated with a higher propensity for drug interactions than other SSRIs, and paroxetine is associated with a higher incidence of discontinuation symptoms than other SSRIs. o Take into account toxicity in overdose when choosing an antidepressant for people at significant risk for suicide. Be aware that compared to other equally effective antidepressants routinely used in primary care, venlafaxine is associated with a greater risk of death from overdose, and tri-cyclic antidepressants (TCAs), except lofepramine, are associated with the greatest risk in overdose. o When prescribing drugs other than SSRIs, take the following into account: the increased likelihood of the person stopping treatment because of side effects with duloxetine, venlafaxine and TCAs, the specific cautions, contraindications and monitoring requirements for some drugs, that non-reversible MAOIs should normally be prescribed only by specialists. • Starting and initial phase of treatment: o When prescribing antidepressants, explore any concerns the patient has. Explain the gradual development of the full antidepressant effect, the importance of taking the medication as prescribed, the need to continue treatment after remission, potential side effects, the potential for interactions with other medications, the risk and nature of discontinuation symptoms with all antidepressants and how these symptoms can be minimized and the fact that addiction does not occur with antidepressants. o If side effects develop early in antidepressant treatment, provide appropriate information and consider one of the following strategies: monitor symptoms closely where side effects are mild and acceptable to the patient, stop the antidepressant, change to a different antidepressant if the person prefers or consider short term concomitant treatment with a benzodiazepine if anxiety, agitation and/or insomnia are problematic (this should usually be for no longer than two weeks in order to prevent the development of dependence). o Patients who start on low dose TCAs and who have clear clinical response can be maintained on that dose with careful monitoring. o If the patient's depression shows no improvement after two to four weeks with the first antidepressant, check that the drug has been taken regularly and in the prescribed dose. o If response is absent or minimal after three to four weeks of treatment with a therapeutic dose of an antidepressant, increase the level of support and consider increasing the dose in line with the summary of product characteristics if there are no significant side effects or switching to another antidepressant. • If the patient's depression shows some improvement by four weeks, continue treatment for another two to four weeks. Consider switching to another antidepressant if response is still not adequate, there are side effects or the person prefers to change treatment.
American College of Physicians: **Clinical Practice Guideline: Using**	<u>Treatment of MDD</u> • When treating acute-phase MDD, the second-generation antidepressants did not significantly differ in efficacy, effectiveness, or quality of life among the SSRIs, SNRIs, selective serotonin norepinephrine reuptake inhibitors (SSNRIs), or

Clinical Guideline	Recommendation(s)
Second-Generation Antidepressants to Treat Depressive Disorders (2008)[40]	other second-generation antidepressants. • Mirtazapine had a significantly faster onset of action; however, after four weeks, most response rates were similar. • Second-generation antidepressants did not differ in the rate of achieving remission. • First-generation antidepressants (TCAs and MAOIs) are less commonly used than second-generation antidepressants, which have similar efficacy to and lower toxicity in overdose than first-generation antidepressants. <u>Treatment of depression in patients with accompanying symptom clusters</u> • When treating symptom clusters in patients with accompanying depression, second-generation antidepressants did not differ in efficacy in treating accompanying anxiety, pain, and somatization. • Limited evidence suggests that some agents may be more effective in treating insomnia. <u>Treatment of depression in selected patient populations</u> • Second-generation antidepressants did not differ in efficacy among subgroups and special populations categorized according to age, sex, race or ethnicity, or comorbid conditions. <u>Risk for harms and adverse events</u> • Most of the second-generation antidepressants had similar adverse effects. • The most commonly reported adverse events were constipation, diarrhea, dizziness, headache, insomnia, nausea, sexual adverse events, and somnolence. Nausea and vomiting were the most common reasons for discontinuation in efficacy studies. • Paroxetine was associated with an increased risk for sexual dysfunction. • SSRIs resulted in an increased risk for nonfatal suicide attempts. <u>Recommendations</u> • Clinicians should select second-generation antidepressants on the basis of adverse effect profiles and patient preferences. • Clinicians should assess patient status, therapeutic response, and adverse effects of antidepressant therapy on a regular basis beginning within one to two weeks of initiation of therapy. • Clinicians should modify treatment if the patient does not have an adequate response to pharmacotherapy within six to eight weeks of the initiation of therapy for major depressive disorder. • Clinicians should continue treatment for four to nine months after a satisfactory response in patients with a first episode of major depressive disorder. For patients who have had two or more episodes of depression, an even longer duration of therapy may be beneficial.
American Academy of Child and Adolescent Psychiatry: **Practice Parameter for the Assessment and Treatment of Children and Adolescents with Depressive Disorders (2007)[41]**	<u>All Types of childhood/adolescent depression</u> • All patients with depression should receive therapy in the acute (six to 12 weeks) and continuation phases (six to 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

Clinical Guideline	Recommendation(s)
	response after four to six 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 Food and Drug Administration (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). • 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 Clinical Excellence: **Generalized Anxiety Disorder and Panic Disorder (With or Without Agoraphobia) in Adults (2011)**[42]	<u>Stepped care for people with generalized anxiety disorder (GAD)</u>
	• If a person with GAD chooses drug treatment, offer an SSRI, specifically sertraline.
	• If sertraline is ineffective, offer an alternative SSRI or a SNRI, taking into account the following factors:
	  o Tendency to produce a withdrawal syndrome (especially with paroxetine and venlafaxine).
	  o The side-effect profile and the potential for drug interactions.
	  o The risk of suicide and likelihood of toxicity in overdose (especially with venlafaxine).
	  o The person's prior experience of treatment with individual drugs (particularly adherence, effectiveness, side effects, experience of withdrawal syndrome and the person's preference).
	• If the person cannot tolerate SSRIs or SNRIs, consider offering pregabalin.
	• Do not offer a benzodiazepine for the treatment of GAD in primary or secondary care except as a short-term measure during crises.
	• Do not offer an antipsychotic for the treatment of GAD in primary care.
	
	<u>Panic disorder general considerations</u>
	• Benzodiazepines are associated with a less effective outcome in the long term and should not be prescribed for panic disorder.
	• Sedating antihistamines or antipsychotics should not be prescribed for panic disorder.
	• Interventions with evidence for the longest duration of effect are listed in descending order, where preference of the patient should be taken into account:

Clinical Guideline	Recommendation(s)
	o Psychological therapy (i.e., cognitive behavioral therapy, structured problem solving, psychoeducation). o Pharmacological therapy (antidepressant therapy). o Self-help interventions (i.e., bibliotherapy, support groups, exercise, CBT via a computer interface). • Antidepressants should be the only pharmacologic intervention used in the longer term. • Two types of medication are considered in the guideline for the treatment of panic disorder; TCAs and SSRIs. • Unless otherwise indicated, an SSRI (e.g., paroxetine, fluvoxamine, citalopram) licensed for panic disorder should be offered. If an SSRI is not suitable or there is no improvement after a 12-week course and if further medication is appropriate, imipramine or clomipramine may be considered. • If the patient is showing improvement, the medication should be continued for at least six months after optimal dose is reached, after which the dose may be tapered slowly over an extended period to minimize the risk of discontinuation/withdrawal symptoms.
American Psychiatric Association: **Practice Guideline for the Treatment of Patients with Panic Disorder, Second Edition (2009)**[43]	• SSRIs, SNRIs, TCAs, and benzodiazepines have demonstrated efficacy in numerous controlled trials and are recommended for treatment of panic disorder. • Because SSRIs, SNRIs, TCAs, and benzodiazepines appear roughly comparable in their efficacy for panic disorder, selecting a medication involves considerations of side effects, pharmacological properties, potential drug interactions, prior treatment history, and comorbid medical and psychiatric conditions. • The relatively favorable safety and side effect profile of SSRIs and SNRIs makes them the best initial choice for many patients with panic disorder. • There is no evidence of differential efficacy between the SSRIs, although differences in the side-effect profile (e.g., potential for weight gain, discontinuation-related symptoms), half-life, propensity for drug interactions, and availability of generic formulations may be clinically relevant. They are safer than TCAs and monoamine oxidase inhibitors. They are rarely lethal in overdose and have few serious effects on cardiovascular function. • Venlafaxine extended release has been shown to be effective for panic disorder. It is generally well tolerated and has a side effect profile similar to the SSRIs. No systematic data are currently available supporting the use of duloxetine, in panic disorder, although its mechanism of action suggests it might be an effective agent. • Although TCAs are effective, the side effects and greater toxicity in overdose limit their acceptability to patients and clinical utility. Given the equivalency of TCAs in treating depression, there is little reason to expect other TCAs to work less well for panic disorder. TCAs that are more noradrenergic (e.g., desipramine, maprotiline) may be less effective than agents that are more serotonergic. • SSRIs, SNRIs, and TCAs are all preferable to benzodiazepines as monotherapies for patients with comorbid depression or substance use disorders. Benzodiazepines may be especially useful adjunctively with antidepressants to treat residual anxiety symptoms. • Benzodiazepines may be preferred for patients with very distressing or impairing symptoms in whom rapid symptom control is critical. The benefit of more rapid response to benzodiazepines must be balanced against the possibilities of troublesome side effects and physiological dependence that may lead to difficulty discontinuing the medication. • MAOIs appear effective for panic disorder but, because of their safety profile, they are generally reserved for patients who have failed to respond to several

Clinical Guideline	Recommendation(s)
	first-line treatments. • Neither trazodone nor nefazodone can be recommended as a first-line treatment for panic disorder. There is minimal support for the use of trazodone in panic disorder and it appears less effective than imipramine and alprazolam. There are a few small, uncontrolled studies showing benefits of nefazodone in some patients with panic disorder; however, its use has been limited by concerns about liver toxicity. • Bupropion was effective in one small trial and ineffective in another. It cannot be recommended as a first line treatment for panic disorder. • Other medications with less empirical data may be considered as monotherapies or adjunctive treatments for panic disorder when patients have failed to respond to several standard treatments or based on other individual circumstances.

American Academy of Child and Adolescent Psychiatry: **Practice Parameter for the Assessment and Treatment of Children and Adolescents with Anxiety Disorders (2007)**[44]	• A multimodal treatment approach for children and adolescents with anxiety disorders should consider education of the parents and the child about the anxiety disorder, consultation with school personnel and primary care physicians, cognitive-behavioral interventions, psychodynamic psychotherapy, family therapy, and pharmacotherapy.
	• Treatment of childhood anxiety disorders of mild severity should begin with psychotherapy.
	• Valid reasons for combining medication and treatment with psychotherapy include the following:
	  o Need for acute symptom reduction in a moderately to severely anxious child.
	  o A comorbid disorder that requires concurrent treatment.
	  o Partial response to psychotherapy and potential for improved outcome with combined treatment.
	• SSRIs have emerged as the medication of choice in the treatment of childhood anxiety disorders.
	• When anxiety disorder symptoms are moderate or severe or impairment makes participation in psychotherapy difficult, or psychotherapy results in a partial response, treatment with medication is recommended.
	• No controlled studies are available for medication treatment of childhood-onset panic disorder. The use of a SSRI in adolescents with panic disorder has shown significant improvement in panic symptoms.
	• Controlled trials have established the safety and efficacy of short-term treatment with SSRIs for childhood anxiety disorders; however, the benefits and risks of long-term use of SSRIs have not been studied. It is recommended that clinicians consider a medication-free trial for children who have a significant reduction in anxiety or depressive symptoms on an SSRI and maintain stability in these symptoms for one year.
	• There is no empirical evidence that a particular SSRI is more effective than another for treatment of childhood anxiety disorders. The choice is often based on side effects, duration of action, or positive response to a particular SSRI in a first-degree relative with anxiety.
	• The risk-benefit ratio for a medication trial needs to be carefully assessed because cognitive-behavioral therapy has been shown to be effective and long-term side effects of medications have not been studied in youths.
	• The safety and efficacy of medications other than SSRIs for the treatment of childhood anxiety disorders have not been established.
	• Noradrenergic antidepressants (venlafaxine and TCAs), buspirone, and benzodiazepines have been suggested as alternatives to be used alone or in combination with the SSRIs.
	• Data are limited in childhood anxiety disorders to guide treatment with combinations of medications when a single medication is not effective in managing anxiety symptoms. Comorbid diagnoses are strongly considered in

Clinical Guideline	Recommendation(s)
	selection of medication. • Preliminary findings from controlled trials of extended-release venlafaxine in the treatment of youths with GAD and social phobia suggest it may be well tolerated and effective relative to placebo. • Controlled trials with TCAs for pediatric anxiety disorders have shown conflicting results and have not established efficacy for this use. • Buspirone may be an alternative to SSRIs for GAD in youths, but there are no published controlled trials. • Benzodiazepines have not shown efficacy in controlled trials in childhood anxiety disorders despite established benefit in adult trials. They are used as an adjunct short-term treatment with SSRIs to achieve rapid reduction in severe anxiety symptoms that may permit initiation of the exposure phase of cognitive-behavioral therapy. Clinicians should use benzodiazepines cautiously because of the possibility of developing dependency.
American Academy of Child and Adolescent Psychiatry: **Practice Parameter for the Assessment and Treatment of Children and Adolescents With Obsessive-Compulsive Disorder (2012)**[45]	• The psychiatric assessment of children and adolescents should routinely screen for the presence of obsessions and/or compulsions or repetitive behaviors. • If screening suggests obsessive-compulsive symptoms, clinicians should fully evaluate the child using the DSM-IV-TR criteria and scalar assessment. • A complete psychiatric evaluation should be performed, including information from all available sources and compromising standard elements of history and a mental state examination, with attention to the presence of commonly occurring comorbid psychiatric disorders. • It is possible that three out of four children with obsessive-compulsive disorder (OCD) meet criteria for at least one comorbid diagnosis, and these children have lower response rates to CBT than children without comorbid diagnoses. • Identification of MDD and bipolar disorder is very important before initiating treatment with a SSRI. • Comorbid eating disorders are infrequent in younger children; however, comorbid eating disorders become more prevalent in adolescents. • A full medical, developmental, family and school history should be included with the psychiatric history and examination. • CBT is the first-line treatment for mild to moderate OCD in children, whenever possible. • For moderate to severe OCD, medication is indicated in addition to CBT. • Serotonin reuptake inhibitors (SRIs) are the first-line medications recommended for OCD in children, including clomipramine (a TCA) and certain SSRIs (fluoxetine, fluvoxamine, paroxetine and sertraline). • There is no SRI that is proven to be more efficacious over another. • The modality of assigned treatment should be guided by empirical evidence on the moderators and predictors of treatment response. • Multimodal treatment with CBT and medication is recommended if CBT fails to achieve a clinical response after several months or in more severe cases. • Medication augmentation strategies are reserved for treatment-resistant cases in which impairments are deemed moderate in at least one important domain of function despite adequate monotherapy. • Adding clomipramine to an SSRI is a useful medication augmentation strategy. • Augmenting with an atypical neuroleptic is also a strategy employed by experts (e.g. haloperidol and risperidone combined) based on studies in adults with OCD; however, controlled data for the use of atypical antipsychotics in children with OCD does not exist. • A minimum of two adequate SSRI trials or an SSRI and clomipramine trial is recommended before atypical augmentation. • Empirically validated medication and psychosocial treatments for comorbid disorders should be considered.

Clinical Guideline	Recommendation(s)
American Psychiatric Association: **Practice Guideline for the Treatment of Patients with Obsessive-Compulsive Disorder (2007)**[46]	<u>General considerations</u> • OCD is a chronic illness which typically waxes and wanes. • Patients who have symptoms interfering with daily functioning should be treated. • Clinical remission and recovery may not always occur and will not occur rapidly. • Goals of treatment include improving symptoms, patient functioning, and quality of life. <u>Initial treatment options</u> • The choice of treatment depends on the patient's ability to comply with therapy, whether psychotherapy, pharmacotherapy, or both. • First-line treatments include cognitive-behavioral therapy, SRIs, or a combination of the two. The choice depends on past treatment history, comorbid psychiatric conditions, severity of symptoms, and functional limitations. • Cognitive-behavioral therapy or SRI therapy may be used alone or in combination, and combination therapy may be considered in patients who do not respond fully to monotherapy, those with severe symptoms, those with comorbid psychiatric illnesses for which an SRI is indicated, or in patients who wish to limit SRI exposure. • All SRIs appear to be equally effective, though patients may respond to agents differently. • Prescribers should consider the safety, side effects, FDA warnings, drug interactions, past response to treatment, and comorbid medical conditions when choosing a medication for treatment. • Most patients do not experience a significant improvement until four to six weeks after treatment initiation, and some may ultimately respond after as many as 10 to 12 weeks. • Patients not responding after 10 to 12 weeks may respond to a higher dose of the same medication. <u>Changing treatments and pursuing sequential treatment trials</u> • Augmentation strategies may be preferred to switching strategies in patients who have a partial response to the initial treatment. • Augmentation of SRIs with trials of different antipsychotic medications or with cognitive-behavioral therapy or augmentation of cognitive-behavioral therapy with an SRI. • Patients who do not respond to their first SRI may have their medication switched to a different SRI. A switch to venlafaxine is less likely to produce an adequate response. • For patients who have not benefitted from their first SSRI trial, a switch to mirtazapine can be considered. • After first- and second-line treatments and well-supported augmentation strategies have been exhausted, less well-supported treatment strategies may be considered. These include augmenting SRIs with clomipramine, buspirone, pindolol, riluzole, or once- weekly oral morphine sulfate. • Evidence for beneficial effects of benzodiazepines as monotherapy for OCD is limited to case reports with clonazepam and alprazolam. Modest doses of benzodiazepines may relieve anxiety and distress in OCD without directly diminishing the frequency or duration of obsessions or compulsions. Given their limited evidence for efficacy, benzodiazepines cannot be recommended as monotherapy for OCD, except in those rare individuals who are unable or unwilling to take standard anti-OCD medications.

Clinical Guideline	Recommendation(s)
American Academy of Child and Adolescent Psychiatry: **Practice Parameter for the Assessment and Treatment of Children and Adolescents With Posttraumatic Stress Disorder (2010)**[47]	• The psychiatric evaluation of children and adolescents should routinely include questions about traumatic experiences and posttraumatic stress disorder (PTSD) symptoms. • If the evaluation indicates symptoms of PTSD, the clinician should formally determine if PTSD is present, the severity of PTSD symptoms and the degree of functional impairment. Caregivers should be included in the formal evaluation. • A differential diagnosis should be conducted in order to rule out diagnoses with symptoms that can mimic PTSD symptoms. • The treatment plan should be comprehensive in approach and should consider the severity of symptoms and impairment, as well as comorbid psychiatric conditions. • Trauma-focused psychotherapies should be considered first-line in children and adolescents with PTSD, including psychoanalytic, attachment and cognitive behavioral treatment models. • SSRIs can be considered for treatment of children and adolescents with PTSD. • The effect of SSRIs in children with PTSD may be more consistent with a placebo effect. • Other medications such as clonidine and propranolol may be useful in decreasing symptoms of hyperarousal, and anticonvulsants may beneficial in treating PTSD symptoms other than avoidance. • Benzodiazepines have not been found to be beneficial in treating PTSD symptoms. • School-based accommodations are recommended for children with PTSD, especially in children with school-based trauma, such as bullying. • The use of restrictive, "rebirthing," binding or other coercive therapies are not recommended. • Screening for PTSD in the school or community should be conducted after traumatic events that affect significant numbers of children.
American Psychiatric Association: **Guideline Watch: Practice Guideline for the Treatment of Patients with Acute Stress Disorder and Posttraumatic Stress Disorder (2009)**[48]	• Meta-analyses and several randomized controlled trials published since 2004 support the greater efficacy of SSRIs and SNRIs over placebo for non-combat-related PTSD. • The evidence base for pharmacological intervention in combat-related PTSD has not been significantly augmented by recent studies. Studies suggest that SSRIs may not be recommended with the previous level of confidence for the treatment of PTSD in this particular population. Further research is needed to answer why these populations have been shown to have differential responses to SSRI treatment. • As described in the 2004 guideline, no significant differences among antidepressants, including the SSRIs, were found in the few head-to-head studies then available. Since that time, studies have been published comparing nefazodone and sertraline, venlafaxine and sertraline, the SNRI reboxetine and fluvoxamine, and fluoxetine, moclobemide, and tianeptine. These studies have generally demonstrated the greater efficacy of antidepressants to placebo but have done little to clarify the relative utility of these different antidepressants. • There is a relatively robust evidence basis for pharmacological treatment with antidepressant medications (particularly SSRIs and SNRIs for noncombat PTSD) as compared to other classes of medications. • Comparison of other treatments with the SSRIs and SNRIs is complicated by methodological differences in the available studies. SSRIs and SNRIs have mostly been studied in rigorous trials compared to placebo; other agents have been studied against "treatment as usual" or as augmentation agents in patients with refractory illness.
American Psychiatric Association: **Practice Guideline for**	• Goals of treatment for patients with PTSD and acute stress disorder (ASD) include lessening the severity of symptoms and preventing trauma-related comorbid conditions.

<table>
<tr><th>Clinical Guideline</th><th>Recommendation(s)</th></tr>
<tr><td>the Treatment of Patients with Acute Stress Disorder and Posttraumatic Stress Disorder (2004)[49]</td><td>

Clinical trial data and randomized studies are limited and difficult to perform.
Treatment includes pharmacotherapy, psychotherapy and supportive measures.
SSRIs are first-line therapy for PTSD and ASD and if found effective, treatment should be continued in order to continue to see benefit.
Second-line treatment agents include TCAs (specifically amitriptyline and imipramine, but not desipramine) and MAOIs.
Benzodiazepines should not be used as monotherapy, but may be effective as sedatives and anxiolytics.
Atypical antipsychotics may be necessary for patients experiencing psychotic symptoms.
Anticonvulsants (divalproex, carbamazepine, topiramate and lamotrigine) have produced mixed results for treating PTSD and ASD but may prove to be beneficial.
Limited data exists for the use of adrenergic inhibitors and their use is not part of the guideline at this time.
An adequate trial of therapy requires a minimum of three months of treatment. If treatment is effective, it should be continued for up to 12 months or longer.

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<tr><td>American College of Obstetricians and Gynecologists: Practice Bulletin: Premenstrual Syndrome (2000)[50]</td><td>

SSRIs have been proven effective in treating premenstrual syndrome (PMS).
Current evidence does not support the use of natural progesterone or primrose oil for the treatment of PMS.
Gonadotropin-releasing hormone agonists and surgical oophorectomy have been shown to be effective, but side effects limit usefulness in most patients.
Alprazolam may be useful in some patients, but side effects prevent it from being used as a first-line agent.
Calcium supplements may be effective.
Magnesium, vitamin B6, and vitamin E are minimally effective in treating PMS.

</td></tr>
<tr><td>American Psychiatric Association: Practice Guideline for the Treatment of Patients with Eating Disorders (2006)[51]</td><td>

Patients with eating disorders should be treated with nutritional rehabilitation.
Psychosocial therapy should be used in the treatment of anorexia.
SSRIs may be considered in the treatment of anorexia.
Bupropion, TCAs, and MAOIs should be avoided in patients with eating disorders.
Atypical antipsychotics may be used in patients with severe symptoms.
SSRIs may be considered in patients with bulimia.

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<tr><td>A Joint Clinical Practice Guideline from the American College of Physicians and the American Pain Society: Diagnosis and Treatment of Low Back Pain (2007)[52]</td><td>

Treatment is based on initial workup, evaluation, additional studies (i.e. imaging or blood work) and duration of symptoms.
The potential interventions for low back pain are outlined below:

<table>
<tr><th colspan="4">Interventions for the Management of Low Back Pain</th></tr>
<tr><th colspan="2">Intervention Type</th><th>Acute pain (duration <4 weeks)</th><th>Subacute or chronic pain (duration >4 weeks)</th></tr>
<tr><td rowspan="3">Self-care</td><td>Advice to remain active</td><td>Yes</td><td>Yes</td></tr>
<tr><td>Application of superficial heat</td><td>Yes</td><td>No</td></tr>
<tr><td>Book, handouts</td><td>Yes</td><td>Yes</td></tr>
<tr><td rowspan="6">Pharmaco-logic Therapy</td><td>Acetaminophen</td><td>Yes</td><td>Yes</td></tr>
<tr><td>TCA</td><td>No</td><td>Yes</td></tr>
<tr><td>Benzodiazepines</td><td>Yes</td><td>Yes</td></tr>
<tr><td>NSAIDs</td><td>Yes</td><td>Yes</td></tr>
<tr><td>Skeletal muscle relaxants</td><td>Yes</td><td>No</td></tr>
<tr><td>Tramadol, opioids</td><td>Yes</td><td>Yes</td></tr>
<tr><td rowspan="3">Non-</td><td>Acupuncture</td><td>No</td><td>Yes</td></tr>
<tr><td>Cognitive behavior therapy</td><td>No</td><td>Yes</td></tr>
<tr><td>Exercise therapy</td><td>No</td><td>Yes</td></tr>
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<table>
<tr><th>Clinical Guideline</th><th>Recommendation(s)</th></tr>
<tr><td></td><td>
<table>
<tr><td rowspan="5">pharmaco-logic Therapy</td><td>Massage</td><td>No</td><td>Yes</td></tr>
<tr><td>Progressive relaxation</td><td>No</td><td>Yes</td></tr>
<tr><td>Spinal manipulation</td><td>Yes</td><td>Yes</td></tr>
<tr><td>Yoga</td><td>No</td><td>Yes</td></tr>
<tr><td>Intensive interdisciplinary rehabilitation</td><td>No</td><td>Yes</td></tr>
</table>
Adapted with permission from Chou R, et al. Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society [published correction appears in Ann Intern Med. 2008;148(3):247-8]. Ann Intern Med. 2007;147(7):482.

• Physicians should conduct a focused history and physical examination to classify patients into one of three categories: (1) nonspecific pain; (2) pain possibly associated with radiculopathy or spinal stenosis; and (3) pain from another specific spinal cause (e.g., neurologic deficits or underlying conditions, ankylosing spondylitis, vertebral compression fracture). Patient history should be assessed for psychosocial risk factors.
• In combination with information and self-care, the use of medications with proven benefits should be considered. Before beginning treatment, physicians should evaluate the severity of the patient's baseline pain and functional deficits and the potential benefits and risks of treatment, including the relative lack of long-term effectiveness and safety data. In most cases, acetaminophen or NSAIDs are the first line options.
• Acetaminophen is considered first-line, even though it is a weaker analgesic compared to NSAIDs, due to more favorable safety profile and low cost. Nonselective NSAIDs are more effective for pain relief but are associated with gastrointestinal and renovascular risks, therefore assessments need to be made before starting a regimen.
• Skeletal muscle relaxants are associated with central nervous system effects (primarily sedation).These agents should be used with caution.
• Benzodiazepines seem similar in efficacy as skeletal muscle relaxants for short term pain relief but are associated with risk of abuse and tolerance.
• Opioid analgesics and tramadol are options for patients with severe, disabling pain that is not controlled with acetaminophen or NSAIDs. Evidence is insufficient to recommend one opioid over another.
• Opioid analgesics and tramadol carry a risk for abuse and addiction especially with long-term use. These agents should be used with caution.
</td></tr>
<tr><td>American College of Rheumatology:
American College of Rheumatology 2012 Recommendations for the Use of Nonpharmacologic and Pharmacologic Therapies in Osteoarthritis of the Hand, Hip, and Knee (2012)[53]</td><td>
Nonpharmacologic recommendations for the management of hand osteoarthritis
• It is recommended that health professionals should:
o Evaluate the ability to perform activities of daily living.
o Instruct in joint protection techniques.
o Provide assistive devices, as needed, to help patients perform activities of daily living.
o Instruct in use of thermal modalities.
o Provide splints for patients with trapeziometacarpal joint osteoarthritis.

Pharmacologic recommendations for the initial management of hand osteoarthritis
• It is recommended that health professionals should use one or more of the following:
o Topical capsaicin.
o Topical NSAIDs, including trolamine salicylate.
o Oral NSAIDs, including cyclooxgenase-2 selective inhibitors.
o Tramadol.
• It is conditionally recommend that health professionals should not use the following:
o Intraarticular therapies.
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</table>

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

Clinical Guideline	Recommendation(s)
	• It is conditionally recommend that patients with knee osteoarthritis not use the following: o Chondroitin sulfate. o Glucosamine. o Topical capsaicin. • No recommendation is made regarding the use of intraarticular hyaluronates, duloxetine, and opioid analgesics. <u>Nonpharmacologic recommendations for the management of hip osteoarthritis</u> • It is strongly recommend that patients with hip osteoarthritis do the following: o Participate in cardiovascular and/or resistance land based exercise. o Participate in aquatic exercise. o Lose weight (for persons who are overweight). • It is conditionally recommend that patients with hip osteoarthritis do the following: o Participate in self-management programs. o Receive manual therapy in combination with supervised exercise. o Receive psychosocial interventions. o Be instructed in the use of thermal agents. o Receive walking aids, as needed. • No recommendation is made regarding the following: o Participation in balance exercises, either alone or in combination with strengthening exercises. o Participation in tai chi. o Receiving manual therapy alone. <u>Pharmacologic recommendations for the initial management of hip osteoarthritis</u> • It is conditionally recommend that patients with hip osteoarthritis use one of the following: o Acetaminophen. o Oral NSAIDs. o Tramadol. o Intraarticular corticosteroid injections. • It is conditionally recommend that patients with hip osteoarthritis not use the following: o Chondroitin sulfate. o Glucosamine. • No recommendation is made regarding the use of the following: o Topical NSAIDs. o Intraarticular hyaluronate injections. o Duloxetine. • Opioid analgesics.
American Academy of Orthopedic Surgeons: **Clinical Practice Guideline on Osteoarthritis of the Knee (2013)**[54]	• Conservative treatments o It is recommended that patients with symptomatic osteoarthritis of the knee participate in self-management programs, strengthening, low-impact aerobic exercises, and neuromuscular education; and engage in physical activity consistent with national guidelines. o Weight loss for patients with symptomatic osteoarthritis of the knee and a body mass index ≥25 is recommended. o The guideline cannot recommend acupuncture in patients with symptomatic osteoarthritis of the knee. o No recommendation can be made concerning the use of physical agents (including electrotherapeutic modalities) in patients with symptomatic osteoarthritis of the knee. o No recommendation can be made concerning manual therapy in

Clinical Guideline	Recommendation(s)
	patients with symptomatic osteoarthritis of the knee. o The guideline cannot suggest a valgus directing force brace (medial compartment unloader) for patients with symptomatic osteoarthritis of the knee. o No recommendation can be made concerning a lateral wedge insoles be used for patients with symptomatic medial compartment osteoarthritis of the knee. o The guideline cannot recommend using glucosamine and chondroitin for patients with symptomatic osteoarthritis of the knee. • Pharmacologic treatments o NSAIDs; oral or topical or tramadol for patients with symptomatic osteoarthritis of the knee are recommended. o No recommendation can be made concerning the use of acetaminophen, opioids, or pain patches for patients with symptomatic osteoarthritis of the knee. • Procedural treatments o No recommendation can be made concerning the use of intraarticular corticosteroids for patients with symptomatic osteoarthritis of the knee. o The guideline cannot recommend using hyaluronic acid for patients with symptomatic osteoarthritis of the knee. o No recommendation can be made concerning growth factor injections and/or platelet rich plasma for patients with symptomatic osteoarthritis of the knee. o The guideline cannot suggest that the practitioner use needle lavage for patients with symptomatic osteoarthritis of the knee. • Surgical treatments o The guideline cannot recommend performing arthroscopy with lavage and/or debridement in patients with a primary diagnosis of symptomatic osteoarthritis of the knee. o No recommendation can be made concerning arthroscopic partial meniscectomy in patients with osteoarthritis of the knee with a torn meniscus. o The practitioner might perform a valgus producing proximal tibial osteotomy in patients with symptomatic medial compartment osteoarthritis of the knee. • In the absence of reliable evidence, it is the opinion of the work group not to use the free-floating (un-fixed) interpositional device in patients with symptomatic medial compartment osteoarthritis of the knee.
European League Against Rheumatism: **Evidence-based Recommendations for the Management of Fibromyalgia Syndrome (2007)**[55]	• Tramadol is recommended for the management of pain in fibromyalgia. • Simple analgesics such as paracetamol and other weak opioids can also be considered in the treatment of fibromyalgia. • Corticosteroids and strong opioids are not recommended. • Amitriptyline, fluoxetine, duloxetine, milnacipran, moclobemide and pirlindole (not available in the United States), reduce pain and often improve function, therefore they are recommended for the treatment of fibromyalgia. • Tropisetron, pramipexole and pregabalin reduce pain and are recommended for the treatment of fibromyalgia.
American Pain Society: **Guideline for the Management of Fibromyalgia Syndrome Pain in Adults and Children (2005)**[56]	Pharmacologic therapies • Use multiple strategies and include both pharmacologic and nonpharmacologic therapies in the management of fibromyalgia syndrome. • For initial treatment of fibromyalgia syndrome, prescribe a TCA for sleep, in particular 10 to 30 mg amitriptyline or cyclobenzaprine at bedtime. • Use SSRIs such as fluoxetine, alone or in combination with TCAs, for pain relief.

Clinical Guideline	Recommendation(s)
	• Do not use NSAIDs as the primary pain medication for people with fibromyalgia syndrome. There is no evidence that NSAIDs are effective when used alone to treat fibromyalgia syndrome patients. NSAIDs, including cycloixegenase-2 selective agents and acetaminophen, may provide some analgesia when used with other medications. • Use tramadol (50 to 100 mg two or three times daily) for pain relief in people with fibromyalgia syndrome. Tramadol can be used alone or in combination with acetaminophen. • Use opioids for management of fibromyalgia syndrome pain only after all other pharmacologic and nonpharmacologic therapies have been exhausted. • Use sleep and anti-anxiety medications such as trazodone, benzodiazepines, nonbenzodiazepine sedatives, or L-dopa and carbidopa in fibromyalgia syndrome, especially if sleep disturbances such as restless leg syndrome are prominent. • Do not use corticosteroids in the treatment of fibromyalgia syndrome unless there is concurrent joint, bursa, or tendon inflammation. <u>Fibromyalgia syndrome in children and adolescents</u> • Utilize pharmacologic and nonpharmacologic strategies in the management of juvenile fibromyalgia syndrome. • Use CBT to reduce pain and psychological disability by enhancing self-efficacy, self-management, and skills for coping with pain. • Use aerobic exercise to minimize pain, improve sleep quality, enhance self-efficacy and increase positive mood. • Emphasize sleep hygiene as part of the treatment plan, using both pharmacologic and nonpharmacologic techniques. • Treat anxiety and depression aggressively with both pharmacologic and nonpharmacologic approaches. • Fluoxetine should be the first antidepressant agent used to treat depression in children and adolescents; however, all of these medications should be used only with extreme caution and extensive parental education.
American Academy of Neurology/American Association of Neuromuscular and Electrodiagnostic Medicine/American Academy of Physical Medicine and Rehabilitation: **Treatment of Painful Diabetic Neuropathy (2011)**[57]	<u>Anticonvulsants</u> • If clinically appropriate, pregabalin should be offered for treatment. • Gabapentin and sodium valproate should be considered for treatment. • There is insufficient evidence to support or refute the use of topiramate for treatment. • Oxcarbazepine, lamotrigine, and lacosamide should probably not be considered for treatment. <u>Antidepressants</u> • Amitriptyline, venlafaxine, and duloxetine should be considered for the treatment of painful diabetic neuropathy. Data are insufficient to recommend one of these agents over another. • Venlafaxine may be added to gabapentin for a better response. • There is insufficient evidence to support or refute the use of desipramine, imipramine, fluoxetine, or the combination of nortriptyline and fluphenazine in the treatment of painful diabetic neuropathy. <u>Opioids</u> • Dextromethorphan, morphine sulfate, tramadol, and oxycodone should be considered for treatment. Data are insufficient to recommend one agent over the other. <u>Other pharmacologic options</u> • Capsaicin and isosorbide dinitrate spray should be considered for treatment.

Clinical Guideline	Recommendation(s)
	• Clonidine, pentoxifylline, and mexiletine should probably not be considered for treatment. • Lidocaine patch may be considered for treatment. • There is insufficient evidence to support or refute the usefulness of vitamins and α-lipoic acid for treatment. <u>Nonpharmacologic options</u> • Percutaneous electrical nerve stimulation should be considered for treatment. • Electromagnetic field treatment, low-intensity laser treatment, and Reiki therapy should probably not be considered for treatment. • Evidence is insufficient to support or refute the use of amitriptyline plus electrotherapy for treatment.
European Federation of Neurological Societies: **Guidelines on the Pharmacological Treatment of Neuropathic Pain (2010)**[58]	<u>Painful polyneuropathy</u> • Diabetic and non-diabetic painful polyneuropathy are similar in symptomatology and with respect to treatment response, with the exception of human immunodeficiency virus (HIV)-induced neuropathy. • Recommended first-line treatments include TCA, gabapentin, pregabalin, and SNRIs (duloxetine, venlafaxine). • Tramadol is recommended second line, except for patients with exacerbations of pain or those with predominant coexisting non-neuropathic pain. • Strong opioids are recommended third-line treatments due to concerns regarding long-term safety, including addiction potential and misuse. • In HIV-associated polyneuropathy, only lamotrigine (in patients receiving antiretroviral treatment), smoking cannabis, and capsaicin patches were found moderately useful. <u>Post herpetic neuropathy</u> • Recommended first-line treatments include a TCA, gabapentin, or pregabalin. • Topical lidocaine with its excellent tolerability may be considered first-line in the elderly, especially if there are concerns of adverse events of oral medications. • Strong opioids and capsaicin cream are recommended as second-line therapies.
American Association of Clinical Endocrinologists: **Medical Guidelines for Clinical Practice for Developing a Diabetes Mellitus Comprehensive Care Plan (2011)**[59]	<u>Diabetic neuropathy</u> • Diabetic painful neuropathy is diagnosed clinically and must be differentiated from other painful conditions. • Interventions that reduce oxidative stress, improve glycemic control, and/or improve dyslipidemia and hypertension might have a beneficial effect on diabetic neuropathy. • Exercise and balance training may also be beneficial. • TCAs, anticonvulsants, and serotonin and norepinephrine reuptake inhibitors are useful treatments. • Large-fiber neuropathies are managed with strength, gait, and balance training; pain management; orthotics to treat and prevent foot deformities; tendon lengthening for pes equinus from Achilles tendon shortening; and/or surgical reconstruction and full contact casting as needed. • Small-fiber neuropathies are managed with foot protection (e.g., padded socks), supportive shoes with orthotics if necessary, regular foot and shoe inspection, prevention of heat injury, and use of emollient creams; however, for pain management, the medications mentioned above must be used.
American Diabetes Association: **Diabetic Neuropathies (2005)**[60]	<u>Algorithm for the management of symptoms diabetic polyneuropathy</u> • Exclude nondiabetic etiologies, followed by, stabilize glycemic control (insulin not always required in type 2 diabetes), followed by, TCA (e.g., amitriptyline 25 to 250 mg before bed), followed by, anticonvulsants (e.g., gabapentin, typical dose 1.8 g/day), followed by, opioid or opioid-like drugs (e.g., tramadol, oxycodone), followed by, consider pain clinical referral.

Clinical Guideline	Recommendation(s)
American Academy of Neurology: **Practice Parameter: Treatment of Postherpetic Neuralgia (2004)**[61]	• TCAs (amitriptyline, nortriptyline, desipramine, maprotiline), gabapentin, pregabalin, opioids, and topical lidocaine patches are effective and should be used in the treatment of post herpetic neuropathy. • There is limited evidence to support nortriptyline over amitriptyline, and the data are insufficient to recommend one opioid over another. • Amitriptyline has significant cardiac effects in the elderly when compared to nortriptyline and desipramine. • Aspirin cream is possibly effective in the relief of pain in patients with postherpetic neuralgia, but the magnitude of benefit is low, as seen with capsaicin. • In countries with preservative-free intrathecal methylprednisolone available, it may be considered in the treatment of postherpetic neuralgia. • Acupuncture, benzydamine cream, dextromethorphan, indomethacin, epidural methylprednisolone, epidural morphine sulfate, iontophoresis of vincristine, lorazepam, vitamin E, and zimelidine are not of benefit. • The effectiveness of carbamazepine, nicardipine, biperiden, chlorprothixene, ketamine, He:Ne laser irradiation, intralesional triamcinolone, cryocautery, topical piroxicam, extract of *Ganoderma lucidum*, dorsal root entry zone lesions, and stellate ganglion block are unproven in the treatment of postherpetic neuralgia. • There is insufficient evidence to make any recommendations on the long-term effects of these treatments.

III. Indications

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

Table 3. FDA-Approved Indications for the Antidepressants[1-35]

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

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

*Extended-release formulation only.
†Immediate-release formulation only.
‡Brisdelle® formulation only.

IV. Pharmacokinetics

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

Table 4. Pharmacokinetic Parameters of the Antidepressants[1-35]

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

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

V. Drug Interactions

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

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

Generic Name(s)	Significance Level	Interaction	Mechanism
MAOIs			
MAOIs	1	Central nervous system depressants (e.g. alcohol, barbiturates, narcotics)	Severe hypertension may occur. Concurrent use is contraindicated.
MAOIs	1	Central nervous system stimulants (e.g. amphetamines, cocaine, methylphenidate, dexmethylphenidate)	Hypertensive crisis may occur. Coadministration is contraindicated.
MAOIs	1	MAOIs	Do not administer MAOIs with other MAOIs because hypertensive crisis and convulsive seizures, coma, or circulatory collapse may occur.
MAOIs	1	Methylphenidates	Pharmacological effects of methylphenidates may be increased by MAOIs. Headache, gastrointestinal symptoms and hypertension may occur. Concomitant use of methylphenidates and MAOIs is contraindicated.
MAOIs	1	Norepinephrine reuptake inhibitors (including tapentadol)	Coadministration may increase risk of toxic effects. Serious and sometimes fatal reactions have occurred. Use of norepinephrine reuptake inhibitors within 14 days of MAOIs is contraindicated.
MAOIs	1	SNRIs and SSRIs	A serotonin syndrome may occur. Concomitant use is contraindicated. At least 14 days should elapse between discontinuation of a MAOI and the start of an SSRI or vice versa. Allow at least five weeks between discontinuation of fluoxetine and initiation of a MAOI and at least 14 days between discontinuation of a MAOI and initiation of fluoxetine.

Generic Name(s)	Significance Level	Interaction	Mechanism
MAOIs	1	Sympathomimetics	The MAOIs' potentiation of indirect- or mixed-acting sympathomimetic substances, including anorexiants, may result in severe headache, hypertension, high fever, and hyperpyrexia, possibly resulting in hypertensive crisis; avoid coadministration.
MAOIs	1	TCAs	Do not administer MAOIs with or immediately following TCAs. There have been reports of serious, sometimes fata, reactions. These reactions include hyperthermia, rigidity, myoclonus, autonomic instability with possible vital sign fluctuations, and mental status changes that can include extreme agitation and confusion progressing to delirium and coma.
MAOIs	1	Triptans	Prolonged vasospastic reaction is a possibility when triptans and MAOIs are coadministered. The potential for development of serotonin syndrome also exists. Coadministration is not recommended.
MAOIs	1	Apraclonidine	Coadministration of MAOIs and apraclonidine is contraindicated. MAOIs and apraclonidine should not be administered within 14 days of discontinuation of either agent.
MAOIs	1	Atomoxetine	Toxic effects may be increased with concurrent administration of atomoxetine and MAOIs. Serious and sometimes fatal reactions have occurred. Use of atomoxetine within 14 days of MAOIs is contraindicated.
MAOIs	1	Bupropion	Coadministration is contraindicated. Risk of acute bupropion toxicity may be increased. Allow at least 14 days to elapse between discontinuing an MAOI and starting bupropion.
MAOIs	1	Buspirone	The risk of hypertension induced by MAOIs may be increased by co-administration of buspirone. It should be noted for selegiline that only higher dosages participate in this interaction. Allow at least 10 days between discontinuation of isocarboxazid and institution of buspirone.
MAOIs	1	Cyclobenzaprine	Because cyclobenzaprine is structurally related to the TCAs, use with caution with MAOIs. It should be noted for selegiline that only higher doses participate in this interaction.
MAOIs	1	Dextromethorphan	Hyperpyrexia, abnormal muscle movement, psychosis, bizarre behavior, hypotension, coma, and death have been associated with this combination.

Generic Name(s)	Significance Level	Interaction	Mechanism
MAOIs	1	Levodopa	Hypertensive reactions occur if levodopa is given to patients receiving MAOIs.
MAOIs	1	Linezolid	Adverse effects may be increased with concurrent administration of linezolid and MAOIs.
MAOIs	1	Meperidine	Coadministration of these agents may result in agitation, seizures, diaphoresis, and fever with the potential to progress to coma, apnea, and death. Reactions may be delayed and occur several weeks following withdrawal of MAOIs. Avoid this combination. Administer other narcotic analgesics with caution.
MAOIs	1	Nefazodone	The combination of MAOIs and nefazodone is contraindicated. The combination may be useful for treating depression; however, unexpected toxicity may occur.
MAOIs	1	Tetrabenazine	The combination of MAOIs and tetrabenazine may produce severe unexpected toxicity. Coadministration is contraindicated.
MAOIs	1	Tramadol	Coadministration may enhance seizure risk, and/or cause a severe reaction potentially involving the respiratory, cardiac, and central nervous system. Avoid coadministration.
MAOIs	1	Trazodone	The potential for the development of serotonin syndrome exists with concurrent use of MAOIs and trazodone.
MAOIs	1	Vilazodone	Do not administer MAOIs and vilazodone within 14 days of one another. Serotonin syndrome may result from concurrent administration.
MAOIs	1	Vortioxetine	Coadministration of MAOI used to treat psychiatric disorders and vortioxetine is contraindicated in the official package labeling of vortioxetine. In addition, the initiation of vortioxetine in patients receiving linezolid is contraindicated. Serotonin syndrome (unexpected irritability, increased muscle tone, altered consciousness and myoclonus) may result from concurrent administration.
MAOIs (selegiline)	1	Methadone	A severe reaction potentially involving the respiratory, cardiac and central nervous systems may occur shortly after administering methadone to patients receiving selegiline. At least 14 days should elapse between discontinuation of selegiline and administration of methadone.
MAOIs	2	Insulins	The hypoglycemic effect of insulin may be increased by MAOIs.
MAOIs	2	Meglitinides	The hypoglycemic effects of

Generic Name(s)	Significance Level	Interaction	Mechanism
			meglitinides may be increased by MAOIs.
MAOIs	2	Sulfonylureas	MAOIs enhance the hypoglycemic action of sulfonylureas.
MAOIs	2	Carbamazepine	While the manufacturer's data states that carbamazepine is contraindicated with MAOIs, other conflicting data suggest safe coadministration. It should be noted that only higher doses of selegiline (e.g. antidepressant doses) participate in this interaction.
MAOIs	2	Ginseng	Use of MAOIs with ginseng may produce unexpected toxic effects.
MAOIs	2	Tryptophan	Coadministration may result in hyperreflexia, confusion, disorientation, shivering, myoclonic jerks, agitation, amnesia, delirium, hypomanic signs, ataxia, ocular oscillations, Babinski signs.
MAOIs (isocarboxazid, phenelzine, tranylcypromine)	2	COMT inhibitors	The combination of these MAOIs with COMT inhibitors may result in inhibition of the majority of pathways responsible for normal catecholamine metabolism. Excessive sympathetic stimulation may result. Coadministration of COMT inhibitors and non-selective MAOIs is not recommended.
MAOIs (isocarboxazid, phenelzine, tranylcypromine)	2	Narcotic analgesics	A severe reaction potentially involving the respiratory, cardiac and central nervous systems may occur shortly after administering narcotic analgesics to patients receiving these MAOIs. At least 14 days should elapse after discontinuation of an MAOI before initiation of treatment with a narcotic analgesic.
SNRIs			
SNRIs	1	MAOIs	Coadministration of SNRIs and MAOIs is contraindicated. Serious, sometimes fatal, reactions may occur, including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. It is recommended that SNRIs not be used within at least 14 days of discontinuing treatment with an MAOI.
SNRIs	1	Linezolid	Serotonin syndrome may occur, possibly due to excessive accumulation of serotonin. Initiation of an SNRI is contraindicated in patients receiving linezolid.
SNRIs	1	Methylene blue	Coadministration of methylene blue and desvenlafaxine may increase the risk of central nervous system toxicity,

Generic Name(s)	Significance Level	Interaction	Mechanism
			including serotonin syndrome.
SNRIs	1	Tramadol	Increased risk of seizures is a possibility when tramadol and SNRIs are coadministered. Serotonin syndrome is also a risk with this combination. Concomitant use is not recommended.
SNRIs (duloxetine)	1	Phenothiazines (thioridazine)	Plasma concentrations and pharmacologic effects of thioridazine may be increased by duloxetine. The possibility of serious ventricular dysrhythmias should be considered. Do not coadminister.
SNRIs (duloxetine)	1	Tamoxifen	Pharmacologic effects of Tamoxifen may be decreased by Duloxetine. Coadministration of Duloxetine with Tamoxifen may increase the risk of breast cancer recurrence.
SNRIs	2	Anticoagulants	The risk of bleeding with Anticoagulants may be potentiated with concomitant use of these SNRIs and patients are at an increased risk of bleeding. The mechanism of this interaction is unknown.
SNRIs	2	SSRIs	The development of serotonin syndrome is possible when the combination of SNRIs and serotonin reuptake blockers are coadministered. In addition, plasma concentrations of SNRIs may be increased by serotonin reuptake blockers.
SNRIs	2	Iobenguane	SNRIs may reduce uptake and diagnostic efficacy of Iobenguane. False-negative Iobenguane imaging tests may result.
SNRIs	2	L-Tryptophan	Coadministration may lead to the development of serotonin syndrome.
SNRIs (desvenlafaxine, venlafaxine)	2	NSAIDs	The toxic effects may be increased with concurrent administration of NSAIDs and desvenlafaxine/venlafaxine. The risk of upper gastrointestinal bleeding may be increased. Patients taking concurrent SNRIs and NSAIDs should be educated about the signs and symptoms of gastrointestinal bleeding.
SNRIs (desvenlafaxine, venlafaxine)	2	Salicylates	The risk of upper gastrointestinal bleeding may be increased with concurrent administration of salicylates and desvenlafaxine or venlafaxine. The mechanism is unknown. Prolonged use of desvenlafaxine or venlafaxine may lead to depletion of serotonin, which is thought to play an important role in hemostasis.
SNRIs (desvenlafaxine, venlafaxine)	2	Cyproheptadine	Decreased pharmacologic effects of venlafaxine may result. Since cyproheptadine is a serotonin antagonist,

Generic Name(s)	Significance Level	Interaction	Mechanism
			the interaction may occur at the receptor level.
SNRIs (desvenlafaxine, venlafaxine)	2	Lithium	Coadministration of lithium and desvenlafaxine or venlafaxine may cause central nervous system toxicity, including serotonin syndrome. Serum lithium concentrations may be increased due to increased serotonergic neurotransmission.
SNRIs (desvenlafaxine, venlafaxine)	2	St. John's wort	Unexpected toxicity may occur when St. John's wort and desvenlafaxine/ venlafaxine are coadministered; the mechanism is unknown.
SNRIs (desvenlafaxine, venlafaxine)	2	Trazodone	Unexpected toxic effects may occur when trazodone is combined with desvenlafaxine or venlafaxine. The mechanism is unknown.
SNRIs (duloxetine)	2	TCAs	Plasma concentrations of TCAs may be increased by duloxetine. Inhibition of cytochrome CYP2D6 isoenzymes by duloxetine may decrease the metabolic elimination of TCAs.
SNRIs (duloxetine)	2	Ciprofloxacin	Plasma concentrations and pharmacologic effects of duloxetine may be increased when coadministered with ciprofloxacin. Inhibition of CYP1A2 by ciprofloxacin may decrease the metabolic elimination of duloxetine.
SNRIs (duloxetine)	2	Flecainide	Plasma concentrations of flecainide may be increased by duloxetine. Clinical outcome is unknown.
SNRIs (duloxetine)	2	Propafenone	Plasma concentrations of propafenone may be increased by duloxetine due to inhibition of CYP2D6 isoenzymes.
SNRIs (levomilnacipran)	2	Alcoholic beverages	Consumption of alcohol may interfere with the delayed release mechanism of levomilnacipran.
SNRIs (venlafaxine)	2	Bupropion	Unexpected adverse effects, including serotonin syndrome, may occur when Venlafaxine and Bupropion are coadministered. The mechanism of this interaction is unknown.
SNRIs (venlafaxine)	2	Terbinafine	Plasma concentrations and pharmacologic effects of venlafaxine may be increased when coadministered with terbinafine. The potential for adverse effects due to venlafaxine may be increased. Inhibition of CYP2D6-mediated metabolism of venlafaxine by terbinafine is suspected.
SSRIs			
SSRIs	1	Linezolid	Serotonin syndrome may occur as a result of excessive accumulation of serotonin. The coadministration of linezolid and SSRIs should be handled with caution.

Generic Name(s)	Significance Level	Interaction	Mechanism
SSRIs	1	Tramadol	Increased risk of seizures is possible when tramadol and SSRIs are coadministered. Serotonin syndrome is also a potential risk when tramadol and SSRIs are coadministered.
SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline)	1	Clozapine	These SSRIs may increase plasma concentrations and pharmacologic effects of clozapine. Severe toxicity may occur. Inhibition of cytochrome P450 1A2 isoenzymes by these SSRIs may decrease the metabolic elimination of clozapine.
SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, sertraline)	1	Pimozide	Plasma concentrations of pimozide may be increased by SSRIs. The risk of life-threatening cardiac arrhythmias, including torsades de pointes, may be increased. The mechanism is unknown.
SSRIs (fluoxetine, fluvoxamine paroxetine)	1	Phenothiazines (chlorpromazine, thioridazine)	Pharmacologic effects and plasma concentrations of phenothiazines may be increased by SSRIs. Neurologic toxicity, including extrapyramidal effects, and cardiac toxicity, including the potential for torsade de pointes, may occur.
SSRIs (fluoxetine, paroxetine sertraline)	1	Tamoxifen	Pharmacologic effects of tamoxifen may be decreased by certain SSRIs. Coadministration may increase the risk of breast cancer recurrence.
SSRIs (citalopram, escitalopram)	1	Cimetidine	Pharmacologic effects and plasma concentrations of citalopram may be increased by cimetidine. Cimetidine may inhibit the metabolic and/or renal elimination of citalopram.
SSRIs (citalopram, fluoxetine)	1	Nilotinib	Additive QT prolongation may occur during coadministration of vandetanib and certain SSRIs. The black box warning contained in the official package labeling for vandetanib states that the use of vandetanib with medications that prolong the QT interval should be avoided.
SSRIs (citalopram, fluoxetine)	1	Vandetanib	Additive QT prolongation may occur during coadministration of vandetanib and certain SSRIs. The black box warning contained in the official package labeling for vandetanib states that the use of vandetanib with medications that prolong the QT interval should be avoided.
SSRIs (fluvoxamine)	1	Ramelteon	Plasma concentrations of ramelteon may be increased by coadministration of fluvoxamine. Coadministration of fluvoxamine and ramelteon is contraindicated.
SSRIs (fluvoxamine)	1	Tizanidine	Tizanidine plasma concentrations and pharmacologic effects may be increased

Generic Name(s)	Significance Level	Interaction	Mechanism
			by fluvoxamine. Adverse effects associated with tizanidine, including significant hypotension, may be expected. Concomitant use is contraindicated.
SSRIs	2	Anticoagulants	The risk of bleeding with anticoagulants may be potentiated with concomitant use of SSRIs and patients are at an increased risk of bleeding.
SSRIs	2	NSAIDs	Toxic effects may be increased with concurrent administration of NSAIDs and SSRIs. The risk of upper gastrointestinal bleeding may be increased. Patients taking both SSRIs and NSAIDs should be educated about the signs and symptoms of gastrointestinal bleeding.
SSRIs	2	Salicylates	Toxic effects may be increased with concurrent administration of salicylates and SSRIs. The risk of upper gastrointestinal bleeding may be increased. Patients taking both salicylates and NSAIDs should be educated about the signs and symptoms of gastrointestinal bleeding.
SSRIs	2	SNRIs	Serotonin syndrome has been reported during coadministration of SSRIs and SNRIs. If coadministration is necessary, the patient should be closely monitored, especially when starting treatment of increasing doses. Plasma concentrations of duloxetine may be increased by CYP2D6 inhibitors, such as fluoxetine and paroxetine.
SSRIs	2	Cyproheptadine	Decreased pharmacologic effects of SSRIs may result. Since cyproheptadine is a serotonin antagonist, the interaction may occur at the receptor level.
SSRIs	2	L-tryptophan	Coadministration may lead to the development of serotonin syndrome.
SSRIs	2	St. John’s wort	Unexpected toxicity may occur when St. John's wort and SSRIs are coadministered.
SSRIs (citalopram, escitalopram, fluoxetine, paroxetine, sertraline)	2	Beta-blockers	Coadministration of SSRIs and beta-blockers may increase risk of bradycardia and hypotension.
SSRIs (fluoxetine, sertraline)	2	Bupropion	Unexpected adverse effects, including serotonin syndrome, may occur when these SSRIs and bupropion are coadministered. The mechanism of this interaction is unknown.
SSRIs (fluoxetine,	2	Carbamazepine	Plasma concentrations and pharmacologic effects of carbamazepine

Generic Name(s)	Significance Level	Interaction	Mechanism
sertraline)			may be increased by these SSRIs. Toxicity may occur. Toxic serotonin syndrome may also occur.
SSRIs (fluoxetine, paroxetine)	2	Iloperidone	Plasma concentrations and pharmacologic effects of iloperidone may be increased by these SSRIs. A modification of the iloperidone dose is recommended.
SSRIs (fluoxetine, paroxetine)	2	Risperidone	These SSRIs may increase plasma concentrations and pharmacologic effects of risperidone. Additionally, concomitant use has resulted in reported cases of serotonin syndrome. Worsening of obsessive-compulsive disorder has also been reported with combined use.
SSRIs (fluoxetine, paroxetine)	2	Tetrabenazine	Plasma concentrations and pharmacologic effects of tetrabenazine may be increased by these SSRIs. Dosage adjustment is recommended.
SSRIs (fluoxetine)	2	HIV protease inhibitors	HIV protease inhibitors may increase plasma concentrations of fluoxetine resulting in possible fluoxetine toxicity. Similarly, fluoxetine may increase plasma concentrations of HIV protease inhibitors.
SSRIs (fluoxetine)	2	Hydantoins	Serum hydantoin concentrations may be elevated. Close monitoring of hydantoin levels and observing patients for toxicity or loss of therapeutic activity if fluoxetine is started or stopped is advised. Fosphenytoin may enhance QTc-prolonging effect of fluoxetine.
SSRIs (fluvoxamine)	2	Theophyllines	Pharmacological effects of the theophyllines may be increased by fluvoxamine. Elevated theophylline concentrations and toxicity including nausea, vomiting, cardiovascular instability and seizures may occur.
SSRIs (paroxetine)	2	Abiraterone	Plasma concentrations and pharmacologic effects of paroxetine may be increased by abiraterone, due to the inhibition of CYP2D6 by abiraterone.
Serotonin Modulators			
Serotonin modulators	1	MAOIs	Coadministration of the Serotonin Modulators and MAOIs is contraindicated due to increased risk for serotonin syndrome.
Serotonin modulators	1	Linezolid	Coadministration of the Serotonin Modulators and linezolid is contraindicated due to risk of serotonin syndrome.
Serotonin modulators (vilazodone, vortioxetine)	1	Methylene blue	Coadministration of certain Serotonin Modulators may increase the risk of central nervous system toxicity, including serotonin syndrome. Initiation of certain Serotonin Modulators in

Generic Name(s)	Significance Level	Interaction	Mechanism
			patients receiving methylene blue is contraindicated.
Nefazodone	1	Statins	The risk of rhabdomyolysis and myositis may be increased with certain statins. Coadministration of nefazodone with lovastatin or simvastatin is contraindicated.
Nefazodone	1	Tyrosine kinase receptor inhibitors	Plasma concentrations and pharmacologic effects of tyrosine kinase receptor inhibitors may be increased by nefazodone due to the inhibition of CYP3A4 by nefazodone.
Nefazodone	1	Vasopressin receptor agonists	Plasma concentrations and pharmacologic effects of vasopressin receptor antagonists may be increased by nefazodone. Coadministration of nefazodone and conivaptan or tolvaptan is contraindicated.
Nefazodone	1	Colchicine	Plasma concentrations of colchicine may be increased by nefazodone and life-threatening and fatal colchicine toxicity may occur. Dosage adjustment of colchicine is required for coadministration of these agents. Coadministration is contraindicated in patients with renal or hepatic impairment.
Nefazodone	1	Docetaxel	Plasma concentrations and pharmacologic effects of docetaxel may be increased by nefazodone. Use of nefazodone with docetaxel may increase the risk and/or severity of docetaxel-related toxicity. Coadministration should be avoided.
Nefazodone	1	Dronedarone	Plasma concentrations and pharmacologic effects of dronedarone may be increased by nefazodone. Coadministration is contraindicated.
Nefazodone	1	Lurasidone	Plasma concentrations and pharmacologic effects of lurasidone may be increased by nefazodone. Coadministration is contraindicated.
Nefazodone	1	Pimozide	Pharmacologic effects of pimozide may be increased by nefazodone. Elevated plasma concentrations and cardiovascular toxicity may occur. Coadministration is contraindicated.
Nefazodone	1	Ranolazine	Plasma concentrations and pharmacologic effects of ranolazine may be increased when coadministered with nefazodone. Coadministration is contraindicated.
Nefazodone	1	Ticagrelor	Plasma concentrations and pharmacologic effects of ticagrelor may be increased by nefazodone. Coadministration of nefazodone and

Generic Name(s)	Significance Level	Interaction	Mechanism
			ticagrelor should be avoided according to official package labeling.
Nefazodone	1	Toremifene	Plasma concentrations and pharmacologic effects of toremifene may be increased by nefazodone. Toxicity, including QT prolongation may occur. Coadministration of nefazodone and toremifene should be avoided according to a black box warning in official package labeling.
Trazodone	1	Sodium oxybate	Concurrent use of sodium oxybate and trazodone may result in an increase in sleep duration and central nervous system depression. Coadministration is contraindicated.
Vilazodone	1	Tramadol	Increased risk of seizures is listed in the manufacturer's package labeling as a possibility when tramadol and vilazodone are coadministered. Serotonin syndrome is also a potential risk with this combination.
Serotonin modulators (nefazodone, vilazodone, vortioxetine)	2	Triptans	Coadministration of certain serotonin modulators and Triptans may cause central nervous system toxicity, and rarely, serotonin syndrome.
Serotonin modulators (nefazodone, vilazodone)	2	Narcotic analgesics	Plasma concentrations and pharmacologic effects of some narcotic analgesics may be increased by certain serotonin modulators. Toxic effects of vilazodone may be increased by fentanyl, resulting in the development of serotonin syndrome.
Serotonin modulators (trazodone, vilazodone)	2	HIV protease inhibitors	HIV protease inhibitors may increase the plasma concentration of trazodone and vilazodone.
Nefazodone	2	Benzodiazepines	Nefazodone may increase the pharmacologic effects of certain benzodiazepines. Impaired psychomotor performance and increased sedation may result from elevated benzodiazepine plasma concentrations.
Nefazodone	2	MTOR inhibitors	Pharmacologic effects of MTOR inhibitors may be increased by nefazodone. Official package labeling for MTOR inhibitors states that coadministration with strong CYP3A4 inhibitors, such as nefazodone, should be avoided.
Nefazodone	2	Muscarinic receptor antagonists	Plasma concentrations and pharmacologic effects of muscarinic receptor antagonists may be increased by nefazodone. Official package labeling recommends a reduced maximum dose of muscarinic receptor antagonists in

Generic Name(s)	Significance Level	Interaction	Mechanism
			patients receiving strong CYP3A4 inhibitors, such as nefazodone.
Nefazodone	2	Brentuximab	Plasma concentrations and pharmacologic effects of brentuximab may be increased by nefazodone. The inhibition of CYP3A4 by nefazodone may increase the plasma concentrations of monomethyl auristatin E, the microtubule disrupting agent in brentuximab.
Nefazodone	2	Budesonide	Plasma concentrations and pharmacologic effects of oral or inhaled budesonide may be increased by nefazodone. Corticosteroid toxicity and/or adrenal suppression may occur.
Nefazodone	2	Buspirone	Plasma concentrations and pharmacologic effects of buspirone may be increased by nefazodone. The risk of buspirone-induced adverse reactions may be increased. Inhibition of CYP3A4 isoenzymes by nefazodone may decrease the metabolic elimination of buspirone.
Nefazodone	2	Cabazitaxel	Plasma concentrations and pharmacologic effects cabazitaxel may be increased by nefazodone due to the inhibition of CYP3A4 by nefazodone.
Nefazodone	2	Cilostazol	Plasma concentration and pharmacologic effects of cilostazol may be increased by nefazodone due to the inhibition of CYP3A4 by nefazodone.
Nefazodone	2	Cyclosporine	Cyclosporine concentration and pharmacologic effects may be increased by nefazodone. Cyclosporine toxicity may occur.
Nefazodone	2	Eszopiclone	Plasma concentrations and the pharmacologic effects of eszopiclone may be increased by nefazodone.
Nefazodone	2	Iloperidone	Plasma concentrations and pharmacologic effects of iloperidone may be increased by nefazodone. A modification of the iloperidone dose is recommended.
Nefazodone	2	Ivacaftor	Plasma concentrations and pharmacologic effects of ivacaftor may be increased by nefazodone. A reduction in the ivacaftor dose is recommended in patients receiving both medications according to the official package labeling.
Nefazodone	2	Ixabepilone	The pharmacologic effects of epothilones may be increased by nefazodone. Strong CYP3A4 inhibitors, such as nefazodone, should be avoided in patients receiving ixabepilone.
Nefazodone	2	Maraviroc	The pharmacologic effects of maraviroc may be increased by nefazodone. A

Generic Name(s)	Significance Level	Interaction	Mechanism
			dosage adjustment is recommended for maraviroc during concomitant therapy with strong CYP3A4 inhibitors, such as nefazodone. Coadministration is contraindicated in patients with severe renal impairment.
Nefazodone	2	Mifepristone	Plasma concentrations and pharmacologic effects of mifepristone may be increased by nefazodone.
Nefazodone	2	Ruxolitinib	Plasma concentrations and pharmacologic effects of ruxolitinib may be increased by nefazodone. A dose reduction of ruxolitinib or avoidance of ruxolitinib is recommended in patients receiving nefazodone.
Nefazodone	2	Saxagliptin	Plasma concentrations and pharmacologic effects of saxagliptin may be increased by nefazodone.
Trazodone	2	SSRIs	Unexpected toxic effects may occur when trazodone and certain SSRIs are coadministered. The mechanism of this interaction is unknown.
Trazodone	2	Delavirdine	Plasma concentrations of trazodone may be increased when coadministered with delavirdine. Inhibition of CYP3A4 isoenzymes by delavirdine may decrease the metabolic elimination of trazodone.
Vilazodone	2	Cyproheptadine	Pharmacologic effects of may be decreased or reversed by cyproheptadine. Symptoms of depression may recur, because cyproheptadine may directly antagonize the serotonin receptor activity of vilazodone.
Vilazodone	2	Lithium	Coadministration of lithium and vilazodone may cause central nervous system toxicity, including serotonin syndrome. Serum lithium concentrations may be increased lithium and vilazodone may increase serotonergic neurotransmission.
Vilazodone	2	L-tryptophan	Both agents acutely increase central nervous system serotonin activity. Coadministration of these two agents could result in serotonin syndrome.
Vilazodone	2	NSAIDs	Toxic effects may be increased with concurrent administration of NSAIDs and vilazodone. The risk of upper gastrointestinal bleeding may be increased. The mechanism of this interaction is unknown.
Vilazodone	2	Salicylates	The risk of upper gastrointestinal bleeding may be increased with concurrent administration of salicylates and vilazodone. The mechanism of this interaction is unknown.

Generic Name(s)	Significance Level	Interaction	Mechanism
Vilazodone	2	SNRIs	The potential exists for the occurrence of additive serotonergic activity. Inhibition of cytochrome P450 2D6 isoenzymes by vilazodone may decrease the metabolic elimination of SNRIs. The development of serotonin syndrome is possible when the combination of SNRIs and vilazodone are coadministered. In addition, plasma concentrations of SNRIs may be increased by vilazodone.
Vilazodone	2	Strong CYP3A4 inhibitors	Strong CYP3A4 inhibitors may decrease the metabolic elimination of vilazodone, increasing the plasma concentrations and pharmacological effects of vilazodone.
Vilazodone	2	St. John's wort	Unexpected toxicity may occur when St. John's wort and vilazodone are coadministered. The mechanism of this is unknown.
Vortioxetine	2	CYP2D6 inhibitors (e.g. bupropion, fluoxetine, paroxetine)	Pharmacologic effects of vortioxetine may be increased by CYP2D6 inhibitors.
Tricyclics and Other Norepinephrine-reuptake Inhibitors			
TCAs	1	MAOIs	Although the combination of MAOIs and TCAs may be useful for treating depression, severe, sometimes lethal, toxicity may occur. Mechanism of this interaction is unknown.
TCAs (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)	1	Mibefradil	Pharmacologic and toxic effects of certain TCAs may be enhanced by mibefradil due to its effect on oxidative metabolism of coadministered agents. Substantial dosage adjustment of TCA may be necessary during concurrent administration with mibefradil.
TCAs (amitriptyline, desipramine, imipramine, maprotiline)	1	Droperidol	Arrhythmias resulting from the potential for additive QT prolongation should be considered as a possibility when droperidol and certain TCAs are coadministered.
TCAs (doxepin, maprotiline, nortriptyline)	1	Arsenic	The rare occurrence of arrhythmias resulting from the potential for additive QT prolongation should be considered as a possibility when these TCAs and Arsenic are coadministered.
TCAs (amitriptyline, desipramine, imipramine)	1	Pimozide	Certain TCAs and pimozide may cause additive adverse effects when coadministered. Cardiovascular toxicity may occur due to additive QT-interval prolongation.
TCAs (doxepin, maprotiline,	1	Toremifene	Prolongation of the QT interval with possible development of cardiac arrhythmias, including torsades de

Generic Name(s)	Significance Level	Interaction	Mechanism
nortriptyline)			pointes, should be considered when toremifene is coadministered with these TCAs.
TCAs (doxepin, maprotiline, nortriptyline)	1	Vandetanib	Additive QT prolongation may occur during coadministration of vandetanib and these TCAs.
TCAs (amitriptyline-chlordiazepoxide)	1	Azole antifungals	Inhibition of cytochrome P450 3A4 isoenzymes by azole antifungals may decrease the metabolic elimination of chlordiazepoxide and amitriptyline, increasing the pharmacological effects and duration of action of chlordiazepoxide and amitriptyline.
TCAs (amitriptyline-chlordiazepoxide)	1	Clozapine	Delirium, sedation, sialorrhea, and ataxia may occur when amitriptyline-chlordiazepoxide and clozapine are coadministered. Severe orthostatic hypotension and respiratory depression may occur when clozapine combined with amitriptyline-chlordiazepoxide. The mechanism of this interaction is unknown. Clozapine and amitriptyline-chlordiazepoxide should not be started simultaneously.
TCAs (amitriptyline-chlordiazepoxide)	1	Sodium oxybate	Concurrent use of sodium oxybate and amitriptyline-chlordiazepoxide may result in an additive increase in sleep duration and central nervous system depression.
TCAs (clomipramine)	1	Methylene blue	Coadministration of clomipramine and methylene blue may increase the risk of central nervous system toxicity, including serotonin syndrome.
TCAs (maprotiline)	1	Class III antiarrhythmics	Additive QT prolongation may occur when class III antiarrhythmics and maprotiline are coadministered. Use of class III antiarrhythmics and maprotiline is not recommended.
TCAs (maprotiline)	1	Quinolones	The risk of life-threatening cardiac arrhythmias may be increased. The exact mechanism is unknown. Levofloxacin should be avoided, while gatifloxacin and moxifloxacin should be used with caution.
TCAs (maprotiline)	1	Furazolidone	Concomitant administration of maprotiline and furazolidone may enhance the sympathomimetic effects of maprotiline. The mechanism is unknown.
TCAs (maprotiline)	1	Halofantrine	Prolonged QT interval and cardiac arrhythmias are a potential when halofantrine and maprotiline are used concomitantly.
TCAs (maprotiline)	1	Nilotinib	Additive QT prolongation may occur during coadministration of nilotinib and

Generic Name(s)	Significance Level	Interaction	Mechanism
			maprotiline.
TCAs (nortriptyline)	1	Quinidine	Pharmacologic effects of nortriptyline may be increased by quinidine. Elevated plasma concentrations with toxicity characterized by QT prolongation including torsades de pointes may occur. Mechanism: Inhibition of CYP2D6 isoenzymes by quinidine may decrease the metabolic elimination of nortriptyline which may increase the risk for concentration-dependent prolongation of the QT interval.
TCAs	2	Tramadol	Increased risk of seizures may occur when tramadol and TCAs are coadministered.
TCAs (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)	2	Cimetidine	Therapeutic efficacy and frequency of side effects of TCAs may be altered by concurrent therapy with cimetidine.
TCAs (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)	2	Clonidine	The antihypertensive effects of clonidine may be decreased by TCAs. TCAs may worsen rebound reactions from abrupt clonidine withdrawal.
TCAs (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)	2	Fluconazole	Fluconazole may increase plasma concentrations and toxic effects of these TCAs.
TCAs (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)	2	Fluoxetine	The pharmacologic and toxic effects of TCAs may be increased by fluoxetine, despite reports of increased clinical efficacy.
TCAs	2	Fluvoxamine	The pharmacologic and toxic effects of

Generic Name(s)	Significance Level	Interaction	Mechanism
(amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)			TCAs may be increased by fluvoxamine. Toxicity may result.
TCAs (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)	2	Guanfacine	The antihypertensive effect of guanfacine may be decreased by TCAs.
TCAs (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)	2	Iobenguane	TCAs may reduce uptake and diagnostic efficacy of iobenguane. False-negative iobenguane imaging tests may result.
TCAs (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)	2	Paroxetine	The pharmacologic/toxic effects and plasma concentrations of TCAs may be increased by paroxetine.
TCAs (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)	2	Rasagiline	The combination of rasagiline and these TCAs may precipitate symptoms of serotonin syndrome.
TCAs (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine,	2	Sertraline	The pharmacologic and toxic effects of TCAs may be increased by sertraline.

Generic Name(s)	Significance Level	Interaction	Mechanism
protriptyline, trimipramine)			
TCAs (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline)	2	Phenothiazines	Plasma concentrations of phenothiazines and TCAs may be increased when coadministered. Risk of toxicity associated with TCAs and/or risk for potential additive QT prolongation is possible with some when some TCAs are coadministered with phenothiazines.
TCAs (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline)	2	Carbamazepine	Serum carbamazepine levels may be elevated, increasing pharmacologic and toxic effects, while TCA levels may be decreased. Carbamazepine may alter the parent drug-hydroxylated metabolite ratio, resulting in increased risk of toxicity or loss of efficacy of TCAs.
TCAs (amoxapine, clomipramine, desipramine, maprotiline, nortriptyline)	2	Abiraterone	Plasma concentrations and pharmacologic effects of these TCAs may be increased by abiraterone. Coadministration of these TCAs and abiraterone should be avoided.
TCAs (amitriptyline, desipramine, doxepin, imipramine, nortriptyline)	2	Duloxetine	Plasma concentrations of these TCAs may be increased by duloxetine. Serotonin syndrome is also a risk with this combination.
TCAs (amitriptyline, clomipramine, desipramine, imipramine, nortriptyline)	2	Terbinafine	The pharmacologic and toxic effects of TCAs may be increased by terbinafine. Toxic signs may occur.
TCAs (amitriptyline, clomipramine, nortriptyline)	2	Valproic acid and derivatives	Plasma concentrations and toxic effects of these TCAs may be increased by valproic acid and its derivatives.
TCAs (amitriptyline-chlordiazepoxide)	2	Hydantoins	Pharmacologic effects of hydantoins may be increased by amitriptyline-chlordiazepoxide. Elevated hydantoin plasma concentrations and toxicity may occur. Serum concentrations and pharmacologic effects of amitriptyline-chlordiazepoxide may be decreased by hydantoins.
TCAs (amitriptyline-chlordiazepoxide)	2	Rifamycins	Pharmacologic effects of chlordiazepoxide-amitriptyline may be decreased by rifamycins.
TCAs (amitriptyline-chlordiazepoxide)	2	Disulfiram	Pharmacologic and toxic effects of amitriptyline-chlordiazepoxide may be increased by disulfiram. Disulfiram may inhibit hepatic metabolism of amitriptyline- chlordiazepoxide.

Generic Name(s)	Significance Level	Interaction	Mechanism
TCAs (amitriptyline-chlordiazepoxide)	2	Nefazodone	Nefazodone may increase the pharmacologic effects of amitriptyline-chlordiazepoxide. Impaired psychomotor performance and increased sedation may result from elevated amitriptyline-chlordiazepoxide plasma concentrations.
Antidepressants, Miscellaneous			
Bupropion	1	MAOIs	The use of bupropion with MAOIs is contraindicated due to the potential for hypertensive crisis. Only very high doses of selegiline participate in this interaction.
Bupropion	1	Linezolid	Manufacturer's literature states that the use of bupropion with linezolid is contraindicated due to risk for hypertensive crisis.
Bupropion	1	Methylene blue	Coadministration of bupropion and methylene blue may increase the risk of hypertensive reactions. The official package labeling of bupropion contraindicates the initiation of bupropion in patients receiving methylene blue.
Bupropion	1	Pimozide	Plasma concentrations of pimozide may be increased by bupropion. Coadministration of pimozide with bupropion is contraindicated.
Bupropion	1	Tamoxifen	Pharmacologic effects of tamoxifen may be decreased by bupropion. Coadministration of bupropion with tamoxifen may increase the risk of breast cancer recurrence.
Mirtazapine	1	MAOIs	Concomitant administration of mirtazapine and MAOIs may enhance the sympathomimetic effects of mirtazapine. Concomitant use of mirtazapine and MAOIs is contraindicated. Only higher doses of selegiline participate in this interaction.
Mirtazapine	1	Furazolidone	Concomitant administration of mirtazapine and furazolidone may enhance the sympathomimetic effects of mirtazapine. The mechanism is unknown.
Mirtazapine	1	Linezolid	Coadministration of mirtazapine and linezolid may increase the risk of central nervous system toxicity, including serotonin syndrome. Coadministration of mirtazapine and linezolid is contraindicated. The initiation of mirtazapine is contraindicated in patients receiving linezolid according to the package labeling of mirtazapine.
Mirtazapine	1	Methylene blue	Coadministration of mirtazapine and methylene blue may increase the risk of central nervous system toxicity,

Generic Name(s)	Significance Level	Interaction	Mechanism
			including serotonin syndrome. The official package labeling of mirtazapine contraindicates the initiation of mirtazapine in patients receiving methylene blue.
Mirtazapine	1	Perampanel	The central nervous system effects of mirtazapine may be enhanced by perampanel. In addition, increased levels of confusion, depression, anger and aggression may occur.
Bupropion	2	Lopinavir/ritonavir	Plasma concentrations and pharmacologic effects of bupropion may be decreased by lopinavir/ritonavir.
Bupropion	2	Rifamycins	Bupropion plasma concentrations may be reduced secondary to increased metabolism of bupropion. In patients receiving bupropion, close monitoring of clinical efficacy is advised when rifamycins is coadministered.
Bupropion	2	Ritonavir	Plasma concentrations and pharmacologic effects of bupropion may be decreased by ritonavir..
Bupropion	2	Tiagabine	The potential exists for seizures to occur in patients receiving tiagabine who are also receiving drugs such as bupropion that are known to lower the seizure threshold.
Mirtazapine	2	Hydantoins	Mirtazapine plasma concentrations may be reduced by hydantoins.

COMT=catechol-O-methyltransferase, HIV=human immunodeficiency virus, MAOI=monoamine oxidase inhibitors, MTOR=mammalian target of rapamycin, NSAIDS=nonsteroidal anti-inflammatory drugs, SNRI=serotonin–norepinephrine reuptake inhibitors, SSRI=selective serotonin re-uptake inhibitors, TCA=tricyclic antidepressants
Significance Level 1=major severity.
Significance Level 2=moderate severity.

VI. Adverse Drug Events

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

Table 6a. Adverse Drug Events (%) Reported with the Monoamine Oxidase Inhibitors[1-35]

Adverse Events	Isocarboxazid	Phenelzine	Selegiline	Tranylcypromine
Cardiovascular				
Arrhythmia	-	-	<1	-
Atrial fibrillation	-	-	<1	-
Bradycardia	-	-	<1	-
Cardiovascular depression	-	✔	-	-
Chest pain	-	-	≥1	-
Hypertension	-	-	≥1	-
Hypotension	-	-	3 to 10	-
Myocardial infarct	-	-	<1	-
Orthostatic hypotension	4	✔	-	✔
Palpitation	2	-	<1	✔
Peripheral edema	-	-	≥1	-

Adverse Events	Isocarboxazid	Phenelzine	Selegiline	Tranylcypromine
Peripheral vascular disorder	-	-	<1	-
Postural hypotension	-	✔	-	-
Syncope	2	-	<1	-
Tachycardia	-	✔	<1	✔
Vasodilation	-	-	<1	-
Central Nervous System				
Abnormal thinking	-	-	>1	-
Agitation	-	-	>1	✔
Akathisia	✔	-	-	-
Akinesia	-	-	-	✔
Amnesia	-	-	>1	-
Anxiety	2	✔	-	✔
Ataxia	✔	✔	<1	✔
Behavior changes	-	-	>1	-
Bradykinesia	-	-	>1	-
Coma	✔	✔	-	-
Confusion	-	-	<1	✔
Convulsions	-	✔	-	-
Delirium	-	✔	-	-
Delusions	-	-	<1	-
Depersonalization	-	-	<1	-
Depression	-	-	<1	-
Disorientation	-	-	-	✔
Dizziness	15 to 29	✔	-	✔
Drowsiness	4	✔	-	✔
Emotional lability	-	-	<1	-
Euphoria	✔	✔	<1	-
Fatigue	-	✔	-	✔
Forgetfulness	2	-	-	-
Hallucinations	<1	-	-	-
Headache	15	✔	18	✔
Hostility	-	-	<1	-
Hyperactivity	2	-	-	-
Hyperesthesia	-	-	<1	-
Hyperkinesias	-	-	<1	-
Hyperreflexia	-	✔	-	✔
Hypersomnia	-	✔	-	-
Insomnia	4 to 6	✔	12	✔
Jitteriness	-	✔	-	-
Lethargy	2	-	-	-
Loss of balance	-	-	<1	-
Manic symptoms	-	✔	<1	✔
Migraine	-	-	<1	-
Neuritis	✔	-	-	-
Neurosis	-	-	<1	-
Numbness	-	-	-	✔
Palilalia	-	✔	-	-
Paranoid reaction	-	-	<1	-
Parasomnia	-	-	>1	-
Paresthesia	2	✔	>1	✔
Restlessness	-	-	-	✔
Schizophrenia precipitation	-	✔	-	-
Sedation	2	-	-	-
Seizure	-	✔	-	-

Adverse Events	Isocarboxazid	Phenelzine	Selegiline	Tranylcypromine
Sleep disturbance	2 to 5	✔	-	✔
Tremor	4	✔	<1	✔
Twitching	-	✔	<1	✔
Vertigo	-	-	<1	-
Weakness	-	✔	-	✔
Dermatological				
Acne	-	-	≥1	-
Alopecia	-	-	<1	✔
Application site reaction	-	-	24	-
Bruising	-	-	≥1	-
Cystic acne flare-up	-	-	-	✔
Maculopapular rash	-	-	<1	-
Photosensitivity	✔	-	<1	-
Pruritus	-	✔	≥1	✔
Rash	-	✔	4	✔
Scleroderma	-	-	-	✔
Skin benign neoplasm	-	-	<1	-
Skin hypertrophy	-	-	<1	-
Urticaria	-	-	<1	✔
Vesiculobullous rash	-	-	<1	-
Gastrointestinal				
Abdominal pain	-	-	-	✔
Anorexia	-	-	≥1	✔
Appetite increased	-	-	<1	-
Black tongue	✔	-	-	-
Colitis	-	-	<1	-
Constipation	7	✔	>11	✔
Dental caries	-	-	<1	-
Diarrhea	2	-	9	✔
Dyspepsia	-	-	4	-
Eructation	-	-	<1	-
Flatulence	≥1	-	≥1	-
Gastritis	<1	-	<1	-
Gastroenteritis	≥1	-	≥1	-
Gastrointestinal disturbances	-	✔	-	-
Melena	<1	-	<1	-
Nausea	6	✔	-	✔
Rectal hemorrhage	<1	-	<1	-
Salivation increased	-	-	<1	-
Taste perversion	-	-	≥1	-
Tongue edema	-	-	<1	-
Vomiting	≥1	✔	≥1	-
Weight gain	-	✔	-	-
Weight loss	-	-	5	-
Xerostomia	6 to 9	✔	8	✔
Genitourinary				
Anorgasmia	-	✔	-	-
Cystitis	-	-	<1	-
Dysmenorrhea	-	-	≤1	-
Dysuria	✔	-	<1	-
Ejaculation disturbances	-	✔	-	✔
Hematuria	-	-	<1	-
Impotence	2	✔	-	✔
Incontinence	✔	-	-	-

Adverse Events	Isocarboxazid	Phenelzine	Selegiline	Tranylcypromine
Kidney calculus	-	-	<1	-
Libido increased	-	-	<1	-
Menorrhagia	-	-	<1	-
Pelvic pain	-	-	<1	-
Polyuria	-	-	<1	-
Prostatic hyperplasia	-	-	<1	-
Sexual disturbances	✔	✔	≤1	-
Urinary frequency	2	-	<1	✔
Urinary hesitancy	1	-	-	-
Urinary retention	✔	✔	<1	✔
Urinary tract infection	-	-	≥1	-
Urinary urgency	-	-	<1	-
Urination impaired	-	-	<1	-
Vaginal hemorrhage	-	-	<1	-
Vaginal moniliasis	-	-	<1	-
Hematologic				
Agranulocytosis	-	-	-	✔
Anemia	-	-	<1	✔
Hematologic changes	✔	-	-	-
Leukocytosis	-	-	<1	-
Leukopenia	-	✔	<1	✔
Thrombocytopenia	-	-	-	✔
Hepatic				
Hepatitis	-	✔ -	-	✔
Jaundice	-	✔	-	-
Liver function tests abnormal	-	-	<1	-
Hepatocellular damage	-	✔	-	-
Transaminases increased	-	✔	-	-
Laboratory Test Abnormalities				
Alkaline phosphatase increased	-	-	<1	-
Hypercholesterolemia	-	-	<1	-
Hyperglycemia	-	-	<1	-
Hypernatremia	-	✔	-	-
Hypoglycemic reaction	-	-	<1	-
Hyponatremia	-	-	<1	✔
Lactate dehydrogenase increased	-	-	<1	-
Musculoskeletal				
Generalized spasm	-	-	<1	-
Heavy feeling	2	✔	-	-
Hypertonia	-	-	<1	-
Myalgia	-	-	≥1	-
Myasthenia	-	-	<1	-
Myoclonic jerks/movements	2	✔	<1	✔
Neck pain	-	-	≥1	-
Tenosynovitis	-	-	<1	-
Respiratory				
Asthma	-	-	<1	-
Bronchitis	-	-	≥1	-
Cough	-	-	≥1	-
Dyspnea	-	-	<1	-
Laryngismus	-	-	<1	-
Pharyngitis	-	-	3	-
Pneumonia	-	-	<1	-

Adverse Events	Isocarboxazid	Phenelzine	Selegiline	Tranylcypromine
Respiratory depression	-	✔	-	-
Sinusitis	-	-	3	-
Special Senses				
Blurred vision	✔	✔	-	✔
Glaucoma	-	✔	-	✔
Nystagmus	-	✔	-	-
Tinnitus	-	-	<1	✔
Visual field defect	-	-	<1	-
Toxic amblyopia	✔	-	-	-
Other				
Bacterial infection	-	-	<1	-
Bilirubinemia	-	-	<1	-
Breast Pain	-	-	<1	-
Chills	2	-	<1	✔
Circumoral paresthesia	-	-	<1	-
Dehydration	-	-	<1	-
Diaphoresis	2	✔	≥1	✔
Edema	-	✔	<1	✔
Edema of the glottis	-	✔	-	-
Epistaxis	-	-	<1	-
Facial edema	-	-	<1	-
Fever	-	✔	<1	-
Fungal infection	-	-	<1	-
Glossitis	-	-	<1	-
Heat stroke	-	-	<1	-
Hernia	-	-	<1	-
Hypermetabolic syndrome	-	✔	-	✔
Impaired water secretion	✔	-	-	✔
Lupus-like syndrome	-	✔	-	-
Lymphadenopathy	-	-	<1	-
Moniliasis	-	-	<1	-
Neoplasia	-	-	<1	-
Osteoporosis	-	-	<1	-
Otitis external	-	-	<1	-
Parasitic infection	-	-	<1	-
Periodontal abscess	-	-	<1	-
Syndrome of inappropriate antidiuretic hormone secretion	✔	✔	-	✔
Suicide attempt	-	-	<1	-
Sweating	2	✔	>1	-
Toxic delirium	-	✔	-	-
Viral infection	-	-	<1	-

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

Table 6b. Adverse Drug Events (%) Reported with the Selective Serotonin- and Norepinephrine-reuptake Inhibitors[1-35]

Adverse Events	Desvenlafaxine	Duloxetine	Levomilnacipran	Venlafaxine
Cardiovascular				
Aneurysm	-	-	-	<1
Angina pectoris	-	-	<2	<1
Arrhythmia	-	-	-	<1
Atrial fibrillation	-	<1	-	-

Adverse Events	Desvenlafaxine	Duloxetine	Levomilnacipran	Venlafaxine
Atrioventricular block	-	-	-	<1
Bigeminy	-	-	-	<1
Blood pressure increase	-	-	3	-
Bradycardia	-	-	-	<1
Bundle branch block	-	<1	-	<1
Cardiovascular disorder	-	-	-	<1
Cerebral ischemia	-	-	-	<1
Chest pain	-	-	<2	2
Congestive heart failure	-	<1	-	<1
Coronary artery disease	-	-	-	<1
Edema	-	-	-	✔
Electrocardiogram abnormalities	-	-	-	<1
Extrasystoles	-	-	<2	<1
Heart arrest	-	-	-	<1
Heart rate increase	-	-	6	-
Hemorrhage	-	-	-	<1
Hypertension, dose related and dose independent	<1	-	3	3 to 13
Hypertensive crisis	-	<1	-	-
Hypotension	-	-	3	<1
Myocardial infarct	<2	<1	-	<1
Myocardial ischemia	<1	-	-	-
Orthostatic hypotension	<2	<1	-	-
Palpitation	≤3	1 to 2	5	3
Peripheral edema	-	<1	-	-
Postural hypotension	-	-	-	1
Syncope	<2	<1	<2	<1
Tachycardia	-	<1	6	2
Vasodilation	-	-	-	3 to 4
Central Nervous System				
Abnormal dreams	2 to 3	2 to 3	-	3 to 7
Abnormal thinking	-	-	-	2
Agitation	-	5 to 6	<2	2 to 4
Aggression	-	<1	<2	-
Amnesia	-	-	-	✔
Anger	-	-	<2	-
Anxiety	3 to 5	3	-	5 to 6
Ataxia	-	<1	-	<1
Blurred vision	-	4	-	4 to 6
Bradykinesia	-	-	-	<1
Chills	-	-	-	3
Concentration decreased	≤1	-	-	-
Confusion	-	-	-	2
Deafness	-	-	-	<1
Delusions	-	-	-	<1
Dementia	-	-	-	<1
Depersonalization	<2	-	-	1
Depression	-	-	-	1 to 3
Diplopia	-	<1	-	-
Disorientation	-	<1	-	-
Dizziness	10 to 13	6 to 17	-	11 to 20
Dystonia	-	-	-	<1
Extrapyramidal symptoms	<2	-	<2	-

Adverse Events	Desvenlafaxine	Duloxetine	Levomilnacipran	Venlafaxine
Fatigue	7	2 to 15	-	-
Fever	-	1 to 3	-	✔
Guillain-Barre syndrome	-	-	-	<1
Hostility	-	-	-	<1
Hypoesthesia	-	1	-	-
Headache	-	13	-	25 to 38
Hypoesthesia	-	1	-	✔
Hypomania	<2	-	-	-
Insomnia	9 to 12	8- to 6	-	15 to 23
Irritability	2	1	-	-
Lethargy	-	1	-	-
Loss of consciousness	-	-	-	<1
Mania	-	<1	-	-
Migraine	-	-	<2	✔
Mood swings	-	<1	-	-
Nervousness	-	1	-	6 to 21
Neuropathy	-	-	-	<1
Neutropenia	-	-	-	<1
Nightmares	-	1	-	-
Panic attack	-	-	<2	-
Paresthesia	≤2	1	<2	2 to 3
Parkinsonism	<1	-	-	-
Photopsia	-	<1	-	-
Photosensitivity	-	<1	-	-
Restlessness	-	1	-	-
Seizure	-	<1	-	<1
Sleep disorder	-	1	-	-
Somnolence	≤9	13 to 20	-	12 to 23
Tension	-	-	<2	-
Trismus	-	-	-	✔
Vertigo	-	1	-	✔
Yawning	-	1	<2	3 to 5
Dermatological				
Acne	-	<1	-	-
Alopecia	-	<1	-	-
Bruising	-	-	-	✔
Ecchymosis	-	<1	-	-
Eczema	-	<1	-	-
Erythema	-	<1	-	-
Erythema multiforme	-	-	-	<1
Exfoliative dermatitis	-	-	-	<1
Dry skin	-	-	<2	-
Hyperhidrosis	-	6 to 8	9	-
Maculopapular rash	-	-	-	<1
Miliaria	-	-	-	<1
Pruritus	-	3	<2	1
Rash	1	4	2	3
Skin atrophy	-	-	-	<1
Stevens-Johnson syndrome	-	<1	-	<1
Toxic epidermal necrolysis	-	-	-	<1
Urticaria	-	<1	<2	-
Endocrine and Metabolic				
Bilirubin increased	-	<1	-	<1
Blood urea nitrogen	-	-	-	<1

Adverse Events	Desvenlafaxine	Duloxetine	Levomilnacipran	Venlafaxine
increased				
Cholesterol increased	3 to 4	<1	-	-
Creatinine increased	-	-	-	<1
Diabetes mellitus	-	-	-	<1
Dyslipidemia	-	<1	-	-
Electrolyte abnormalities	-	-	-	<1
Hepatic steatosis	-	<1	-	-
Hepatitis	-	<1	-	<1
Hot flushes	-	2	<2	-
Hypercalcinuria	-	-	-	<1
Hyperchlorhydria	-	-	-	<1
Hypercholesterolemia	-	<1	-	<15
Hyperglycemia	-	-	-	<1
Hyperkalemia	-	-	-	<1
Hyperlipidemia	-	<1	-	<1
Hyperphosphatemia	-	-	-	<1
Hyperthyroidism	-	-	-	<1
Hypertriglyceridemia	-	<1	-	-
Hyperuricemia	-	-	-	<1
Hypocholesterolemia	-	-	-	<1
Hypoglycemia	-	1	-	<1
Hypokalemia	-	-	-	<1
Hyponatremia	-	<1	-	<1
Hypophosphatemia	-	-	-	<1
Hypothyroidism	-	-	-	<1
Increased blood cholesterol	-	-	<2	-
Increased liver function tests	-	-	<2	-
Jaundice	-	<1	-	<1
Kidney function abnormal	-	-	-	<1
Low-density lipoprotein increased	≤1	-	-	-
Liver enzymes increased	≤2	-1	-	<1
Syndrome of inappropriate antidiuretic hormone secretion	-	<1	-	<1
Transaminase elevation	-	1	-	-
Triglycerides increased	-	-	-	✔
Weight gain	-	<1	-	✔
Weight loss	≤2	1 to 2	-	1 to 4
Gastrointestinal				
Abdominal pain	-	<1	<2	6
Abnormal taste	-	-	-	2
Anorexia	5 to 8	3 to 5	-	8 to 20
Aphthous stomatitis	-	<1	-	-
Appetite decreased	-	3 to 11	3	-
Appetite increased	-	-	-	✔
Bloody stools	-	<1	-	-
Cholelithiasis	-	-	-	<1
Colitis	-	<1	-	-
Constipation	9 to 11	5 to 15	9	8 to 15
Diarrhea	9 to 11	7 to 13	-	6 to 8
Diverticulitis	-	<1	-	-
Dyspepsia	-	4 to 5	-	7
Dysphagia	-	<1	-	-

Adverse Events	Desvenlafaxine	Duloxetine	Levomilnacipran	Venlafaxine
Eructation	-	<1	-	-
Esophageal stenosis	-	<1	-	-
Flatulence	-	-	<2	3 to 4
Gastric emptying impaired	-	<1	-	-
Gastric irritation	-	<1	-	-
Gastric ulcer	-	<1	-	<1
Gastritis	-	1	-	-
Hematemesis	-	-	-	<1
Intestinal obstruction	-	-	-	<1
Irritable bowel syndrome	-	<1	-	-
Loose stools	-	2 to 3	-	-
Melena	-	<1	-	-
Nausea	22 to 26	14 to 30	17	21 to 58
Vomiting	≤4	1 to 6	5	3 to 6
Xerostomia	11 to 17	5 to 18	-	12 to 22
Genitourinary				
Crystalluria	-	-	-	<1
Dysuria	-	1	-	-
Ejaculation abnormality	≤1	1 to 4	5	2 to 19
Erectile dysfunction	3 to 6	1 to 5	6	-
Hematuria	-	-	<2	-
Impotence	-	-	-	4 to 10
Libido decreased	4 to 5	2 to 4	-	3 to 9
Menstrual abnormalities	-	-	-	<1
Micturition urgency	-	<1	-	-
Nocturia	-	<1	-	-
Pollakiuria	-	1 to 5	<2	-
Prostatic disorder	-	-	-	✔
Proteinuria	6 to 8	-	<2	-
Pyelonephritis	-	-	-	<1
Pyuria	-	-	-	<1
Testicular pain	-	-	4	-
Urinary frequency	-	-	-	3
Urinary hesitation	-	-	4	-
Urinary retention	-	<1	-	1
Urinary symptoms	≤1	1	-	-
Urination impaired	-	-	-	2
Hematologic				
Agranulocytosis	-	-	-	<1
Anemia	-	<1	-	-
Aplastic anemia	-	-	-	<1
Bleeding time increased	-	-	-	<1
Eosinophilia	-	-	-	<1
Hypoproteinemia	-	-	-	<1
Leukocytosis	-	-	-	<1
Leukoderma	-	-	-	<1
Leukopenia	-	<1	-	<1
Lymphadenopathy	-	<1	-	<1
Lymphocytosis	-	-	-	<1
Pancytopenia	-	-	-	<1
Thrombocytopenia	-	<1	-	<1
Thrombophlebitis	-	-	-	<1
Musculoskeletal				
Arthralgia	-	-	-	✔

Adverse Events	Desvenlafaxine	Duloxetine	Levomilnacipran	Venlafaxine
Dysarthria	-	<1	-	-
Extrapyramidal symptoms	-	-	<2	<1
Hypertonia	-	-	-	3
Malaise	-	<1	-	-
Muscle cramp	-	4 to 5	-	-
Muscle pain	-	1 to 5	-	-
Muscle tightness	-	1	-	1 to 2
Muscle twitching	-	4	-	<1
Myalgia	-	1 to 3	-	-
Myasthenia	-	-	-	<1
Myopathy	-	-	-	<1
Neck pain/rigidity	-	-	-	✔
Neuroleptic malignant-like syndrome	-	-	-	<1
Osteoporosis	-	-	-	<1
Rhabdomyolysis	-	-	-	<1
Rheumatoid arthritis	-	-	-	<1
Rigors	-	1	-	-
Tendon rupture	-	-	-	<1
Tremor	≤3	3 to 4	-	4 to 10
Weakness	≤2	2 to 8	-	8 to 19
Respiratory				
Asthma	-	-	-	<1
Atelectasis	-	-	-	<1
Cough	-	3 to 6	-	✔
Dyspnea	-	-	-	✔
Epistaxis	<2	-	-	-
Nasopharyngitis	-	7 to 9	-	-
Pharyngitis	-	-	-	7
Pharyngolaryngeal pain	-	1 to 6	-	-
Pleurisy	-	-	-	<1
Pneumonia	-	-	-	<1
Sinusitis	-	-	-	2
Upper respiratory infection	-	7	-	-
Other				
Anaphylactic reaction	-	<1	-	<1
Angioneurotic edema	-	<1	-	-
Arteritis	-	-	-	<1
Bacteremia	-	-	-	<1
Basophilia	-	-	-	<1
Blurred/abnormal vision	-	1 to 3	<2	4 to 6
Bruxism	-	<1	<2	-
Cataract	-	-	-	<1
Catatonia	-	-	-	<1
Cellulites	-	-	-	<1
Conjunctival hemorrhage	-	-	<2	-
Cyanosis	-	-	-	<1
Deep vein thrombosis	-	-	-	<1
Dehydration	-	<1	-	<1
Diaphoresis increased	10 to 14	6	-	10 to 14
Embolus	-	-	-	<1
Facial edema	-	<1	-	-
Facial paralysis	-	-	-	<1
Fasciitis	-	-	-	<1

Adverse Events	Desvenlafaxine	Duloxetine	Levomilnacipran	Venlafaxine
Flu-like syndrome	-	<1	-	6
Gingivitis	-	<1	-	-
Glaucoma	-	<1	-	<1
Homicidal ideation	-	-	-	<1
Hot flushes	-	2 to 3	<2	-
Hyperacusis	-	-	-	<1
Hypersensitivity reaction	<2	-	-	-
Infection	-	-	-	6
Keratoconjunctivitis sicca	-	<1	-	-
Larynx edema	-	-	-	<1
Macular degeneration	-	<1	-	-
Maculopathy	-	<1	-	-
Moniliasis	-	-	-	<1
Multiple myeloma	-	-	-	<1
Mydriasis	2	-	-	2
Nephropathy	-	<1	-	-
Night sweats	-	1	-	-
Oropharyngeal edema	-	<1	-	-
Phlebitis	-	<1	-	-
Retinal detachment	-	<1	-	-
Serotonin syndrome	-	-	-	<1
Stomatitis	-	<1	-	-
Suicidal ideation/attempt	-	<1	-	<1 to 2
Thirst	-	<1	<2	-
Tinnitus	2	-	-	2
Trauma	-	-	-	2
Trismus	-	-	-	✔
Visual disturbance	-	<1	-	-
Withdrawal syndrome	-	<1	-	<1

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

Table 6c. Adverse Drug Events (%) Reported with the Selective Serotonin-reuptake Inhibitors[1-35]

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

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

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

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

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

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

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

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

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

Table 6d. Adverse Drug Events (%) Reported with the Serotonin Modulators[1-35]

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

Adverse Events	Nefazodone	Trazodone	Vilazodone	Vortioxetine
Liver function tests abnormal	<1	-	-	-
Prolactin increased	<1	-	-	-
Weight gain	-	1 to 10	-	-
Weight loss	-	1 to 10	-	-
Gastrointestinal				
Abnormal taste	1 to 10	-	-	-
Appetite decreased	-	-	1 to 10	-
Appetite increased	1 to 10	-	2	-
Constipation	>10	1 to 10	-	3 to 6
Diarrhea	1 to 10	1 to 10	28	7 to 10
Dry mouth	-	-	-	6 to 8
Dyspepsia	1 to 10	-	3	-
Flatulence	-	-	3	1 to 3
Gastroenteritis	1 to 10	-	3	-
Nausea	>10	>10	23	21 to 32
Vomiting	1 to 10	-	5	3 to 6
Xerostomia	>10	>10	8	-
Genitourinary				
Ejaculation delayed	-	-	2	-
Erectile dysfunction	-	-	2	-
Impotence	1 to 10	-	-	-
Libido decreased	1 to 10	-	3 to 5	-
Orgasm abnormal	-	-	2 to 4	-
Priapism	<1	<1	-	-
Sexual dysfunction	-	-	<2	-
Urinary frequency	1 to 10	-	-	-
Urinary retention	1 to 10	<1	-	-
Hematologic				
Hematocrit decreased	1 to 10	-	-	-
Leukopenia	<1	-	-	-
Thrombocytopenia	<1	-	-	-
Musculoskeletal				
Arthralgia	1 to 10	-	3	-
Extrapyramidal symptoms	-	<1	-	-
Hypertonia	1 to 10	-	-	-
Jittery	-	-	2	-
Myalgia	-	1 to 10	-	-
Neck rigidity	1 to 10	-	-	-
Rhabdomyolysis	<1	-	-	-
Tremor	1 to 10	1 to 10	2	-
Weakness	>10	-	-	-
Respiratory				
Bronchitis	1 to 10	-	-	-
Cough	1 to 10	-	-	-
Dyspnea	1 to 10	-	-	-
Nasal congestion	-	1 to 10	-	-
Pharyngitis	1 to 10	-	-	-
Other				
Abnormal feeling	-	-	<1	-
Abnormal taste	-	-	<1	-
Allergic reaction	<1	<1	-	-
Angioedema	<1	-	-	-
Blurred/abnormal vision	7 to 9	>10	1 to 10	-
Breast pain	1 to 10	-	-	-

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

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

Table 6e. Adverse Drug Events (%) Reported with the Tricyclics and Other Norepinephrine-reuptake Inhibitors[1-35]

Adverse Events	Single Entity Agents										Combination Products
	Amitrip-tyline	Amox-apine	Clomip-ramine	Desip-ramine	Dox-epin	Imip-ramine	Mapro-tiline	Nortrip-tyline	Protrip-tyline	Trimip-ramine	Amitriptyline/ Chlordiazepoxide
Cardiovascular											
Aneurysm	-	-	<1	-	-	-	-	-	-	-	-
Arrhythmia	✔	✔	<1	✔	-	✔	✔	✔	✔	✔	✔
Atrial flutter	-	-	<1	-	-	-	-	-	-	-	-
Atrioventricular conduction changes	✔	-	-	-	-	-	-	-	-	-	✔
Bradycardia	-	-	<1	-	-	-	-	-	-	-	-
Bundle branch block	-	-	<1	-	-	-	-	-	-	-	-
Cardiac arrest	-	-	<1	-	-	-	-	-	-	-	-
Cardiomyopathy	✔	-	-	-	-	-	-	-	-	-	✔
Cerebral hemorrhage	-	-	<1	-	-	-	-	-	-	-	-
Chest pain	-	-	4	-	-	-	-	-	-	-	-
Chills	-	-	2	-	-	-	-	-	-	-	-
Congestive heart failure	-	-	-	-	-	✔	-	-	-	-	-
Cyanosis	-	-	<1	-	-	-	-	-	-	-	-
Electrocardiogram changes	✔	-	<1	-	-	✔	-	-	-	-	✔
Edema	✔	>1	3	✔	-	-	-	✔	-	-	-
Encephalopathy	-	-	<1	-	-	-	-	-	-	-	-
Extrasystole	-	-	<1	-	-	-	-	-	-	-	-
Heart block	✔	✔	<1	-	-	✔	✔	✔	✔	✔	✔
Hypertension	✔	<1	-	✔	✔	✔	✔	✔	✔	✔	✔
Hypotension	✔	<1	1 to 10	✔	✔	-	✔	✔	✔	✔	✔
Myocardial infarction	✔	✔	<1	✔	-	✔	-	✔	✔	✔	✔
Myocardial ischemia	-	-	<1	-	-	-	-	-	-	-	-
Orthostatic hypotension	✔	-	6	-	-	✔	-	✔	-	-	✔
Palpitations	✔	>1	4	✔	-	✔	-	✔	✔	✔	✔
Peripheral ischemia	-	-	<1	-	-	-	-	-	-	-	-
Stroke	✔	✔	-	✔	-	✔	-	✔	✔	✔	✔
Syncope	✔	<1	>1	-	-	-	✔	✔	-	-	✔
Tachycardia	✔	<1	4	✔	✔	✔	-	✔	✔	✔	✔
Vasospasm	-	-	<1	-	-	-	-	-	-	-	-
Central Nervous System											
Abnormal dreaming	-	-	3	-	-	-	-	-	-	-	-
Aggressiveness	-	-	2	-	-	-	-	-	-	-	-
Agitation	-	-	3	✔	-	✔	1 to 10	✔	✔	✔	-
Akathisia	-	-	-	-	-	-	<1	-	-	-	1 to 10
Anxiety	✔	1 to 10	9	✔	-	✔	1 to 10	✔	✔	✔	✔
Aphasia	-	-	<1	-	-	-	-	-	-	-	-
Apraxia	-	-	<1	-	-	-	-	-	-	-	-
Ataxia	✔	1 to 10	<1	✔	✔	-	<1	✔	✔	-	>10
Catalepsy	-	-	<1	-	-	-	-	-	-	-	-
Confusion	-	-	3	-	-	-	-	✔	✔	-	1 to 10
Cognitive function (impaired)	✔	-	-	-	-	-	-	-	-	-	✔
Coma	✔	-	<1	-	-	-	-	-	-	-	✔

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

Adverse Events	Single Entity Agents										Combination Products
	Amitrip-tyline	Amox-apine	Clomip-ramine	Desip-ramine	Dox-epin	Imip-ramine	Mapro-tiline	Nortrip-tyline	Protrip-tyline	Trimip-ramine	Amitriptyline/ Chlordiazepoxide
Neuropathy	-	-	<1	-	-	-	-	-	-	-	-
Nightmares	✔	>1	-	-	-	✔	✔	✔	✔	✔	✔
Oculogyric crisis	-	-	<1	-	-	-	-	-	-	-	-
Oculomotor nerve paralysis	-	-	<1	-	-	-	-	-	-	-	-
Panic	-	-	1	-	-	-	-	✔	✔	-	-
Paranoia	-	-	<1	-	-	-	-	-	-	-	-
Paresis	-	-	9	-	-	-	-	-	-	-	-
Paresthesia	-	-	2	-	-	-	-	-	-	-	-
Parkinsonian syndrome	-	-	-	✔	-	-	-	-	-	-	-
Psychosis exacerbation	-	-	<1	✔	-	✔	-	✔	✔	✔	-
Psychosomatic disorder	-	-	3	-	-	-	-	-	-	-	-
Restlessness	✔	1 to 10	-	✔	-	✔	-	✔	✔	✔	✔
Sedation	✔	-	-	-	-	-	-	-	-	-	✔
Sensory disturbance	-	-	<1	-	-	-	-	-	-	-	-
Seizure	✔	<1	<1	✔	✔	✔	<1	✔	✔	✔	✔
Somnolence	✔	-	-	-	-	-	-	-	-	-	✔
Sleep Disorder	-	-	4	-	-	-	-	-	-	-	-
Speech disorder	-	-	3	-	-	-	-	-	-	-	-
Stupor	-	-	<1	-	-	-	-	-	-	-	-
Syncope	-	<1	-	-	-	-	<1	-	-	-	-
Twitching	-	-	7	-	-	-	-	-	-	-	-
Yawning	-	-	3	-	-	-	-	-	-	-	-
Dermatological											
Acne	-	-	2	-	-	-	-	-	-	-	-
Alopecia	✔	-	<1	✔	✔	<1	-	✔	✔	✔	✔
Cellulitis	-	-	<1	-	-	-	-	-	-	-	-
Cheilitis	-	-	<1	-	-	-	-	-	-	-	-
Dermatitis	-	-	2	-	-	-	-	-	-	-	-
Dry skin	-	-	2	-	-	-	-	-	-	-	-
Petechiae	-	-	-	✔	-	<1	-	✔	✔	✔	-
Photosensitivity	✔	<1	<1	✔	✔	<1	<1	✔	✔	✔	✔
Pruritus	-	<1	6	✔	✔	<1	-	✔	✔	✔	✔
Rash	✔	>1	8	✔	✔	<1	<1	✔	✔	✔	✔
Skin discoloration	-	-	<1	-	-	-	-	-	-	-	-
Skin ulceration	-	-	<1	-	-	-	-	-	-	-	-
Urticaria	✔	<1	1	✔	-	<1	-	✔	✔	✔	✔
Endocrine and Metabolic											
Breast enlargement	✔	-	2	✔	✔	✔	-	✔	✔	✔	✔
Breast pain	-	-	1	-	-	-	-	-	-	-	-
Diabetes mellitus	-	-	<1	-	-	-	-	-	-	-	-
Galactorrhea	✔	<1	<1	✔	✔	✔	-	✔	✔	✔	✔
Goiter	-	-	<1	-	-	-	-	-	-	-	-
Glycosuria	-	-	<1	-	-	-	-	-	-	-	-
Gynecomastia	✔	-	<1	-	-	✔	-	✔	✔	-	✔

Adverse Events	Single Entity Agents										Combination Products
	Amitrip-tyline	Amox-apine	Clomip-ramine	Desip-ramine	Dox-epin	Imip-ramine	Mapro-tiline	Nortrip-tyline	Protrip-tyline	Trimip-ramine	Amitriptyline/ Chlordiazepoxide
Hyperglycemia	✔	-	<1	✔	✔	✔	-	✔	-	✔	✔
Hypoglycemia	✔	-	-	✔	✔	✔	-	-	-	✔	✔
Lactation	-	-	4	-	-	-	-	-	-	-	-
Prolactin levels increased	-	>1	-	-	-	-	-	-	-	-	-
Syndrome of inappropriate antidiuretic hormone secretion	✔	<1	<1	✔	✔	✔	-	✔	✔	✔	✔
Thirst	-	-	2	-	-	-	-	-	-	-	-
Gastrointestinal											
Abdominal pain/cramps	-	<1	11	✔	<1	✔	-	✔	-	✔	-
Anorexia	✔	-	12	✔	✔	✔	-	✔	✔	✔	✔
Appetite decreased	-	-	11	-	<1	-	-	✔	-	-	✔
Appetite increased	-	>1	11	-	<1	-	-	✔	✔	✔	✔
Black tongue	✔	✔	-	✔	-	✔	-	✔	-	✔	✔
Blood in stool	-	-	<1	-	-	-	-	-	-	-	-
Chronic enteritis	-	-	<1	-	-	-	-	-	-	-	-
Constipation	✔	12	47	✔	<1	✔	6	✔	✔	✔	✔
Diarrhea	✔	<1	13	✔	✔	✔	-	✔	✔	✔	✔
Dysphagia	-	-	2	-	-	-	-	-	-	-	-
Dyspepsia	-	-	22	✔	<1	-	-	✔	-	-	-
Eructation	-	-	>1	-	-	-	-	-	-	-	-
Esophageal sphincter tone decrease	-	-	-	✔	✔	-	-	-	✔	✔	-
Esophagitis	-	-	1	-	-	-	-	-	-	-	-
Flatulence	-	<1	6	-	-	-	-	-	-	-	-
Gastric/peptic ulcer	-	-	<1	-	-	-	-	-	-	-	-
Indigestion	-	-	-	-	✔	-	-	-	✔	✔	-
Intestinal obstruction	-	-	<1	-	-	-	-	-	-	-	-
Irritable bowel syndrome	-	-	<1	-	-	-	-	-	-	-	-
Nausea	✔	>1	33	✔	✔	✔	2	✔	✔	✔	✔
Paralytic ileus	✔	✔	<1	✔	-	✔	-	-	-	✔	✔
Reflux	-	-	<1	-	<1	-	-	✔	-	-	-
Salivation decreased	-	-	-	-	-	-	✔	-	-	-	✔
Salivation increased	-	-	<1	-	-	-	-	-	-	-	✔
Stomatitis	✔	✔	>1	✔	✔	✔	-	-	-	✔	✔
Taste changes	✔	<1	8	✔	✔	✔	-	✔	✔	✔	✔
Tongue ulceration	-	-	<1	-	-	-	-	-	-	-	-
Vomiting	✔	<1	7	✔	<1	✔	<1	✔	✔	✔	✔
Weight gain	✔	<1	18	✔	✔	✔	-	✔	✔	✔	✔
Weight loss	✔	<1	>1	✔	-	✔	-	✔	✔	✔	✔
Xerostomia	✔	>10	84	✔	✔	✔	>10	✔	✔	✔	✔
Genitourinary											
Albuminuria	-	-	<1	-	-	-	-	-	-	-	-
Cervical dysplasia	-	-	<1	-	-	-	-	-	-	-	-
Cystitis	-	-	2	-	-	-	-	-	-	-	-
Dysmenorrhea	-	-	12	-	-	-	-	-	-	-	-

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

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

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

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

Table 6f. Adverse Drug Events (%) Reported with the Antidepressants, Miscellaneous[1-35]

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

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

Adverse Events	Bupropion	Mirtazapine
Intestinal perforation	✔	-
Nausea	1 to 18	<1
Pancreatitis	✔	-
Stomach ulcer	✔	<1
Vomiting	2 to 4	>1
Xerostomia	17 to 26	25
Genitourinary		
Cystitis	✔	-
Dyspareunia	✔	-
Ejaculation abnormality	✔	-
Impotence	<1	<1
Libido decreased	3	-
Libido increased	✔	-
Menopause	✔	-
Menstrual complaints	2 to 5	<1
Painful erection	✔	-
Prostate disorder	✔	-
Salpingitis	✔	-
Urinary frequency	2 to 5	2
Urinary incontinence	✔	<1
Urinary retention	✔	<1
Urinary tract infection	<1	>1
Urinary urgency	<2	-
Vaginal hemorrhage	<2	-
Vaginitis	✔	>1
Hematologic		
Agranulocytosis	-	<1
Anemia	✔	-
Leukocytosis	✔	-
Leukopenia	✔	-
Neutropenia	-	<1
Pancytopenia	✔	-
Thrombocytopenia	✔	-
Musculoskeletal		
Arthralgia	1 to 4	2
Arthritis	2	-
Back pain	-	2
Dysarthria	✔	-
Extrapyramidal syndrome	✔	-
Musculoskeletal chest pain	✔	-
Myalgia	2 to 6	2
Neck pain	✔	<1
Rhabdomyolysis	✔	-
Rigidity	✔	-
Tardive dyskinesia	✔	-
Tremor	3 to 6	2
Twitching	1 to 2	<1
Weakness	2 to 4	8
Respiratory		
Bronchospasm	✔	-
Cough	1 to 4	-
Dyspnea	-	1
Pharyngitis	3 to 13	-
Pneumonia	✔	-

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

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

Table 7. Boxed Warning for the Antidepressants[1]

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

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

Table 8. Boxed Warning for Bupropion[1]

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

Table 9. Boxed Warning for Nefazodone[1]

WARNING
Cases of life-threatening hepatic failure have been reported in patients treated with nefazodone. The reported rate in the United States is approximately one case of liver failure resulting in death or transplant per 250,000 to 300,000 patient-years of nefazodone treatment. The total patient-years is a summation of each patient's duration of exposure expressed in years. For example, one patient-year is equal to two patients each treated for six months, three patients each treated for four months, etc. Ordinarily, treatment with nefazodone should not be

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

VII. Dosing and Administration

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

Table 10. Usual Dosing Regimens for the Antidepressants[1-35]

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

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	30 mg/day; maintenance, 60 mg once- daily; maximum, 60 mg/day Neuropathic pain associated with diabetic peripheral neuropathy: Delayed-release capsule: 60 mg once-daily Generalized anxiety disorder: Delayed-release capsule: initial, 60 mg/day; maintenance, 60 mg once-daily; maximum, 120 mg/day Major depressive disorder: Delayed-release capsule: initial, 40 to 60 mg/day; maintenance (acute treatment), 40 (20 mg twice-daily) to 60 mg/day (once-daily or 30 mg twice-daily); maintenance, 60 mg/day; maximum, 120 mg/day		
Levomilnacipran	Major depressive disorder: Extended-release capsule: initial, 20 mg once daily for two days, then increase to 40 mg once daily; maintenance, 40 to 120 mg once daily; maximum, 120 mg once daily	Safety and efficacy in children have not been established.	Extended-release capsules: 20 mg 40 mg 80 mg 120 mg
Venlafaxine	Generalized anxiety disorder: Extended-release capsule: initial, 75 mg once-daily; maximum, 225 mg/day Major depressive disorder: Extended-release capsule: initial, 75 mg once-daily; maximum, 225 mg/day Extended-release tablet: 37.5 to 75 mg/day; maximum, 225 mg/day Tablet: initial, 75 mg/day administered in two or three divided doses; maintenance, 150 to 225 mg/day; maximum, 375 mg/day Treatment of panic disorder, with or without agoraphobia: Extended-release capsule: initial, 37.5 mg once-daily for one week; maximum, 225 mg/day	Safety and efficacy in children have not been established.	Extended-release capsule: 37.5 mg 75 mg 150 mg Extended-release tablet: 37.5 mg 75 mg 150 mg 225 mg Tablet: 25 mg 37.5 mg 50 mg 75 mg 100 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Treatment of social anxiety disorder: Extended-release capsule, extended-release tablet: 75 mg once-daily		
Selective Serotonin-reuptake Inhibitors			
Citalopram	Depression: Solution, tablet: initial, 20 mg/day, generally with an increase to 40 mg/day; doses of more than 40 mg are not usually necessary; should a dose increase be necessary, it should occur in 20 mg increments at intervals of no less than one week; maximum dose, 60 mg/day	Safety and efficacy in children have not been established.	Solution: 10 mg/5 mL Tablet: 10 mg 20 mg 40 mg
Escitalopram	Depression: Solution, tablet: initial, 10 mg/day; dose may be increased to 20 mg/day after at least one week Generalized anxiety disorder: Solution, tablet: Initial, 10 mg/day; dose may be increased to 20 mg/day after at least one week	Depression ≥12 years of age: Solution, tablet: initial, 10 mg/day; dose may be increased to 20 mg/day after at least three weeks	Solution: 5 mg/5 mL Tablet: 5 mg 10 mg 20 mg
Fluoxetine	Bulimia nervosa: Immediate release capsule and tablet, solution: 20 mg once daily; usual dose: 60 mg/day; maximum, 80 mg/day; doses >20 mg may be given once daily or divided twice daily Delayed release capsule: patients maintained on fluoxetine immediate release 20 mg/day may be changed to fluoxetine delayed release capsule 90 mg/week, starting dose seven days after the last 20 mg/day dose Depression: Immediate release capsule and tablet, solution: 20 mg once daily; usual dose, 20 to 40 mg/day; maximum, 80 mg/day; doses >20 mg may be given once daily or divided twice daily Delayed release capsule: patients maintained on fluoxetine immediate release 20 mg/day	Depression eight to 18 years of age: Immediate release capsule and tablet, solution: 10 to 20 mg/day; lower-weight children may be started on 10 mg/day; may increase to 20 mg/day after one week if needed Obsessive-compulsive disorder seven to 18 years of age: Immediate release capsule and tablet, solution: 10 mg/day; in adolescents and higher-weight children, dose may be increased to 20 mg/day after two weeks; range, 10 to 60 mg/day	Delayed release capsule: 90 mg Immediate release capsule: 10 mg 20 mg 40 mg Immediate release tablet: 10 mg 20 mg Solution: 20 mg/5 mL

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	may be changed to fluoxetine delayed release capsule 90 mg/week, starting dose seven days after the last 20 mg/day dose Obsessive-compulsive disorder: Immediate release capsule and tablet, solution: 20 mg once daily; usual dose: 40 to 80 mg/day; maximum, 80 mg/day; doses >20 mg may be given once daily or divided twice daily Delayed release capsule: patients maintained on fluoxetine immediate release 20 mg/day may be changed to fluoxetine delayed release capsule 90 mg/week, starting dose seven days after the last 20 mg/day dose Panic disorder: Immediate release capsule and tablet, solution: initial, 10 mg/day; after one1 week, increase to 20 mg/day; may increase after several weeks; doses >60 mg/day have not been evaluated Delayed release capsule: patients maintained on fluoxetine immediate release 20 mg/day may be changed to fluoxetine delayed release capsule 90 mg/week, starting dose seven days after the last 20 mg/day dose Premenstrual dysphoric disorder: Immediate release capsule and tablet, solution: 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) Delayed release capsule: patients maintained on fluoxetine immediate release 20 mg/day may be changed to fluoxetine delayed release capsule 90 mg/week, starting dose seven		

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	days after the last 20 mg/day dose		
Fluvoxamine	Obsessive-compulsive disorder: Immediate release tablet: initial, 50 mg at bedtime; adjust dose in 50 mg increments every four to seven days; usual dose, 100 to 300 mg/day; divide total daily dose into two doses; administer larger portion at bedtime; when total daily dose exceeds 100 mg, the dose should be given in two divided doses Extended release capsule: initial, 100 mg at bedtime; may be increased in 50 mg increments at intervals of at least one week; usual dose range, 100 to 300 mg/day	Obsessive-compulsive disorder eight to 17 years of age: Immediate release tablet: initial, 25 mg at bedtime; adjust in 25 mg increments at four to seven day intervals; range, 50 to 200 mg/day	Extended release capsule: 100 mg 150 mg Immediate release tablet: 25 mg 50 mg 100 mg
Paroxetine	Depression: Immediate release tablet, suspension: initial, 20 mg once daily; increase by 10 mg/day increments at intervals of at least one week; maximum dose, 50 mg/day Extended release tablet: initial, 25 mg once daily; increase if needed by 12.5 mg/day increments at intervals of at least one week; maximum dose, 62.5 mg/day Generalized anxiety disorder: Immediate release tablet, suspension: initial, 20 mg once daily; increase if needed by 10 mg/day increments at intervals of at least one week; doses of 20 to 50 mg/day were used in clinical trials; however, no greater benefit was seen with doses >20 mg Obsessive-compulsive disorder: Immediate release tablet, suspension: initial, 20 mg once daily; increase if needed by 10 mg/day increments at intervals of at least one week; recommended dose, 40 mg/day; range, 20 to 60 mg/day Moderate to severe vasomotor	Safety and efficacy in children have not been established.	Extended release tablet: 12.5 mg 25 mg 37.5 mg Immediate release capsule: 7.5 mg Suspension: 10 mg/5 mL Immediate release tablet: 10 mg 20 mg 30 mg 40 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	symptoms associated with menopause: Immediate release capsule: 7.5 mg once daily Panic disorder: Immediate release tablet, suspension: initial, 10 mg once daily; increase if needed by 10 mg/day increments at intervals of at least one week; recommended dose, 40 mg/day; range, 10 to 60 mg/day Extended release tablet: initial, 12.5 mg once daily in the morning; increase if needed by 12.5 mg/day increments at intervals of at least one week; maximum dose, 75 mg/day Premenstrual dysphoric disorder: Extended release tablet: initial, 12.5 mg once daily in the morning; dose may be increased to 25 mg/day; dosing changes should occur at intervals of at least one week; may be given daily throughout the menstrual cycle or limited to the luteal phase Posttraumatic stress disorder: Immediate release tablet, suspension: initial, 20 mg once daily; increase if needed by 10 mg/day increments at intervals of at least one week; range, 20 to 50 mg; limited data suggest doses of 40 mg/day were not more efficacious than 20 mg/day Social anxiety disorder: Immediate release tablet, suspension: initial, 20 mg once daily, preferably in the morning; recommended dose, 20 mg/day; range, 20 to 60 mg/day; doses >20 mg/day may not have additional benefit Extended release tablet: initial, 12.5 mg once daily; increase if needed by 12.5 mg/day increments at intervals of at least one week; maximum dose, 37.5		

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	mg/day		
Sertraline	Depression: Oral concentrate, tablet: initial, 50 mg/day; may increase daily dose, at intervals of not less than one week; maximum, 200 mg/day; if somnolence is noted, give at bedtime Obsessive-compulsive disorder: Oral concentrate, tablet: initial, 50 mg/day; may increase daily dose, at intervals of not less than one week; maximum, 200 mg/day; if somnolence is noted, give at bedtime Panic disorder: Oral concentrate, tablet: initial, 25 mg once daily; increased after one week to 50 mg once daily Posttraumatic stress disorder: Oral concentrate, tablet: initial, 25 mg once daily; increased after one week to 50 mg once daily Premenstrual dysphoric disorder: Oral concentrate, tablet: 50 mg daily throughout menstrual cycle or limited to the luteal phase of menstrual cycle; patients not responding to 50 mg/day may benefit from dose increases (50 mg increments per menstrual cycle) up to 150 mg/day when dosing throughout menstrual cycle or up to 100 mg/day when dosing during luteal phase only	Obsessive-compulsive disorder six to 12 years of age: Oral concentrate, tablet: initial, 25 mg once daily Obsessive-compulsive disorder 13 to 17 years of age: Oral concentrate, tablet: initial, 50 mg once daily May increase daily dose, at intervals of not less than one week; maximum, 200 mg/day; if somnolence is noted, give at bedtime	Oral concentrate: 20 mg/mL Tablet: 25 mg 50 mg 100 mg
Serotonin Modulators			
Nefazodone	Depression: Tablet: 200 mg/day divided in two doses initially, with a range of 300m to 600 mg/day in two divided doses thereafter	Safety and efficacy in children have not been established.	Tablet: 50 mg 100 mg 150 mg 200 mg 250 mg
Trazodone	Major depressive disorder: Extended-release tablet: initial, 150 mg once daily; maintenance, may increase by 75 mg/day every three days; maximum, 375 mg/day Tablet: initial, 150 mg/day in three divided doses; maintenance, dose may be	Safety and efficacy in children have not been established.	Extended release tablet: 150 mg 300 mg Immediate release tablet: 50 mg 100 mg 150 mg 300 mg

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

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

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

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	tolerated, may increase after one week to 300 mg/day Smoking cessation: Immediate release tablet: initial, 150 mg once daily for three days; increase to 150 mg twice daily; treatment should continue for seven to twelve weeks		
Mirtazapine	Depression: Orally disintegrating tablet, tablet: initial, 15 mg at bedtime; titrate up to 15 to 45 mg/day with dose increases made no more frequently than every one to two weeks	Safety and efficacy in children have not been established.	Orally disintegrating tablet: 15 mg 30 mg 45 mg Tablet: 7.5 mg 15 mg 30 mg 45 mg

VIII. Effectiveness

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

Table 11. Comparative Clinical Trials with the Antidepressants

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Depression				
Koshino et al.[62] (2013) Buproprion SR 150 mg daily vs bupropion SR 150 mg BID vs placebo	DB, MC, PC, RCT Patients 18 to 64 years of age with MDD in Japan or South Korea	N=569 8 weeks	Primary: Mean change from baseline in MADRS total score at week eight Secondary: Comparison of change from baseline for each group in MADRS total scores and IDS-SR total scores at weeks one, two, four, six and eight; MADRS total scores stratified by location at week eight for each group	Primary: The mean change from baseline in MADRS total scores was decreased for bupropion SR 150 mg daily, bupropion 150 mg BID and placebo; however no significant difference from placebo (-14.4; P=0.853, -12.9; P value not reported, -13.9; P value not reported, respectively). Secondary: Both MADRS and IDS-SR total scores consistently decreased (weeks one, two, four, six and eight) throughout the study for all groups, including placebo; however, neither bupropion treatment group significantly differed from placebo in either MADRS or IDS-SR in total scores. When MADRS results were stratified by location (Japan or South Korea), no significant differences were observed in change from baseline in MADRS total score at week eight.
Clayton et al.[63] (2006) Bupropion ER 300 to 450 mg daily vs escitalopram 10 to 20 mg daily	DB, PC, RCT Adult outpatients with moderate-to-severe MDD with normal sexual function	N=830 8 weeks	Primary: Orgasm dysfunction at eight weeks and incidence of worsened sexual functioning; CSFQ, HAM-D_{17} Secondary:	Primary: The incidence of worsened sexual functioning at the end of the treatment period was statically significantly lower with bupropion ER than with escitalopram (P<0.05), not statistically different between bupropion ER and placebo (P>0.067), and statistically significantly higher with escitalopram than with placebo (P<0.001). The percentages of patient with orgasm dysfunction at week eight were 15% with bupropion ER, 30% with escitalopram, and 15% with placebo.

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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				compared to the placebo group. Response rates were 57% for bupropion ER (P=0.033), 65% for venlafaxine ER (P<0.001), and 46% for placebo. Remission rates were 47% for bupropion ER (P=0.004), 51% for venlafaxine ER (P<0.001), and 32% for placebo. CGI-I response rates for both active treatment groups were significantly better than placebo with 68% of bupropion ER patients (P<0.001) and 65% of venlafaxine ER patients (P=0.009) rated 'much improved' or 'very much improved' at week eight compared to 53% of placebo patients. Significantly greater mean decreases from baseline in SDS total scores were observed for bupropion ER (-8.4; P=0.003) and venlafaxine ER (-9.0; P<0.001) compared to placebo (-6.2). The mean change from baseline in patient satisfaction with study medication was significantly greater for bupropion ER (4.9; P=0.005) and venlafaxine ER (5.2; P<0.001) than placebo (4.4).
Weihs et al.[65] (2000) Bupropion SR 100 to 300 mg/day vs paroxetine 10 to 40 mg/day	DB, MC, RCT Patients ≥60 years of age with MDD	N=100 6 weeks	Primary: HAM-D, HAMA, CGI-I, CGI-S scores Secondary: Adverse effects	Primary: Measurements of efficacy were similar between the treatment groups, with both showing improved scores on all depression rating scales. Secondary: Somnolence and diarrhea were more common in paroxetine-treated patients (P<0.05). Headache, insomnia, dry mouth, agitation, dizziness, and nausea occurred in >10% of patients in both groups.
Kavoussi et al.[66] (1997) Bupropion SR 100 to 300 mg/day vs sertraline 50 to 200 mg/day	DB, PG, RCT Outpatients with moderate-to-severe MDD	N=248 16 weeks	Primary: HAM-D, HAMA, CGI-I, CGI-S Secondary: Adverse effects	Primary: Mean HAM-D, HAMA, CGI-I, and CGI-S scores improved over the course of treatment in both the bupropion SR group and the sertraline group; no between-group differences were observed on any of the scales. Secondary: Orgasm dysfunction was significantly (P<0.001) more common in sertraline-treated patients compared to bupropion SR-treated patients. Adverse events (nausea, diarrhea, somnolence, and sweating) were

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				experienced more frequently (P<0.05) in sertraline-treated patients. No differences were noted between the treatments for vital signs and weight.
Rocca et al.[67] (2005) Citalopram 20 mg/day vs sertraline 50 mg/day	DB, RCT Patients >65 years of age with minor depressive disorder or subsyndromal depressive symptomatology	N=138 8 weeks	Primary: Change in depressive symptoms and remission rates (HAM-D) Secondary; Not reported	Primary: Both treatments induced notable improvement of depressive symptoms. No statistically significant differences were found between the two treatments in decreases from baseline HAM-D scores. At the end of the trial, the mean total HAM-D score had fallen 55.0% in the citalopram group and 52.7% in the sertraline group. No significant differences in remission rates were observed between the two agents. For one month, three month, and end follow-up periods, P=0.3466, 0.7570, and 0.2537, respectively. Secondary; Not reported
Clayton et al.[68] (2013) Desvenlafaxine 50 mg/day vs placebo	DB Adult outpatients with MDD	N=422 12 weeks	Primary: Mean change from baseline Arizona Sexual Experiences Scale scores Secondary: Not reported	Primary: Among women (desvenlafaxine, n=184; placebo, n=92), baseline scores were 20.0 (5.2) and 20.5 (5.3) for desvenlafaxine and placebo, respectively; mean changes at week 12 were -1.93 (0.37) and -1.03 (0.54), respectively (mean difference: 0.90 [-0.38, 2.18]; P=0.169). Among men (desvenlafaxine, n=97; placebo, n=49), baseline scores were 16.4 (4.9) and 15.9 (4.8) for desvenlafaxine and placebo, respectively; mean changes at week 12 were -1.13 (0.47) and -1.06 (0.70), respectively (mean difference: 0.07 [-1.59, 1.74]; P=0.932). Significantly greater orgasmic dysfunction at week 12 was observed in the subgroup of men without baseline sexual dysfunction treated with desvenlafaxine relative to placebo. Conversely, women without baseline sexual dysfunction experienced poorer overall sexual functioning and orgasm satisfaction at week 12 with placebo relative to desvenlafaxine treatment. Subgroup analyses of treatment responders and nonresponders found no difference in the proportion of men or women that developed or had resolution of sexual dysfunction in the desvenlafaxine and placebo groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Rosenthal et al.[69] (2013) Desvenlafaxine 50 mg/day vs placebo	DB, MC, PC, RCT Adult outpatients age >18 years of age with MDD (DSM-IV criteria) and a HDRS17 total score >20 at screening and baseline	N=874 11 months	Primary: Time to relapse (HDRS17 total score >16, discontinuation for unsatisfactory response, hospitalization for depression, suicide attempt, or suicide) Secondary: Safety and tolerability	Primary: Time to relapse was significantly shorter for placebo vs desvenlafaxine (P<0.001). At the end of the six-month DB treatment, the estimated probability of relapse was 30.2% for placebo vs 14.3% for desvenlafaxine 50 mg/day. Secondary: Safety and tolerability results were generally consistent with those in short-term studies of desvenlafaxine 50 mg/day.
Dunlop et al.[70] (2011) Desvenlafaxine 50 mg/day vs placebo	DB, PC, RCT Gainfully employed (≥20 hours/week) outpatients with MDD	N=427 12 weeks	Primary: HAM-D-17 total score Secondary: SDS, safety	Primary: Desvenlafaxine demonstrated superiority over placebo beginning at week two, which continued through week 12. Adjusted mean endpoint scores with desvenlafaxine and placebo were 9.33 and 11.45, respectively. Mean change scores were -12.61±0.45 and -10.50±0.60 with desvenlafaxine and placebo, respectively. The adjusted mean difference in change from baseline between desvenlafaxine and placebo at week 12 was 2.12 (95% CI, 0.78 to 3.46; P=0.002). Secondary: The adjusted mean difference in change from baseline score on the SDS between the desvenlafaxine and placebo at week 12 was 1.33 (95% CI, -0.09 to 2.76), which narrowly missed significance (P=0.067). There were six serious adverse events (no deaths) that occurred in four and two desvenlafaxine- and placebo-treated patients. None of these events were considered non-treatment related. No new safety concerns about desvenlafaxine were identified from safety analyses.
Kornstein et al.[71] (2010) Desvenlafaxine 100 or 200 mg/day	DB, MC, PC, RCT Perimenopausal and post-menopausal women 40 to 70	N=387 8 weeks	Primary: HAM-D-17 total score Secondary:	Primary: Baseline reductions in HAM-D-17 total scores were significantly greater with desvenlafaxine (adjusted mean change, -12.64) compared to placebo (-8.33; P<0.01). Significant differences between treatments were observed at week one (P=0.044) and were sustained though week eight (week two;

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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Rickels et al.[72] (2010) Desvenlafaxine 200 to 400 mg/day vs placebo After 12 weeks of OL treatment with desvenlafaxine, patients with HAM-D-17 total score ≤11 were randomized to continue desvenlafaxine or be switched to placebo.	DB, PC, RCT Patients 18 to 75 years of age with MDD, single or recurrent episode, without psychotic features	N=374 (DB phase) N=575 (OL phase) 12 weeks of OL treatment, followed by a 6 month, DB phase	Primary: Time until relapse (HAMD-D-17 total score ≥16 at any visit, CGI-I score ≥6 at any visit, or discontinuation due to unsatisfactory response) Secondary: HAM-D-17 total score, CGI-I, CGI-S, HAM-D-6, Covi Anxiety score, safety	Primary: Patients receiving desvenlafaxine experienced significantly longer times to relapse of MDD compared to patients receiving placebo during DB treatment (P<0.0001). The proportions of patients relapsing were 42 and 24% of patients receiving placebo and desvenlafaxine, respectively (P<0.001). Secondary: A significant difference in HAM-D-17 total scores in favor of desvenlafaxine was observed from DB week three onward (P<0.001). At the final evaluation, adjusted mean changes were 0.85 and 5.03 for desvenlafaxine and placebo, respectively. Desvenlafaxine was also associated with significant differences compared to placebo on CGI-I, CGI-S, HAM-D-6, and Covi Anxiety scores. The most common primary reason cited for discontinuation of treatment during the OL phase was adverse events (19%), which consisted of nausea, dizziness, and insomnia. A total of 101 (55%) and 58 (31%) patients receiving placebo and desvenlafaxine discontinued treatment during the DB phase. The most frequent adverse event reported as the reason for discontinuation during the DB phase was depression (14 patients receiving placebo vs seven patients receiving desvenlafaxine). During the OL phase the most commonly reported adverse events with desvenlafaxine were nausea (42%), dry mouth (32%), headache (26%), dizziness (23%), hyperhidrosis (21%), insomnia (20%), constipation (15%), decreased appetite (12%), fatigue (12%), somnolence (11%), diarrhea (10%), tremor (10%), vomiting (8%), sedation (5%), and blurred vision (5%). During the DB phase, treatment-emergent adverse events were reported by 73 and 82% of patients receiving desvenlafaxine and placebo, respectively. The most commonly reported events with desvenlafaxine were headache (24%), dizziness (15%), nausea (14%), fatigue (13%), hyperhidrosis (13%), diarrhea (9%), abnormal dreams (9%), depression (8%), insomnia (8%), influenza (7%), irritability (7%) , back pain (6%), upper respiratory tract infection (6%), abdominal pain (5%), anxiety (5%), muscle spasms (5%), nasopharyngitis (5%), tremor

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(5%), delayed ejaculation (5% in men), erectile dysfunction (5% in men), vomiting (4%), vertigo (3%), myalgia (2%), paresthesia (2%), and altered mood (1%).
Clayton et al.[73] (abstract) (2009) Desvenlafaxine 50 to 400 mg/day vs placebo	DB, PC, RCTs (integrated analysis of short-term 9 trials) Adult outpatients with MDD	N=2,950 8 weeks	Primary: Treatment-emergent adverse events, laboratory values, vital signs, discontinuation symptoms Secondary: Not reported	Primary: The most common treatment-emergent adverse event was transient nausea that was generally mild to moderate. The most common sexual dysfunction associated with desvenlafaxine treatment was erectile dysfunction in men (7 vs 1%) and anorgasmia in women (1 vs 0%). One patient receiving desvenlafaxine died of a completed suicide; there were four suicide attempts (three vs one patient[s]) and eight cases of suicidal ideation (five vs three patients) during the on-therapy period. Desvenlafaxine was associated with small but significant mean changes in laboratory assessments, particularly lipid and liver enzyme elevations, and ECGs; few cases of these changes were clinically relevant. Small but significant changes in mean blood pressure occurred with all desvenlafaxine doses; clinically meaningful changes were observed in 1 and 2% of placebo- and desvenlafaxine-treated patients. In the overall population, adverse events resulted in discontinuations in 3 and 12% of placebo- and desvenlafaxine-treated patients; in the subset of fixed-dose trials, the rates were 4 and 4 to 18% with placebo and desvenlafaxine. Secondary: Not reported
Feiger et al.[74] (2009) Desvenlafaxine 200 to 400 mg/day vs placebo	DB, MC, PC, PG, RCT Outpatients ≥18 years of age with MDD	N=235 8 weeks (plus a 2 week tapering phase)	Primary: HAM-D-17 Secondary: CGI-I, CGI-S, MADRS, HAM-D-6, safety	Primary: No significant difference was observed in the adjusted mean change from baseline in the HAM-D-17 total score between desvenlafaxine and placebo at the final evaluation (difference in adjusted means, 1.6; 95% CI, -0.2 to 3.4). No significant differences were observed between desvenlafaxine and placebo groups for HAM-D-17 clinical response rates at the final evaluation; the logistic regression analysis demonstrated adjusted ORs of 1.456 (95% CI, 0.85 to 2.50; P=0.175) for HAM-D-17 response. No

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				significant difference in HAM-D-17 remission rates was observed between desvenlafaxine and placebo groups at final evaluation; the logistic regression analysis showed an adjusted OR of 1.158 (95% CI, 0.60 to 2.22; P=0.66). Secondary: At final evaluation, significant differences between desvenlafaxine and placebo were observed for the CGI-I (difference in adjusted means: 0.3; 95% CI, 0.0 to 0.6), CGI-S (0.3; 95% CI, 0.0 to 0.6), MADRS (2.9; 95% CI, 0.3 to 5.4), and HAM-D-6 (1.5; 95% CI, 0.5 to 2.6). A significant difference was observed between desvenlafaxine and placebo groups for MADRS clinical response rates; the logistic regression analysis demonstrated an adjusted OR of 1.754 (95% CI, 1.03 to 3.00; P=0.04). Treatment-emergent adverse events were reported by 112 patients (96%) and 101 patients (86%) receiving desvenlafaxine and placebo. Treatment-emergent adverse events reported by ≥5% of patients receiving desvenlafaxine and at a frequency at least twice that of the placebo group included nausea, dry mouth, hyperhidrosis, insomnia, somnolence, decreased appetite, tremor, blurred vision, yawning, sedation, vomiting, mydriasis, middle insomnia, initial insomnia, erectile dysfunction, constipation, feeling jittery, and dyspepsia. Nausea, the most frequently reported adverse event in patients receiving desvenlafaxine (36%), was mild to moderate in the majority of cases (88%). Treatment-emergent adverse events resulted in reduction in dose of study medication for six (5%) and two (2%) patients receiving desvenlafaxine and placebo. Taper/post-study-emergent adverse events were consistent with what has been seen in pervious trials of desvenlafaxine and with the SNRIs. Significantly more patients receiving desvenlafaxine (12%) discontinued the study because of treatment-emergent adverse events compared to patients receiving placebo (3%; P=0.008). No deaths or serious adverse events occurred during the study.
Thase et al.[75] (2009)	MA (9 trials) Outpatients ≥18	N=3,023 8 weeks	Primary: HAM-D-17 total score	Primary: Significantly greater improvement with desvenlafaxine vs placebo on HAM-D-17 total scores was observed for the full data set (difference in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Desvenlafaxine 50 to 400 mg/day vs placebo	years of age with MDD		Secondary: MADRS, HAM-D-6, CGI-I, CGI-S, remission and response rates, safety	adjusted means, -1.9; P<0.001). Significance was observed in all fixed-dose (P<0.001 for all) and flexible-dose trials (P=0.24). Secondary: For the overall desvenlafaxine group significant improvement from baseline was observed on all secondary outcome measures at the final evaluation. Overall, desvenlafaxine had a significantly greater change from baseline compared to placebo on the CGI-I, CGI-S, and MADRS total scores from week two onward and in the core symptoms of depression (HAM-D-6 total score) from week one onward. Overall rates of HAM-D-17 response (53 vs 41%) and remission (32 vs 23%) were significantly greater with desvenlafaxine vs placebo (P<0.001 for all). Discontinuation rates due to adverse events increased with desvenlafaxine dose (4 to 18 vs 3%). The most common treatment-emergent adverse events in the overall data set were nausea, dry mouth, hyperhidrosis, dizziness, and constipation.
Boyer et al.[76] (2008) Desvenlafaxine 50 and 100 mg/day vs placebo	DB, MC, PC, PG, RCT Outpatients ≥18 years of age with MDD, depressive symptoms for ≥30 days before screening and baseline HAM-D-17 total score ≥20; HAM-D-17 item 1 (depressed mood) score ≥2; and CGI-S ≥4	N=438 8 weeks (plus a 1 week taper phase)	Primary: HAM-D-17 total score Secondary: CGI-I, MADRS, CGI-S, VAS-PI, Covi Anxiety Scale total scores, remission rates, responder rates, safety	Primary: In a LOCF analysis, adjusted mean baseline changes in HAM-D-17 total scores were significantly greater with desvenlafaxine 50 (-13.2; P=0.002) and 100 mg/day (-13.7; P<0.001) compared to placebo (-10.7). Secondary: Significant differences on CGI-I scores were observed with desvenlafaxine 50 (P=0.002) and 100 mg/day (P<0.001) compared to placebo. For MADRS total score, the between-group difference vs placebo in adjusted mean was 3.1 (95% CI, 1.0 to 5.2) with desvenlafaxine 50 mg/day and 4.2 (95% CI, 2.1 to 6.3) with desvenlafaxine 100 mg/day. Adjusted mean changes from baseline were significantly greater with desvenlafaxine compared to placebo starting at week four (P=0.036 and P=0.004, respectively), and were sustained until the final evaluation (P=0.004 and P<0.001, respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				For CGI-S score at final evaluation, adjusted mean changes from baseline were significantly greater than placebo for desvenlafaxine 50 (P=0.003) and 100 mg/day (P<0.001). Significant separation from placebo was observed beginning at week six and four for desvenlafaxine 50 (P=0.002) and 100 mg/day (P=0.027), and both groups remained significantly different through the final evaluation. Results of the VAS-PI are not reported because of the heterogeneity of the format of the translated scale; it was impossible to properly analyze the corresponding data. For Covi Anxiety Scale total score at final evaluation, adjusted mean changes from baseline were significantly greater than placebo for desvenlafaxine 50 (P=0.001) and 100 mg/day (P=0.004). The adjusted OR for response relative to placebo was 1.943 (95% CI, 1.24 to 3.05) and 1.798 (95% CI, 1.14 to 2.83) with desvenlafaxine 50 and 100 mg/day (P=0.004 and P=0.011). For remission rates, the adjusted OR for remission relative to placebo was 1.488 (95% CI, 0.93 to 2.38) and 2.117 (95% CI, 1.32 to 3.39) with desvenlafaxine 50 and 100 mg/day (P=0.099 and P=0.002). Responder rates were significantly higher with desvenlafaxine 50 (65%) and 100 mg/day (63%) compared to placebo (50%; P=0.005 and P=0.018, respectively; NNT, 6.5 and 7.4). Significantly more patients receiving desvenlafaxine 100 mg/day achieved remission compared to patients receiving placebo (45 vs 29%, respectively; P=0.003; NNT, 6.1). Most of the treatment-emergent adverse events were mild or moderate in severity. The most common treatment-emergent adverse events were nausea, dizziness, insomnia, constipation, fatigue, anxiety, and decreased appetite.
Liebowitz et al.[77] (abstract) (2008) Desvenlafaxine 50 or 100 mg/day	DB, MC, PC, PG, RCT Patients 18 to 75 years of age with a primary diagnosis	N=447 8 weeks (plus a 1 week taper)	Primary: Change from baseline to final on-therapy evaluation on HAM-D-17score	Primary: There was a significant decrease in the HAM-D-17 score from baseline in the desvenlafaxine 50 mg group (-11.5; P=0.018) but not for the desvenlafaxine 100 mg group (-11; P=0.065) compared to the placebo group (-9.53).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	of MDD, depressive symptoms ≥30 days prior to screening, HAM-D-17 total score ≥20, and CGI-S score ≥4		Secondary: Change from baseline in CGI-I, CGI-S, MADRS, VAS-PI, HAM-D-17 rate of response (percentage of patients with a HAM-D-17 score decrease of ≥50%), HAM-D-17 rate of remission (percentage of patients with a HAM-D-17score decrease to ≤7%), SDS, WHO-5, safety	Secondary: The decrease from baseline in the CGI-I score was not considered significant for the desvenlafaxine 50 mg group (P=0.085) and the 100 mg group (P=0.076) compared to the placebo group. The decrease from baseline in CGI-S scores were not significantly different than the desvenlafaxine 50 mg (P=0.074) and 100 mg groups (P=0.208) compared to the placebo group. There was a significant decrease from baseline in MADRS scores in the desvenlafaxine 50 mg group (P=0.022) but not the 100 mg group (P=0.095). VAS-PI overall pain score showed significant improvement compared to baseline in the 100 mg group (P=0.041) but not for the 50 mg group (P=0.223). There was no significant difference between the desvenlafaxine 50 and 100 mg groups compared to the placebo group in terms of HAM-D-17 rates of response (P=0.133, P=0.246, respectively) and remission (P=0.075, P=0.194, respectively). The desvenlafaxine 50 mg group showed significant improvements from baseline in SDS score (-8.96; P=0.012) and WHO-5 score (6.68; P=0.020) compared to the placebo group. There were no significant differences from baseline in the 100 mg group compared to the placebo group in SDS or WHO-5 score. The most common adverse events seen (incidence ≥10% and at twice the rate in the placebo group) with desvenlafaxine treatment included: dry mouth, constipation, insomnia, decreased appetite, hyperhidrosis and dizziness (P values not reported).
Liebowitz et al.[78] (2007) Desvenlafaxine 100 mg/day for days 1 to 14,	DB, MC, PC, PG, RCT Patients 18 to 75 years of age with a primary diagnosis	N=247 8 weeks	Primary: Change from baseline to final on-therapy evaluation on HAM-D-17 score	Primary: There was no significant difference in the reduction of HAM-D-17 score from baseline between the desvenlafaxine and placebo group (14.1 vs 15.1 respectively; P=0.277). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
increasing to 200 mg/day vs placebo	of MDD, depressive symptoms ≥30 days prior to screening, HAM-D-17 total score ≥20, a HAM-D item 1 (depressed mood) score ≥2 and CGI-S score ≥4		Secondary: Change from baseline in CGI-I, MADRS, CGI-S, VAS-PI, vital signs, safety	There was no significant difference between CGI-I scores between the desvenlafaxine and the placebo group compared to baseline (2.5 vs 2.7 respectively; P value not reported). The CGI-S showed no difference from baseline between the desvenlafaxine and placebo groups (3.1 vs 3.3 respectively; P value not reported). Improvement was demonstrated at final evaluation between desvenlafaxine and placebo on the MADRS scale (16.8 vs 19.5 respectively; P=0.047), the VAS-PI overall pain scale (15.6 vs 11.6 respectively; P=0.008), the VAS-PI back pain scale (13.1 vs 20.5 respectively; P=0.006) and the VAS-PI arm, leg or joint pain scale (13.3 vs 21.6 respectively; P<0.001). There was a significant increase from baseline in supine SBP (3.76 vs -1.59; P<0.001, respectively) and supine DBP (1.85 vs -0.91; P=0.003 respectively) in the desvenlafaxine group compared to the placebo group. There was a significant decrease in body weight seen in the desvenlafaxine group compared to the placebo group (-0.74 vs 0.36 kg; P<0.001). There was an increase in heart rate from baseline observed in the desvenlafaxine group (4.27 beats per minute; P<0.01) and a decrease from baseline in the placebo group (-2.27 beats per minute; P<0.01). A decrease in the QT interval was observed in the desvenlafaxine group from baseline (-4.27 ms; P value not significant) and an increase in QT interval from baseline was observed in the placebo group (4.90; P<0.05). The difference in these values was considered to be statistically significant (P=0.01). Anorexia (P<0.001), constipation (P<0.05), dry mouth (P<0.01), nausea (P<0.001), tremor (P<0.01) and yawning (P<0.01) were seen more commonly in the desvenlafaxine group compared to the placebo group.
Demartinis et al.[79] (2007) Desvenlafaxine	DB, MC, PC, PG, RCT Patients 18 to 75	N=461 8 weeks (plus a 2 week	Primary: Change from baseline to final on-therapy	Primary: Decrease in HAM-D-17 score from baseline was significantly greater at final on-therapy evaluation in the 100 mg (-10.60; P=0.0038) and 400 mg (-10.75; P=0.0023) groups compared to the placebo group (-7.65).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
100, 200, or 400 mg/day vs placebo	years of age with a primary diagnosis of MDD, depressive symptoms ≥30 days prior to screening, HAM-D-17 total score ≥20, a Ham-D item 1 (depressed mood) score ≥2 and CGI-S score ≥4	taper)	evaluation on HAM-D-17 score Secondary: Change from baseline in CGI-I, CGI-S, MADRS, VAS-PI, HAM-D-17 rate of response (percentage of patients with a HAM-D-17 score decrease ≥50%), HAM-D-17 rate of remission (percentage of patients with a HAM-D-17 score decrease to ≤7%), SDS, WHO-5, vital signs, safety	However, the decrease in HAM-D-17 score from baseline in the 200 mg group was not significant (-9.63; P=0.0764) compared to the placebo group. Secondary: There were significant decreases in CGI-I score from baseline for the 100 mg (2.3; P=0.008), 200 mg (2.5; P=0.0462) and 400 mg (2.4; P=0.0129) groups compared to the placebo treated group (2.8). There were significant decreases in CGI-S scores from baseline in the 100 mg (-1.5; 95% CI, 0.2 to 0.8; P=0.002) and 400 mg (-1.5; 95% CI, 0.2 to 0.9; P<0.001) groups compared to the placebo group (-1.0). The CGI-S score difference observed in the 200 mg group was not significant (-1.13; 95% CI, 0.0 to 0.6; P=0.056). The decrease from baseline in MADRS score was significant for the 100 mg group (-13.6; 95% CI, 1.3 to 6.4; P=0.004), the 200 mg group (-13.5; 95% CI, 1.3 to 6.2; P=0.005), and the 400 mg group (-15.2; 95% CI, 3.1 to 8.3; P<0.001) compared to the placebo group (-9.9). Patients in the desvenlafaxine 100 mg group showed a significant improvement from baseline in overall pain score compared to the placebo group on the VAS-PI scale (-13.9 vs 5.9; P=0.002, respectively). There was no significant difference in either the 200 mg (-5.4; P=0.357) or the 400 mg (-10.1; P=0.069) groups. There was a significantly higher OR for response to the 100 mg group (2.15; 95% CI, 1.25 to 3.73; P=0.006) and 400 mg group (1.91; 95% CI, 1.11 to 3.32; P=0.020). The OR for response to the 200 mg group was not significant (1.60; 95% CI, 0.93 to 2.76; P=0.089) compared to the placebo group. There was a significantly higher OR for remission in the 400 mg group compared to the placebo group (2.20; 95% CI, 1.17 to 4.14; P=0.014). The OR of the 100 mg group (1.86; 95% CI, 0.99 to 3.52; P=0.053) and 200 mg group (1.73; 95% CI, 0.92 to 3.26; P=0.088) were not significant compared to the placebo group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There was a statistically significant increase in supine pulse rate in the desvenlafaxine 400 mg group compared to baseline (4.19; P<0.001). The increase was considered statistically significant when compared to the placebo group (0.15; P<0.05). The change in supine pulse rate from baseline in the desvenlafaxine 100 mg (-0.03) and 200 mg (1.06) groups were not considered significant compared to the placebo group (P value not significant). The mean increase in supine SBP was considered significant in all groups compared to baseline compared to the placebo group (P<0.05). The increase in DBP was considered significant in all treatment groups compared to baseline (P<0.001 for the 200 and 400 mg groups and P<0.01 for 100 mg group). There was a significant increase in DBP from baseline in both the desvenlafaxine 200 and 400 mg groups compared to the placebo group (P<0.05). The increase in DBP from baseline in the 100 mg group was not considered significant compared to the placebo group (P value not significant). There was a significant decrease in body weight in all desvenlafaxine treatment groups compared to baseline (P<0.001) and to the placebo group (P<0.05). Adverse events that occurred at twice the rate of placebo in at least 5% of desvenlafaxine-treated subjects included: nausea, somnolence, insomnia, dry mouth, sweating, dizziness, nervousness, anorexia, constipation, abnormal ejaculation/orgasm, asthenia and tremor (P values not reported).
Septein-Velez et al.[80] (2007) Desvenlafaxine 200 or 400 mg/day vs placebo	DB, MC, PC, PG, RCT Outpatients 18 to 75 years of age with a primary diagnosis of MDD, depressive symptoms ≥30 days prior to screening, HAM-D-17 total score ≥20, and CGI-S score ≥4	N=369 8 weeks (plus a 2 week taper)	Primary: Change from baseline to final on-therapy evaluation on HAM-D-17 score Secondary: Change from baseline in CGI-I, CGI-S, MADRS, VAS-PI, HAM-D-	Primary: The decrease from baseline in HAM-D-17 score was significantly greater in the 200 mg group (-12.6; P=0.002) and the 400 mg group (-12.1; P=0.008) compared to the placebo group (-9.3). Secondary: A lower CGI-I score was observed in the 200 mg group (P=0.004) and the 400 mg group (P=0.028) compared to the placebo group. There was a significant difference in change in MADRS score from baseline favoring desvenlafaxine in the 200 mg (P=0.001) and 400 mg (P=0.005) groups compared to the placebo group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			17 rate of response (percentage of patients with a HAM-D-17 score decrease ≥50%), HAM-D-17 rate of remission (percentage of patients with a HAM-D-17 score decrease to ≤7%), SDS, WHO-5	There was a significant difference in change in CGI-S score from baseline favoring patients treated with desvenlafaxine compared to patient treated with placebo (P=0.001 and P=0.013 for the desvenlafaxine 200 and 400 mg groups, respectively). There was a greater response on the HAM-D-17 rate of response assessment for the 200 mg (60%; P<0.001) and 400 mg (56%; P=0.005) groups compared to the placebo group (38%). A greater degree of remission was observed for the 200 mg group (37%; P=0.017) compared to the placebo group (23%). The degree of remission was not significant for the 400 mg group (P value not reported). The change in VAS-PI overall pain score from baseline favored the desvenlafaxine 200 mg group (P=0.002) compared to the placebo group. The difference between the 400 mg group and the placebo group was not considered significant (P=0.053). There was a significant improvement from baseline in SDS total score for the desvenlafaxine 200 mg (P=0.004) and 400 mg (P=0.004) groups compared to the placebo group. There was a significant improvement from baseline in WHO-5 score for the desvenlafaxine 200 mg (P=0.001) and 400 mg (P=0.005) groups compared to the placebo group.
Tourian et al.[81] (2013) Desvenlafaxine 25 mg/day from days 1 to 14, with subsequent upward titration, to a maximum of 100 mg/day, determined by clinical response	MC, OL Japanese patients with MDD who had completed an 8-week, DB, PC study in which patients received 25 or 50 mg/day desvenlafaxine or placebo	N=304 10 weeks	Primary: Safety, HAM-D17 Secondary: Not reported	Primary: Treatment-emergent adverse events were reported by 240 patients (78.9%) during the on-therapy period; the most common adverse events were nasopharyngitis (37.2%), somnolence (11.5%), headache (10.5%), and nausea (10.2%). For the ITT-LOCF population, the mean change from baseline in the HAM-D17 total score was -4.76 (95% CI, -5.47 to -4.05). Continued numerical improvements in the HAM-D17 total scores and other depression outcome measures were observed irrespective of treatment in the previous study. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Soares et al.[82] (2011) Desvenlafaxine 100 to 200 mg/day	MC, OL Post-menopausal women 40 to 70 years of age with MDD who did not achieve clinical response to acute, DB treatment with desvenlafaxine or escitalopram	N=123 6 months	Primary: HAM-D-17 total score Secondary: CGI-I, HAMA, QIDS-SR, VAS-PI, MADRS, CSFQ, EQ-5D, health state today, MRS, SDS, treatment response (HAM-D-17 and MADRS based), safety	Primary: At final evaluation, mean reductions from acute-phase baseline HAM-D-17 total scores were -11.33 and -11.41 with desvenlafaxine/desvenlafaxine and escitalopram/desvenlafaxine. Mean reductions from week eight of acute phase at the final evaluation of the OL extension phase were -6.13 and -6.59, respectively. Consistent improvements in mean HAM-D-17 total scores were observed among patients in both treatment groups from baselines of both the DB acute phase and the OL extension phase. Secondary: Improvements were demonstrated for additional efficacy and health outcome measures for patients in both groups during the OL extension phase. Throughout the course of the overall study, desvenlafaxine/ desvenlafaxine patients achieved mean improvements from baseline in CSFQ total scores after the acute phase and OL extension phase of 1.58±6.84 and 1.84±4.01, respectively; escitalopram/desvenlafaxine patients experienced improvements of 0.71±6.08 and 2.60±6.28 from respective baselines. HAM-D-17 response or remission rates after six months were achieved in 56 to 58 and 41 to 48% of desvenlafaxine/desvenlafaxine and escitalopram/desvenlafaxine patients. MADRS response rates were 72 and 64%, respectively. The median time to remission was 68 (95% CI, 41 to 84) and 70 days (95% CI, 44 to 125) with desvenlafaxine/desvenlafaxine and escitalopram/ desvenlafaxine patients. Treatment-emergent adverse events were reported by 91% of patients, the most common being headache (17%), insomnia (17%), nausea (16%), dizziness (15%), infection (15%), abnormal dreams (12%), dry mouth (11%), pain (11%), and sweating (10%).
Ferguson et al.[83] (2010) Desvenlafaxine 100 or 200 mg/day	MC, OL Outpatients ≥65 years of age with MDD	N=52 (safety analysis) ≤6 months	Primary: Safety Secondary: HAM-D-17 total scores	Primary: The most frequently reported adverse events were mild or moderate nausea (40%), dizziness (25%), and headache (21%). Primary and secondary adverse events led to discontinuation of treatment for 18 (35%) patients. The most common event cited as reasons for discontinuation were hypertension (10%) and nausea (10%). Two patients experienced three serious adverse events.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: After three months of treatment, mean total HAM-D-17 score decreased 9.20 points (LOCF) from a baseline score of 21.68±3.20. This improvement was maintained for the duration of the trial; the mean change from baseline at final evaluation at month six was -9.28 points, resulting in a mean HAM-D-17 total score of 12.40±7.19. These improvements were maintained without dose escalation. HAM-D-17 based response rates were 42% (LOCF) at month three. The clinical responses were maintained by 65% of patients at month six. HAM-D-17 based remission rates were 28% at month two, which were maintained by 30% of patients at month six.
Soares et al.[84] (2010) Desvenlafaxine 100 to 200 mg/day vs escitalopram 10 to 20 mg/day	AC, DB, MC, RCT Postmenopausal women 40 to 70 years of age with MDD	N=607 Acute phase: 8 weeks Continuation phase: 6 months	Primary: HAM-D_{17} total score, response and remission rates, anxiety scores, QOL, menopause-related symptoms, safety and tolerability Secondary: Not reported	Primary: <u>Acute phase</u> There was no significant difference in HAM-D_{17} total score with desvenlafaxine and escitalopram (-13.63 vs -14.30, respectively; P=0.243). There were no significant differences in secondary efficacy and health outcomes data related to depression between treatment groups. On assessments of menopause-related symptoms, there were no significant between-group differences, and improvements from baseline were comparable for both groups. Significantly higher rates were found for escitalopram compared to desvenlafaxine for HAM-D_{17} remission (48 vs 38%, respectively; P<0.01) and response (73 vs 64%, respectively; P<0.05). No significant differences between the escitalopram and desvenlafaxine groups were observed in rates of response on the MADRS (70 and 67%, respectively) and CGI-I (75 and 70%, respectively). <u>Continuation phase</u> The proportion of women who maintained or improved their HAM-D_{17} response to treatment was similar between the treatment groups (desvenlafaxine, 82%; escitalopram, 80%; P=0.702).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There were no significant differences between treatment groups in the proportion of women who achieved HAM-D_{17} remission during the continuation phase or at endpoint (desvenlafaxine, 68%; escitalopram, 61%; P=0.234). There were no significant differences between the desvenlafaxine and escitalopram groups in rates of response on the MADRS (92 and 88%, respectively) and CGI-I (90 and 86%, respectively). No significant differences between groups were found at endpoint in the analyses of secondary efficacy data or core health outcome measures, including assessments of menopause-related symptoms. In both phases, desvenlafaxine and escitalopram were generally safe and well tolerated. Secondary: Not reported
Acharya et al.[85] (2006) Duloxetine 40 to 120 mg daily vs placebo	MA (12 trials) Patients taking duloxetine for MDD	N=2,996 Duration varied	Primary: Incidence of suicide-related events with duloxetine (MHID, MHRD, HAM-D Item-3) Secondary: Not reported	Primary: There were no significant differences in the incidence of suicide-related events with duloxetine vs placebo. The MHID for suicide-related behaviors was -0.03% (95% CI, -0.48 to 0.42) and MHRD -0.002 (95% CI, -0.02 to 0.02). Changes in HAM-D Item-3 suicidality scores showed a greater improvement with duloxetine (P<0.001) and less worsening of suicidal ideation with duloxetine (P<0.001). Secondary: Not reported
Gaynor et al.[86] (2011) Duloxetine 60 mg QD	DB, MC, PC, RCT Patients ≥18 years of age with a current episode of	N=528 8 weeks	Primary: Mean change in MADRS total score and BPI average pain rating	Primary: Treatment with duloxetine resulted in a significantly greater improvement in MADRS total score compared to treatment with placebo (-16.77 vs -12.73, respectively; 57.9 vs 44.3% improvement from baseline, respectively; P<0.001). Duloxetine was more effective than placebo

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	MDD and at least moderate pain		Secondary: Remission, PGI-I, SDS global functional impairment score, safety	beginning at week two and at all remaining visits (P≤0.001). There was a significantly greater reduction in average pain rating from baseline to week eight with duloxetine compared to placebo (-1.93 vs -1.31, respectively; 35.1 vs 22.9% reduction in pain, respectively; P≤0.001). Patients also had a greater improvement in their average pain rating at weeks one, two, four, and eight with duloxetine compared to placebo (all P≤0.005). Secondary: A significantly greater proportion of patients receiving duloxetine met the criteria for remission than patients receiving placebo (P≤0.01). Overall scores for 'worst pain' and 'least pain' in the last 24 hours and for 'pain right now' were also reduced with duloxetine vs placebo (all P≤0.001). The least squares mean PGI-I score demonstrated significantly greater improvements with duloxetine compared to placebo (P≤0.021). Scores of 1 ('very much better') or 2 ('much better') were reported by a significantly greater percentage of patients in the duloxetine group (50.8%) compared to the placebo group (35.2%; P≤0.001). Patients receiving duloxetine demonstrated significantly greater improvements in the SDS global functional impairment score compared to patients receiving placebo (48.2 vs 37.7%, respectively; P=0.019). Improvements in the individual items addressing social life/leisure activities and family life/home responsibilities were greater with duloxetine compared to placebo (P≤0.05). The improvement in the item addressing school/work life was not significantly different between duloxetine and placebo (P=0.112). Treatment emergent adverse events with duloxetine were nausea, somnolence, constipation, decreased appetite, and hyperhidrosis. Rates of discontinuation due to adverse events were greater for duloxetine than placebo (8.0 vs 3.4%, respectively; P=0.024).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Gaynor et al.[87] (2011) Duloxetine 60 mg QD vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with a current episode of MDD and at least moderate pain	N=527 8 weeks	Primary: Mean change in MADRS total score and BPI average pain rating Secondary: Remission, PGI-I, SDS global functional impairment score	Primary: Treatment with duloxetine resulted in a significantly greater improvement in MADRS total score compared to treatment with placebo (-14.96 vs -10.77, respectively; 48.3 vs 34.8% improvement from baseline, respectively; P<0.001). There was a significantly greater reduction in average pain rating from baseline to week eight with duloxetine compared to placebo (-1.66 vs -1.17, respectively; 27.7 vs 18.9% reduction in pain, respectively; P<0.001). Patients also had greater improvement in their average pain rating at weeks two, four, and eight with duloxetine compared to placebo (all P<0.01). Secondary: A significantly higher percentage of patients receiving duloxetine (37.3%) met the criteria for remission compared to patients receiving placebo (23.0%; P<0.001). Greater improvements were observed for the other pain severity ratings (worst pain; P<0.001, least pain; P=0.003, pain right now; P<0.001), as well as ratings of interference of pain with functioning (all P<0.05) with duloxetine vs placebo. The least squares mean PGI-I score demonstrated significantly greater improvements with duloxetine compared to placebo (P≤0.01). Scores of 1 (‘very much better’) or 2 (‘much better’) were reported by a significantly greater percentage of patients in the duloxetine group compared to the placebo group (53.3 vs 26.8%, respectively; P<0.001). Patients receiving duloxetine demonstrated significantly greater improvements in the SDS global functional impairment score compared to placebo (46.4 vs 31.8%, respectively; P<0.001).
Rosso et al.[88] (2012) Duloxetine 120 mg/day	RCT, SB Patients ≥18 years of age with MDD who failed to	N=49 6 weeks	Primary: Change in HAM-D-17 Secondary:	Primary: There was no significant difference in HAM-D-17 total score among the treatment groups (P=0.793). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs bupropion ER 300 mg/day	respond to 2 consecutive antidepressant trials with SSRIs		CGI-S, GAF	There was no significant difference in CGI-S (P=0.653) or GAF (P=0.565) scores among the treatment groups. Compared to baseline, there was a significant improvement in HAM-D-17 and CGI-S total scores with duloxetine and bupropion ER compared to baseline (all P<0.001). The 6-item-HAM-D mean score decreased significantly by week two with duloxetine (from 11.84 to 6.04; P<0.001) and bupropion ER (from 12.05 to 5.52; P<0.001). There was no difference in the success rates (HAM-D response, HAM-D remission) between the treatment groups. Additional information obtained by the CGI-S success rate confirmed this finding.
Nierenberg et al.[89] (2007) Duloxetine 60 mg daily vs escitalopram 10 mg daily vs placebo	AC, DB, PC, RCT Patients ≥18 years of age with MDD	N=547 8 weeks	Primary: Percentage of patients achieving onset criteria at week two (defined as 20% decrease from baseline in HAM-D) Secondary: Not reported	Primary: No significant difference was observed in the probability of patients meeting onset criteria at week two between the duloxetine group and the escitalopram group (P=0.097). Duloxetine and escitalopram both showed significant improvement compared to placebo on primary efficacy analysis at week one and week eight (P≤0.05). Secondary: Not reported
Pigott et al.[90] (2007) <u>Acute Phase</u> Duloxetine 60 mg/day vs	DB, MC, PC, RCT Patients >18 years of age with MDD	N=684 <u>Acute Phase</u> 8 weeks <u>Extension Phase</u> 24 weeks	Primary: HAM-D_{17}, CGI-S, PGI-I, HAMA, remission rates Secondary: Not reported	Primary: After eight months of treatment, there were no significant differences in efficacy between duloxetine and escitalopram as assessed by mean changes from baseline in the HAM-D_{17} total score and the HAM-D_{17} Maier, anxiety/somatization, and retardation/ somatization subscales. The only HAM-D_{17} subscale with a significant drug difference was the HAM-D_{17} sleep subscale, which demonstrated that escitalopram was associated with a significantly greater improvement in insomnia than

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
escitalopram 10 mg/day vs placebo Extension Phase Duloxetine 60 to 120 mg/day vs escitalopram 10 to 20 mg/day				duloxetine at the eight-month study endpoint. There were no significant differences in efficacy among the treatment groups as assessed by the CGI-S and the PGI-I. After eight months of treatment, there were no significant differences between the treatment groups with regards to anxiety symptoms as measured by the HAMA total score and the HAMA subscales (psychic and somatic). There was no significant difference in remission at eight weeks (duloxetine 40%, escitalopram 33%; P=0.25) or at eight months (duloxetine 70%, escitalopram 75%; P=0.44). Secondary: Not reported
Detke et al.[91] (2004) Duloxetine 40 or 60 mg BID vs paroxetine 20 mg/day vs placebo After acute treatment, patients who had a ≥30% reduction in baseline HAM-D-17 total score were	DB, PC, RCT Outpatients ≥18 years of age with MDD	N=367 (acute phase) N=273 (continuation phase) 8 weeks of acute treatment plus a 6 month continuation phase	Primary: HAM-D-17 total scores Secondary: HAM-D-17 subscales, MADRS, HAMA, VAS for pain, CGI-S, PGI-I, SSI, SDS, safety	Primary: In the acute phase, patients treated with duloxetine had significantly greater improvement in HAM-D-17 total scores at week eight (P=0.001 and P<0.001) compared to patients treated with placebo. Paroxetine also demonstrated significant superiority over placebo at week eight (P<0.001). In the acute phase, estimated probabilities of response at week eight for patients receiving duloxetine 80 (70%) and 120 mg/day (77%) were significantly more efficacious to that of placebo (47%; P=0.005 and P<0.001). The estimated probability of response for paroxetine-treated patients was also significantly greater compared to placebo-treated patients (P<0.001). In the acute phase, estimated probabilities of remission for patients receiving duloxetine 80 and 120 mg/day, and paroxetine 20 mg/day were significantly more efficacious to patients receiving placebo at week eight. In the continuation phase, patients within each active treatment group demonstrated significant within-group improvement in HAM-D-17 total score.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
allowed to continue on the same (blinded) treatment for a 6 month continuation phase.				In the continuation phase, a log-rank test demonstrated that duloxetine 80 mg/day, duloxetine 120 mg/day, and paroxetine each had a significantly longer time to loss of response compared to placebo (P=0.002, P=0.018, and P=0.002, respectively). Secondary: In the acute phase, duloxetine 80 mg/day, duloxetine 120 mg/day, and paroxetine showed significantly greater improvement on the HAM-D-17 anxiety/somatization, core factor, maier, and retardation subscales compared to placebo. Paroxetine-treated patients showed a significant improvement on the sleep subscale compared to patients receiving placebo. In the acute phase, patients receiving duloxetine 80 mg/day, duloxetine 120 mg/day, or paroxetine 20 mg/day has significantly greater improvements in MADRS (P≤0.001 vs placebo for all, P≤0.05 for duloxetine 120 vs 80 mg/day), HAMA (P≤0.01 for duloxetine 80 mg/day vs placebo, P≤0.001 for duloxetine 120 mg/day and paroxetine vs placebo), CGI-S (P≤0.001 for all comparisons), and PGI-I (P≤0.01 for duloxetine 80 mg/day vs placebo, P≤0.001 for duloxetine 120 mg/day and paroxetine vs placebo, P≤0.05 for duloxetine 80 mg/day vs paroxetine) scales compared to patients receiving placebo. In the acute phase, patients receiving duloxetine or paroxetine showed significantly greater improvement on both SSI 26- and 28-Item Averages compared to placebo-treated patients. Using mean change analysis, in the acute phase patients treated with duloxetine and paroxetine showed significantly greater improvement on the SDS work item, social life item, family life item, and total score compared to patients receiving placebo. In the continuation phase, patients within each active treatment group demonstrated significant within-group improvement in MADRS, HAMA, CGI-S, and PGI-I. Patients receiving placebo exhibited significant within-group improvement in HAMA and PGI-I.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				In the continuation phase, patients receiving duloxetine 120 mg/day showed marginally significant improvement from baseline on the SSI 28-Item Average (P=0.054), while improvement was significant for the Pain Item Average (P=0.034). There were no deaths during the acute treatment phase. One serious adverse event occurred in a patient receiving paroxetine, but was considered to be non-treatment related. The proportion of patients who discontinued the study due to adverse events did not differ significantly across treatment groups (4.2, 3.2, 3.5, and 3.2%; P=1.00). The only adverse event leading to discontinuation in more than one patient within any treatment group was headache (two patients receiving duloxetine 120 mg/day). Treatment-emergent adverse events experienced by ≥5% of patients receiving duloxetine 120 mg/day are constipation, dry mouth, increased sweating, somnolence, nausea, headache, and insomnia. Three patients died during the six-month continuation phase (one patient receiving duloxetine 120 mg/day and placebo died as a result of suicide, while one patient receiving duloxetine 80 mg/day died as a result of pulmonary edema). All three deaths were considered to be non-treatment related. Serious adverse events were reported by one placebo-treated patient, one duloxetine 80 mg/day-treated patient, and four duloxetine 120 mg/day-treated patients. The proportions of patients discontinuing treatment due to an adverse event were similar across groups.
Goldstein et al.[92] (2004) Duloxetine 20 to 40 mg BID vs paroxetine 20 mg daily vs	DB, PC, RCT Outpatients with depression	N=353 8 weeks	Primary: HAM-D Secondary: Adverse effects	Primary: Duloxetine 80 mg/day was more effective than placebo on mean HAM-D-17 total change by 3.62 points (95% CI, 1.38 to 5.86; P=0.002). Duloxetine 40 mg/day was also significantly more efficacious than placebo by 2.43 points (95% CI, 0.19 to 4.66; P=0.034), while paroxetine was not (1.51 points; 95% CI, -0.55 to 3.56; P=0.150). Duloxetine 80 mg/day was more efficacious than placebo for most other measures, including overall pain severity, and was more efficacious than paroxetine on the HAM-D-17 improvement (by 2.39 points; 95% CI, 0.14 to 4.65; P=0.037) and estimated probability of remission (57% for duloxetine 80 mg/day, 34% for paroxetine; P=0.022).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				Secondary: The only adverse event reported significantly more frequently for duloxetine 80 mg/day than for paroxetine was insomnia (19.8% for duloxetine 80 mg/day, 8.0% for paroxetine; P=0.031).
Perahia et al.[93] (2006) Duloxetine 40 mg BID vs duloxetine 60 mg BID vs paroxetine 20 mg daily vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with MDD	N=392 8 months	Primary: Mean change from baseline in HAM-D-17 Secondary: Discontinuation of study drug due to adverse drug events	Primary: Patients treated with duloxetine 80 and 120 mg/day had significantly greater improvement in HAM-D-17 total scores at week eight compared to placebo-treated patients (P=0.045 and P=0.014, respectively). Paroxetine was not significantly different from placebo (P=0.089) on mean change on the HAM-D-17. Secondary: The proportion of patients who discontinued the study due to adverse events did not differ significantly (P=0.836) across treatment groups; placebo (2.0%), duloxetine 80 mg/day (4.3%), duloxetine 120 mg/day (3.9%), and paroxetine 20 mg (4.1%).
Goldstein et al.[94] (abstract) (2002) Duloxetine, titrated from 20 to 60 mg BID vs placebo vs	DB, MC, PC, RCT Patients 18 to 75 years of age with MDD	N=173 8 weeks	Primary: HAM-D-17 total score Secondary: MADRS, CGI-S, CGI-I, PGI-I, safety	Primary: Duloxetine was more efficacious to placebo in change in HAM-D-17 total score (P=0.009). Estimated probabilities of response and remission were 64 and 56%, respectively, with duloxetine compared to 52 and 30% with fluoxetine, and 48 and 32% with placebo. Duloxetine was numerically more efficacious to fluoxetine on the primary outcome. Secondary: Duloxetine was numerically more efficacious to fluoxetine on most secondary outcomes.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
fluoxetine 20 mg/day				Duloxetine was well tolerated; 76% of patients achieved the maximum dose, and insomnia and asthenia were the only adverse events reported significantly more frequently compared to placebo (P<0.05).
Martinez et al.[95] (2012) Duloxetine 30 to 120 mg QD vs generic SSRIs (citalopram 20 to 40 mg/day, fluoxetine 20 to 80 mg/day, paroxetine 20 to 50 mg/day, or sertraline 50 to 200 mg/day at the investigator's discretion)	AC, MC, RCT Adult outpatients with severe MDD	N=750 12 weeks	Primary: Remission at week 12 as measured by QIDS-SR Secondary: Response as measured by QIDS-SR, probability of response and remission as measured by HAM-D_{17}, BPI, SDS	Primary: Remission rates derived from the QIDS-SR at week 12 did not significantly differ between the duloxetine and SSRI treatment groups (36 vs 32%, respectively). The groups did not differ significantly with respect to changes in QIDS-SR scores across 12 weeks of therapy. Secondary: The QIDS-SR estimated probability of response did not differ significantly between duloxetine-treated and SSRI-treated patients (71 vs 64%; P=0.085). On the HAM-D_{17}, patients treated with duloxetine had significantly greater probabilities of response compared to patients treated with SSRIs (73 vs 61%; P=0.001) and remission (53 vs 44%; P=0.034). The NNT for one additional case of remission was 25 for the QIDS-SR, and was 12 for the HAM-D_{17}. The NNT for one additional case of response was 15 for the QIDS-SR, and was 9 for the HAM-D_{17}. Patients treated with duloxetine demonstrated significantly greater mean changes on the HAM-D_{17} total score and HAM-D subscales (anxiety/ somatization, Bech, Maier, and retardation). Improvement in associated painful symptoms was significantly greater with duloxetine compared to SSRIs as measured by the mean change in the BPI 24-hour average pain score in both the pain-enriched cohort of patients (P=0.034) and in the entire study population (P=0.030). Patients receiving duloxetine demonstrated significantly greater improvements on the SDS global functional score (P=0.002), and on each of the individual items that measure work/school (P=0.013), family functioning (P=0.015), and social functioning (P=0.005) compared to SSRIs. Dry mouth and constipation occurred at a significantly greater rate in patients treated with duloxetine vs patients treated with SSRIs (P=0.023 and 0.003, respectively). There was no significant difference between

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				duloxetine and the SSRI group in the occurrence of any of the other most commonly reported treatment emergent adverse events.
Mancini et al.[96] (2012) Duloxetine vs placebo	MA (6DB, PC, PG, RCT) Patients with MDD	N=2,496 Short-term (7 to 13 weeks) and the long-term (>24 weeks) endpoint	Primary: SDS total score Secondary: Functional remission (SDS total< 6) rates, VAS	Primary: The between-treatment difference of -2.52 between duloxetine and placebo in the SDS total score at the short-term endpoint was statistically significant in favor of duloxetine vs placebo (95% CI, -3.17, -1.87; P<0.001). Secondary: The endpoint functional remission rates were 39.5% with duloxetine and 28.7% with placebo. Time since first depression episode, antidepressant pretreatment (yes/no), baseline VAS pain (<30/>30 mm), and sex were significant prognostic factors. The effect of duloxetine was maintained at the long-term endpoint.
Van Baardewijk et al.[97] (2005) Duloxetine 40 to 120 mg daily for at least 8 weeks vs venlafaxine ER 75 to 225 mg daily for at least 8 weeks	MA Adults with moderate to severe MDD 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 <7, or a score ≤10 on the MADRS scale), symptom-free days Secondary: Not reported	Primary: Patients receiving duloxetine and venlafaxine ER experienced similar success rates after six months of treatment, 53 and 57%, respectively (P value not reported). Patients receiving duloxetine and venlafaxine ER experienced similar number of symptom-free days after six months of treatment, 52.72 and 57.03%, respectively (P value not reported). Duloxetine therapy was associated with a greater hospitalization rate compared to venlafaxine ER therapy, 47 and 43%, respectively (P value not reported). Secondary: Not reported
Vis et al.[98] (2005) Duloxetine 40 to 120 mg/day vs	MA (8 trials) Outpatients >18 years of age with MDD	N=1,754 (efficacy) N=1,791 (safety) 8 weeks	Primary: Remission and response (HAM-D, MADRS) Secondary: Dropout rates and rates of adverse	Primary: Both treatment groups demonstrated a significant difference compared to placebo for both remission and response (P<0.001 for all). Secondary: More patients receiving placebo dropped out due to lack of efficacy compared to patients in the treatment arms (P<0.001 for both drugs).

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venlafaxine ER 75 to 225 mg/day vs placebo			events	Dropout rates due to adverse reactions were also significant when active drugs were compared to placebo (P value not reported). More patients in the treatment groups than in the placebo groups dropped out due to adverse reactions (venlafaxine ER; P<0.001 and duloxetine; P=0.008).
Perahia et al.[99] (2008) Duloxetine 60 to 120 mg/day vs venlafaxine ER 75 to 225 mg/day	DB, MC, RCT (pooled analysis of 2 trials) Patients >18 years of age with MDD	N=667 12 weeks	Primary: GBR (remission at endpoint using HAM-D-17 ≤7) Secondary: Efficacy	Primary: There were no significant differences in GBR with duloxetine and venlafaxine ER at the end of six weeks of therapy (-1.418 vs -1.079; P=0.217) or 12 weeks (-0.349 vs -0.121; P=0.440). Secondary: Mean changes from baseline to endpoint in the HAM-D-17 total scores were not different between the duloxetine and venlafaxine ER treatment groups. Comparisons of mean change from baseline to endpoint on secondary efficacy measures (HAM-D-17 item 1, HAM-D-17 subscales [core, Maier, anxiety/somatization, retardation and sleep], HAMA total score, CGI-S, and PGI-I) were not significantly different between the treatment groups. Response and remission rates were not significantly different between duloxetine and venlafaxine ER at six weeks (response rate for duloxetine, 51.6%; venlafaxine, 54.5%; remission rate for duloxetine, 31.4%; venlafaxine, 35.2%) or 12 weeks (response rate for duloxetine, 62.6%; venlafaxine, 69.1%; remission rate for duloxetine, 48.1%; venlafaxine, 50.3%). Estimates of remission rates at two, four, eight and 12 weeks were 11.1, 36.6, 53.0, and 71.0% for the duloxetine-treated group and 10.4, 32.1, 51.7, and 67.4% for the venlafaxine-treated group, respectively (P=0.309).
Rush et al.[100] CO-MED (2011) Escitalopram 10 to 20 mg/day and	MC, PC, RCT, SB Patients 18 to 75 years of age with MDD	N=665 7 months	Primary: Symptom remission (QIDS-SR), attrition, anxiety (IDS-C), functioning, QOL,	Primary: At 12 weeks, the remission rates were 38.8% for escitalopram plus placebo, 38.9% for bupropion SR plus escitalopram, and 37.7% for venlafaxine ER plus mirtazapine. The response rates were 51.6 to 52.4%. The treatment groups did not differ in the percentage of change in QIDS-SR score or in effects on QOL.

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placebo vs bupropion SR 300 to 400 mg/day and escitalopram 10 to 20 mg/day vs venlafaxine XR 150 to 300 mg/day and mirtazapine 15 to 45 mg/day			adverse events Secondary: Not reported	At seven months, the treatment groups were not different in terms of remission rate (range, 41.8 to 46.6%), response rate (range, 57.4 to 59.4%), or attrition rate. There was no difference in the percentage of change in QIDS-SR, QOL, or work and social adjustment. The venlafaxine ER plus mirtazapine group had greater side effect frequency and intensity at 12 weeks and greater side effect frequency, intensity, and burden at seven months as compared to escitalopram plus placebo. Secondary: Not reported
Kerber et al.[101] CO-MED (2012) Escitalopram 10 to 20 mg/day plus placebo vs bupropion SR 300 to 400 mg/day plus escitalopram 10 to 20 mg/day vs venlafaxine ER 150 to 300 mg/day plus mirtazapine 15 to 45 mg/day	Subgroup analysis of CO-MED Patients 18 to 75 years of age with MDD, with and without heart disease	N=665 (6% [n=40] reported having and being treated for heart disease) 7 months	Primary: Symptom remission (QIDS-SR), attrition, anxiety (IDS-C), functioning, QOL, adverse events Secondary: Not reported	Primary: In general, patients with heart disease had fewer problems with treatment side effects at week 12 compared to patients without heart disease. At week 12, there were no significant differences between those with and without heart disease in terms of remission, response, QOL, or functional measures. This pattern was also seen with regard to measures at trial end (week 28). There were no significant differential treatment effects among those with and without heart disease in side effect burden and symptom severity at weeks 12 and 28. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Morris et al.[102] CO-MED (2012) Escitalopram 10 to 20 mg/day plus placebo vs bupropion SR 300 to 400 mg/day plus escitalopram 10 to 20 mg/day vs venlafaxine ER 150 to 300 mg/day plus mirtazapine 15 to 45 mg/day	Subgroup analysis of CO-MED Patients 18 to 75 years of age with MDD, with and without general medical conditions	N=665 (49.5% reported having no treated general medical conditions, 23.8% reported having 1, 14.8% reported having 2, and 11.9% reported having ≥3) 7 months	Primary: Symptom remission (QIDS-SR), attrition, anxiety (IDS-C), functioning, QOL, adverse events Secondary: Not reported	Primary: No differences in outcomes between antidepressant monotherapy and either of the antidepressant combination therapies, regardless of the number of general medical conditions a patient had. Specifically, within each group having a given number of conditions, the three treatments did not differ significantly with respect to any of the measures of efficacy or tolerability assessed, either at week 12 or 28. Secondary: Not reported
Moore et al.[103] (2005) Escitalopram 20 mg daily vs citalopram 40 mg daily	DB, MC, RCT Outpatients with MDD having an MADRS score of ≥30 at baseline	N=280 8 weeks	Primary: Change from baseline in the MADRS total score, adverse events, response to treatment, remission rate Secondary; Not reported	Primary: Escitalopram group exhibited a greater improvement in the MADRS score compared to the citalopram arm (–22.4 vs –20.3; P<0.05). There were more treatment responders with escitalopram than with citalopram (76.1 vs 61.3%; P<0.01). Remission rate was higher among patients on escitalopram compared to the citalopram group (56.1 vs 43.6%; P<0.05). Tolerability was similar in both treatment groups. Secondary; Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Colonna et al.[104] (2005) Escitalopram 10 mg daily vs citalopram 20 mg daily	DB, RCT Patients with moderate-to-severe MDD	N=357 24 weeks	Primary: Change from base-line in MADRS Secondary: Change from baseline in CGI-S	Primary: No significant difference was observed between groups in the MADRS at week 24. Secondary: Escitalopram patients had significantly better scores on the CGI-S at week 24 compared to citalopram patients.
Burke et al.[105] (2002) Escitalopram 10 mg daily vs escitalopram 20 mg daily vs citalopram 40 mg daily vs placebo	DB, MC, RCT Outpatients 18 to 65 years of age with MDD	N=491 8 weeks	Primary: Change from baseline in the MADRS total score at week eight Secondary: Change from baseline in the MADRS total score at weeks one, two, four, and six, change from baseline in the HAM-D, CGI-S, CGI-I, HAMA, QOL, and CES-D	Primary: Mean changes from baseline for the MADRS score were significantly greater compared to placebo in the two escitalopram groups (P<0.01) and in the citalopram group (P<0.05). There were no significant differences in the mean change of MADRS score from baseline to endpoint between the escitalopram 20 mg daily and citalopram 40 mg daily groups (P=0.09). Secondary: Patients randomized to the two escitalopram groups and the citalopram arm exhibited significantly greater improvement in the HAM-D score from baseline compared to placebo (P<0.01 and P<0.05, respectively). Response to treatment was observed in 50% of escitalopram 10 mg, 51.2% of escitalopram 20 mg, and 45.6% of citalopram 40 mg groups; the difference in response rate was significantly greater than that of placebo group (P<0.01) but not statistically different among the three active groups. There were no significant differences in the mean change of CGI-I, HAM-D, and CGI-S scores from baseline to endpoint between the escitalopram 20 mg daily and citalopram 40 mg daily groups (P=0.09). All three treatment groups exhibited significantly improved HAM-D depressed mood scores from baseline to endpoint (P<0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Patients randomized to the escitalopram 10 and 20 mg group exhibited significantly greater improvement in the HAMA score from baseline compared to placebo (P=0.04 and P<0.01, respectively). Mean changes from baseline for the QOL score were significantly greater compared to placebo in the escitalopram 10 mg group (P=0.04) and in the escitalopram 20 mg group (P<0.01). Mean changes from baseline for the CES-D score were significantly greater compared to placebo in the escitalopram 10 mg group (P=0.02) and in the escitalopram 20 mg group (P<0.01). There was no statistically significant difference in the discontinuation rates due to adverse events between the escitalopram 10 mg and placebo groups; however, escitalopram 20 mg and citalopram 40 mg groups had significantly greater discontinuation rates compared to placebo (P<0.05). The rate of adverse effects was not significantly different between the escitalopram 10 mg group and placebo (79 vs 70.5%; P=0.14). Escitalopram 20 mg and citalopram 40 mg groups were associated with significantly greater adverse event rates compared to placebo (85.6 vs 86.4%; P<0.01).
Yevtushenko et al.[106] (2007) Escitalopram 10 mg/day vs citalopram 10 mg/day vs	AC, DB, MC, RCT Patients 25 to 45 years of age with MDD	N=330 6 weeks	Primary: MADRS total score Secondary: MADRS total score in severely depressed patients, MADRS core depression subscale score, CGI-S and CGI-I scores, proportions of patients	Primary: The mean changes in MADRS total score were significantly greater in patients receiving escitalopram than citalopram 10 or 20 mg (-28.70 vs -20.11 and -25.19; both, P 0.001). The difference between the two citalopram groups was also significant (P<0.001). Secondary: In the severely depressed subpopulation, the differences in the mean change in MADRS score between the escitalopram group and the citalopram 10 and 20 mg groups were -9.46 and-3.99, respectively (both, P<0.001). The difference between the citalopram 20 and 10 mg groups was -5.47 (P<0.001). The differences in mean change in MADRS core depression subscale

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
citalopram 20 mg/day			classified as responders and remitters	scores between the escitalopram group and citalopram 10 and 20 mg groups were -6.00 and -2.48, respectively (both, P<0.001). The difference between the citalopram 20 and 10 mg groups was -3.52 (P<0.001) The mean changes in CGI-S score were -2.60, -1.61, and -2.05 in the escitalopram, citalopram 10 mg, and citalopram 20 mg groups, respectively (all, P<0.001 vs baseline). The differences in mean changes from baseline between the escitalopram and citalopram 10 and 20 mg groups were -0.99 and -0.55, respectively (both, P<0.001). The difference between the citalopram 20 and 10 mg groups was significant at end point (-0.44; P<0.001). Response rates were 95.4 vs 44.3 and 83.3% in the escitalopram vs citalopram 10 and 20 mg groups, respectively (both, P<0.001). Remission rates were 89.8 vs 25.5 and 50.9% in the escitalopram vs citalopram 10 and 20 mg groups, respectively (both, P<0.001).
Lam et al.[107] (2006) Escitalopram 10 to 20 mg daily vs citalopram 20 to 40 mg daily	MA Outpatients with MDD	N=1,321 (3 trials) 8 weeks	Primary: MADRS, response rate Secondary: CGI-I, CGI-S, HAM-D	Primary: No significant difference in response rate between the two treatment groups was seen at week eight. The analysis of pooled data demonstrated that the difference between citalopram and placebo was approximately constant; however, the difference between escitalopram and placebo (P=0.0010) and escitalopram and citalopram (P=0.0012) became greater the more severely depressed the patient was at baseline. Secondary: Similar results were seen in the secondary outcomes.
Gorman et al.[108] (2002) Escitalopram 10 to 20 mg daily vs	MA Outpatients with MDD	N=1,321 (3 trials) 8 weeks	Primary: MADRS, CGI-I Secondary; Not reported	Primary: Mean change in MADRS score from baseline at week eight was significantly improved in both treatment groups compared to baseline (P<0.05). Mean change in MADRS score from baseline at week eight was significantly improved in the escitalopram group compared to the citalopram group (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
citalopram 20 to 40 mg daily				Mean change in CGI-I score from baseline at week eight was significantly improved in both treatment groups compared to baseline (P<0.05). No significant difference in CGI-I scores between the two treatment groups was reported at week eight (P>0.05).
Llorca et al.[109] (2005) Escitalopram 10 to 20 mg daily vs citalopram 20 to 40 mg daily vs placebo	MA Patient 18 to 80 years of age with depression	N=506 (3 trials) 8 weeks	Primary: MADRS Secondary: HAM-D, CGI-I, CGI-S	Primary: Mean change from baseline in MADRS total scores was significantly higher in the escitalopram-treated group compared to the citalopram-treated group (P=0.003). Response rates to escitalopram were 56% compared to 41% with citalopram (P=0.007). Secondary: The mean change in HAM-D from baseline between escitalopram and citalopram was in favor of escitalopram at endpoint (P=0.007). On both the CGI-I and CGI-S scales, patients showed a significant improvement at treatment endpoint in favor of escitalopram when compared to citalopram treatment (P=0.01 and P=0.001 for CGI-I and CGI-S, respectively).
Ou et al.[110] (2011) Escitalopram 10 to 20 mg/day vs citalopram 20 to 40 mg/day	DB, MC, RCT Patients 18 to 65 years of age with MDD	N=240 6 weeks	Primary: Change in HAM-D_{17} total score Secondary: Response and remission rates	Primary: At all time points, there was no significant difference in HAM-D_{17} total score, score change, or rate change among the treatment groups (all P>0.05). At the end of the study, the mean rate change was 62.5% in the escitalopram group and 60.7% in the citalopram group (P=0.653). Secondary: Overall, response rates were 72.17% with escitalopram compared to 74.36% with citalopram (P=0.707). Remission rates were 60.87% with escitalopram compared to 56.41% with citalopram (P=0.982). For severe MDD patients, response rates were 72.50 vs 71.79% with escitalopram and citalopram, respectively (P=0.991). Remission rates were 57.50 and 46.15% with escitalopram and citalopram, respectively (P=0.350).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There was no significant difference in adverse events with escitalopram and citalopram (28.7 vs 29.9%, respectively; P=0.8384). Nausea and other gastrointestinal reactions (including stomach discomfort, burning sensation) were the most frequently reported adverse events. No serious adverse events were observed.
Wade et al.[111] (2007) Escitalopram 20 mg/day vs duloxetine 60 mg/day	DB, RCT Patients 18 to 65 years of age with MDD	N=294 24 weeks	Primary: Mean change in MADRS total score from baseline to week 24 Secondary: MADRS total score, HAM-D_{17}, $CGI^{8}I$, $CGI^{8}S$, HAMA scores	Primary: The mean change from baseline in MADRS total scores was –23.4 for escitalopram-treated patients and –21.7 for duloxetine treated patients (P=0.055). Secondary: At week eight, the mean change from baseline in MADRS total scores was –19.5 for escitalopram-treated patients and –17.4 for duloxetine-treated patients (P<0.05). There was no significant difference in the mean change from baseline in HAM-D_{17} (7.13 vs 8.47; P=0.096), HAMA (7.73 vs 8.62; P=0.267), CGI-I (1.76 vs 1.99; P=0.077), CGI-S (2.11 vs 2.28; P=0.214) at 24 weeks between escitalopram-treated patients and duloxetine-treated patients.
Khan et al.[112] (2007) Escitalopram 10 to 20 mg daily vs duloxetine 60 mg daily	DB, MC, PG, RCT Patients with MDD	N=278 8 weeks	Primary: Change from base-line to week eight in MADRS scores using the LOCF Secondary: Not reported	Primary: At week eight, a significantly greater decrease in MADRS scores (LOCF) was observed in the escitalopram group compared to the duloxetine group (P<0.05). No significant differences in MADRS scores were observed between groups in the observed case analysis (P=0.79). Secondary: Not reported
Boulenger et al.[113] (2006) Escitalopram 20 mg daily vs	DB, MC, RCT Patients with MDD	N=459 24 weeks	Primary: Change in MADRS score, withdrawal Secondary: HAMA, CGI-S,	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
paroxetine 40 mg daily			remitters	Secondary: The difference in HAMA scores at 24 weeks compared to baseline was –15.1 for the escitalopram-treated patients compared to –13.2 for the paroxetine-treated patients (P=0.01). The difference in CGI-S scores at 24 weeks compared to baseline was –2.8 for the escitalopram-treated patients compared to –2.6 for the paroxetine-treated patients (P=0.05). After 24 weeks of treatment the proportion of remitters was 75% in the escitalopram group compared to 66.8% in the paroxetine group (P<0.05).
Montgomery et al.[114] (2004) Escitalopram 10 to 20 mg daily vs venlafaxine ER 75 to 150 mg daily	DB, RCT Patients with MDD	N=293 8 weeks	Primary: Change from baseline in MADRS scores Secondary: Not reported	Primary: No significant difference between groups was observed at week eight in MADRS scores. Escitalopram-treated patients achieved remission significantly faster compared to venlafaxine patients in a post-hoc analysis. Secondary: Not reported
Fava et al.[115] (2002) Fluoxetine 20 mg daily vs sertraline 50 mg daily vs paroxetine 20 mg	DB, MC, RCT Patients ≥18 years of age with depression	N=284 10 to 16 weeks	Primary: HAM-D_{17} scores Secondary: Improvement in insomnia/sleep disturbances	Primary: As indicated by baseline-to-endpoint improvement on the HAM-D_{17}, there were no statistically significant differences between fluoxetine, sertraline, and paroxetine on all outcome measures (P=0.365). Secondary: Insomnia improvement when using the sleep disturbance factor was similar in all patients with no significant difference between groups (P=0.868).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
daily				
Thase et al.[116] (2002) Imipramine (mean dosage, 221 mg/day) vs sertraline (mean dosage, 163 mg/day)	DB, SC Patients with chronic major depression who failed to respond to 12 weeks of treatment with either imipramine or sertraline	N=168 12 weeks	Primary: HAM-D, CGI Secondary; Not reported	Primary: The two groups were equal in response rates for completers, 63 and 55% for the sertraline and imipramine groups, respectively (P=0.16). However, in the ITT analysis there was a statistically better outcome for the sertraline group (P=0.03). Those patients going from sertraline to imipramine experienced significant increases in eight adverse events and significant reductions in three adverse events while those patients going from imipramine to sertraline experienced a significant reduction in seven adverse events and no increase in any adverse event. Secondary; Not reported
Asnis et al.[117] (2013) Levomilnacipran 40 mg QD or levomilnacipran 80 mg QD or levomilnacipran 120 mg QD vs placebo	DB, MC, PC, RCT Patents 18 to 65 years of age, met the diagnostic criteria of MDD per the DSM-IV-TR, current ongoing depressive episode ≥8 weeks in duration, MADRS score ≥30 at baseline, MADRS-SR ≥26 at baseline	N=708 N=506 completed study 8 weeks	Primary: Mean reduction of MADRS score from baseline at week eight (reported as LSMD from placebo) Secondary: Mean reduction of SDS score from baseline at week eight, mean reduction on $HDRS_{17}$ from baseline at week eight, mean change from baseline of CGI-S total score at week eight and mean reduction from baseline of	Primary: The LSMD from placebo of MADRS scores for levomilnacipran 40, 80 and 120 mg at week eight were -3.23; P=0.0186, -3.99; P=0.0038 and -4.86; P=0.0005, respectively. Secondary: The LSMD from placebo on the SDS total score for levomilnacipran 40, 80 and 120 mg was -1.4; P>0.05, -2.51; P<0.05, -2.57; P<0.05, respectively. The LSMD from placebo on the $HDRS_{17}$ for levomilnacipran 40, 80 and 120 mg was -1.2; P>0.05; -2.09; P<0.05 and -2.34; P<0.05, respectively. The LSMD from placebo on the CGI-S for levomilnacipran 40, 80 and 120 mg was -.04; P>0.05, -0.43; P<0.01 and -0.35; P<0.05, respectively. The LSMD from placebo on the CGI-I score for levomilnacipran 40, 80 and 120 mg was -0.1; P>0.05, -0.34; P<0.05 and -0.32; P<0.05, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			CGI-I total score at week eight (all reported as LSMD from placebo)	
Bakish et al.[118] (2013) Levomilnacipran 40 mg QD or levomilnacipran 80 mg QD vs placebo	DB, MC, PC, RCT Patients 18 to 75 years of age, met diagnostic criteria per the DSM-IV-TR for recurrent MDD, current ongoing depressive episode 6 weeks to 12 months in duration, 5 or fewer major depressive episodes within the previous 5 years, MADRS score ≥26 at baseline, CGI-S score ≥4 at baseline	N=557 N=441 completed study 8 weeks	Primary: Mean reduction of MADRS score from baseline at week eight (reported as LSMD from placebo) Secondary: Mean reduction of SDS score from baseline at week eight, mean reduction on $HDRS_{17}$ from baseline at week eight and mean reduction from baseline of CGI-S total score at week eight (all reported as LSMD from placebo)	Primary: The LSMD from placebo week eight for levomilnacipran 40 and 80 mg was -3.3; P=0.003 and -3.1; P=0.004, respectively. Secondary: The LSMD from placebo at week eight for levomilnacipran 40 and 80 mg was -1.8; P=0.046 and - 2.7; P=0.003, respectively. The LSMD from placebo on $HDRS_{17}$ scores for levomilnacipran 40 and 80 mg were -2.2; P=0.007 and -1.6; P=0.043. The LSMD from placebo on CGI-S scores for levomilnacipran 40 and 80 mg was -0.3 for both arms with P=0.020 and P=0.015, respectively.
Sambunaris et al.[119] (2013) Levomilnacipran 40 to 120 mg vs placebo	DB, FD, MC, PC, RCT Patients 18 to 80 years of age, met the diagnostic criteria for MDD per the DSM-IV-TR, ongoing major depressive episode	N=429 N=335 completed study 8 weeks	Primary: Mean reduction of MADRS score from baseline at week eight (reported as LSMD from placebo Secondary: Mean reduction of	Primary: The LSMD from placebo on the MADRS score at week eight was -3.095; P=0.0051 for levomilnacipran 40 to 120 mg. Secondary: The LSMD from placebo on the SDS at week eight was -2.632; P=0.0010 for levomilnacipran 40 to 120 mg. The LSMD from placebo on the $HDRS_{17}$ score for levomilnacipran 40 to 120 mg was -2.146; P=0.0038. Levomilnacipran 40 to 120 mg did not show statistically significant results for the LSMD from placebo on the CGI-I total score at week eight (-0.207;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	of at least 4 weeks in duration, MADRS score ≥30 at baseline and MADRS-SR ≥26 at baseline		SDS score from baseline at week eight, mean reduction on $HDRS_{17}$ from baseline at week eight, mean change from baseline of CGI-I total score at week eight, mean reduction from baseline of CGI-S total score at week eight and mean change from baseline on MEI-SF total score at week eight (all reported as LSMD from placebo)	P=0.0881). Levomilnacipran 40 to 120 mg showed a LSMD from placebo on the CGI-S at week eight of -0.352; P=0.0083. The LSMD from placebo on the MEI-SF for levomilnacipran 40 to 120 mg at week eight was 5.048; P=0.0382.
Montgomery et al.[120] (2013) Levomilnacipran 75 or 100 mg QD Levomilnacipran dose was increased to 100 mg/day over 12 days. vs placebo	DB, FD, MC, PC, RCT Outpatients 18 to 70 years of age who met DSM-IV criteria for MDD (duration > 1 month) with a HDRS17 score > 22 and SDS score > 10	N=553 10 weeks	Primary: MADRS score change from baseline to week 10 Secondary: HDRS17, SDS, CGI-I, MADRS response (>50% decrease from baseline) and remission (score <10), safety	Primary: Levomilnacipran was significantly "superior" to placebo on MADRS total score change from baseline to week 10 (LSMD, -4.2; 95% CI, -5.7 to -2.6; P<.0001). Secondary: Statistical significance in favor of levomilnacipran was demonstrated on change from baseline to week 10 in HDRS17 total score (LSMD, -3.4; 95% CI, -4.7 to -2.2; P<0.0001) and SDS total score (LSMD, -3.4; 95% CI, -4.6 to -2.2; P<0.0001) and subscales. Significantly more levomilnacipran patients vs placebo patients achieved MADRS response (59.1 vs 42.2%; P<0.0001) and remission (46.4 vs 26.0%; P<0.0001). Levomilnacipran was generally safe and well tolerated; more levomilnacipran patients (9.4%) vs placebo patients (6.5%) discontinued due to adverse events, but more placebo patients vs levomilnacipran patients discontinued overall (24.9 vs 20.2%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Versiani et al.[121] (2005) Mirtazapine 15 to 60 mg daily vs fluoxetine 20 to 40 mg daily	DB, RCT Patients 18 to 65 years of age with MDD	N=297 8 weeks	Primary: Change from baseline in HAM-D_{17} score Secondary: MADRS, CGI	Primary: No statistically significant differences were noted between the two groups in change from baseline HAM-D_{17} score at any time point. Secondary: Mirtazapine treatment was associated with greater change in MADRS score at day 14 (–10.9 vs –8.5; P=0.006) and the proportion of patients with ≥50% decrease in MADRS score (21.4 vs 10.9%; P=0.031). On the CGI, the proportion of "much/very much improved" patients tended to be greater with mirtazapine (significant at day seven; 9.7 vs 3.4%, P=0.032). No significant between-group differences were observed for the majority of QOL measures. Mirtazapine produced significantly better improvements on "sleeping assessment 1" (14.9±5.2 vs 13.7±5.4; P=0.028) and "sleeping assessment 2" (P=0.013) than fluoxetine. Both agents were generally well tolerated but mirtazapine-treated patients experienced a mean weight gain of 0.8±2.7 kg compared to a mean decrease in weight of 0.4±2.1 kg for fluoxetine-treated patients (P<0.001).
Wheatley et al.[122] (1998) Mirtazapine 15 to 60 mg/day vs fluoxetine 20 to 40 mg/day	DB, MC, RCT Patients with MDD 18 to 75 years of age	N=123 6 weeks	Primary: HAM-D Secondary; Not reported	Primary: The mean HAM-D_{17} scores were not different at week six for the two groups; although at week three (the estimated treatment difference was -3.4 in favor of mirtazapine; 95% CI, –6.1 to –0.76; P=0.006) and week four (the estimated treatment difference was -3.8 in favor of mirtazapine: 95% CI, –6.61 to –1.02; P=0.009), statistical significance was reported for mirtazapine. No other assessment endpoints were statistically different between the two groups at week six.
Blier et al.[123] (2009) Mirtazapine 30 mg	DB, RCT Patients with MDD	N=61 8 weeks	Primary: MADRS, HAM-D_{17}, CGI	Primary: There was a greater improvement on the MADRS at day 28 with combination therapy (P=0.045) when compared to monotherapy (mirtazapine; P=0.046, paroxetine; P=0.02).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
at bedtime (may be increased to 45 mg after 4 weeks) vs paroxetine 20 mg in the morning (may be increased to 30 mg after 4 weeks) vs mirtazapine 30 mg/day plus paroxetine 20 mg/day for 6 weeks After 6 weeks, non-responders on monotherapy had the second trial drug added to their current regimen. Non-responders on combination therapy had the dosage of both drugs increased by 50%.			Secondary; Not reported	There was a greater improvement on the MADRS at days 35 (P=0.006) and 42 (P=0.002) with combination therapy compared to monotherapy (mirtazapine; P=0.003 and 0.001, respectively; paroxetine; P=0.011 and 0.003, respectively). Statistical significance was achieved on the HAM-D_{17} in the combination group at day 35 (P=0.02) when compared to mirtazapine (P=0.005), and at day 42 (P=0.007) when compared to both drugs alone (mirtazapine; P=0.002, paroxetine; P=0.04). Statistical significance was achieved on the CGI in the combination group at day 35 vs mirtazapine (P=0.004) and for both drugs at day 42 (mirtazapine; P=0.002, paroxetine; P=0.04). Four patients remitted by day 42 in the mirtazapine group (19%) and 5 in the paroxetine group (26%) compared to 9 patients remitted in the combination group (43%; P>0.05). At day 42, 10 patients in each of the monotherapy arms received the other drug in combination. The mean scores improved rapidly in both groups with seven and five patients achieving remission in the subsequent two weeks in the mirtazapine and paroxetine groups, respectively. Five patients on the combination had their regimens increased to 45 mg/day of mirtazapine and paroxetine 30 mg/day. Two of these patients achieved remission by day 56. Secondary; Not reported
Behke et al.[124] (2003) Mirtazapine orally	DB, RCT Patients with MDD	N=345 8 weeks	Primary: HAM-D Secondary:	Primary: Mirtazapine was significantly (P<0.05) more effective than sertraline at all assessments during the first two weeks of the study. After this time, HAM-D total scores were similar in both groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
disintegrating tablets 30 to 45 mg/day vs sertraline 50 to 150 mg/day			CSFQ	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.[125] (2001) Mirtazapine 15 to 60 mg/day vs venlafaxine 75 to 375 mg/day	DB, MC, RCT Hospitalized patients with severe depressive episode with melancholic features	N=157 8 weeks	Primary: HAM-D, MADRS Secondary: Adverse effects	Primary: A significant difference favoring mirtazapine was found on the HAM-D Sleep Disturbance factor at all assessment points (P≤0.03). Secondary: A significantly higher percentage of patients treated with venlafaxine (15.3%) than mirtazapine (5.1%) dropped out because of adverse events (P=0.037).
Feighner et al.[126] (1998) Nefazodone 200 mg BID vs placebo	DB, PC, PG Patients that were hospitalized due to depression	N=120 6 weeks	Primary: HAM-D_{17}, CGI-I, MADRS Secondary: Not reported	Primary: Nefazodone treatment resulted in a significant reduction (P<0.01) of the HAM-D_{17} total score compared to placebo from the end of the first treatment week through the end of the study (–12.2 nefazodone vs –7.7 placebo). At the end of the trial, significantly more nefazodone-treated patients (50%) than placebo-treated patients (29%) had responded, as indicated by their CGI-I score (P=0.021) or by a ≥50% reduction in their HAM-D_{17} scores (P=0.017). Significantly more patients treated with nefazodone (36%) than placebo-treated patients (14%) had a HAM-D_{17} score ≤10 at the end of treatment (P=0.004). Significant treatment differences (P<0.01) in favor of nefazodone were also seen in the MADRS; the HAM-D retardation, anxiety, and sleep disturbance factors; and HAM-D item 1 (depressed mood). Patients with dysthymia in addition to major depression also showed significant improvement (P<0.05) when treated with nefazodone, with significant differences in response rates seen as early as week two and through the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				end of the trial. Secondary: Not reported
Dunner et al.[127] (2005) Paroxetine CR 12.5 to 62.5 mg vs placebo	DB, PC, RCT (Pooled analysis) Adults with MDD	N=303 (4 trials) 8 to 12 weeks	Primary: Changes in depressive symptoms according to HAM-D_{17} and CGI-I, patients achieving remission Secondary; Not reported	Primary: Statistically significant improvements in depressive symptoms in favor of paroxetine CR compared to placebo were observed in patients with both severe MDD (HAM-D treatment difference, –4.37; 95% CI, –6.31 to –2.42; P<0.001) and nonsevere MDD (HAM-D_{17} treatment difference, -1.89; 95% CI, –2.91 to –0.87; P<0.001). The odds of CGI-Improvement response were also significantly higher for patients receiving paroxetine CR than those receiving placebo, regardless of baseline depressive symptomatology (severe MDD: OR, 2.42; 95% CI, 1.50 to 3.91; P<0.001, nonsevere MDD: OR, 1.63; 95% CI, 1.21 to 2.19; P<0.002).
Birkenhager et al.[128] (2004) Phenelzine 10 mg BID vs tranylcypromine 10 mg BID	DB, RCT Patients 18 to 65 years of age with depression	N=77 5 weeks	Primary: HAM-D Secondary: Side effects	Primary: Seventeen patients (44%) responded to tranylcypromine and 18 patients (47%) responded to phenelzine (≥50% reduction in HAM-D; P=0.82). The mean reduction in HAM-D score was 10.4 for the tranylcypromine group vs 8.3 for the phenelzine group (P=0.23). No significant differences in response rates were demonstrated between the treatment groups (P=0.97). Secondary: A substantial number of patients experienced severe side effects, mainly dizziness, agitation, and insomnia. The incidence was the same in both samples (21%).
Rossini et al.[129] (2005) Sertraline 150 mg daily vs	DB, RCT Patients >59 years of age with MDD	N=88 7 weeks	Primary: Response rate (HAM-D) Secondary; Not reported	Primary: Response rates were 55.6% for sertraline and 71.8% for fluvoxamine. No significant difference in final response rates were observed between treatment groups (P=0.12). Secondary; Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
fluvoxamine 200 mg daily				
Sheehan et al.[130] (2009) Trazodone ER 150 to 375 mg/day vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with MDD, current episode of MDD for a minimum of 1 month, dysphoria for most days over the previous 4 weeks, and a MADRS total score ≥26 at screening and baseline	N=412 8 weeks	Primary: Change from baseline in HAM-D-17 total score Secondary: HAM-D-17 responders, HAM-D-17 remitters, change in HAM-D-17 depressed mood item from baseline, change in MADRS total score from baseline, CGI-I responders, PGI-I responders, change in CGI-S from baseline, CGI-I at last study visit, PGI-I at last study visit, discontinuations due to lack of efficacy, and overall quality of sleep	Primary: The change in the HAM-D-17 total score from baseline decreased by an average of 11.4±8.2 and 9.3±7.9 in the trazodone and placebo groups, which statistically favored treatment with trazodone (P=0.012). Results demonstrated a significantly greater improvement in the mean HAM-D-17 total score in the trazodone group compared to the placebo group by the first week of treatment (day seven of titration: 5.6±5.2 vs 3.9±4.8, respectively; P=0.005). The significantly greater differences were maintained throughout the study. Secondary: The number of HAM-D-17 responders (decrease ≥50% from baseline HAM-D-17 total score) in the trazodone group was significantly greater compared to the placebo group (54.0 vs 41.2%; P=0.003). No difference in the proportion of HAM-D-17 remitters (HAM-D-17 total score ≤7) was observed between treatment groups (35.6 vs 31.9%; P=0.22). The change in the HAM-D-17 depressed mood item from baseline decreased by average of 1.6±1.3 and 1.3±1.2 in the trazodone and placebo groups, which statistically favored treatment with trazodone (P=0.030). The change in MADRS total score from baseline also statistically favored treatment with trazodone (-16.6±11.3 vs -14.1±11.9; P=0.036). No difference in the proportion of CGI-I responders (“much improved” or “very much improved” at last study visit) was observed between treatment groups (53.3 vs 48.6%; P=0.22). No difference in the proportion of PGI-I responders (“much improved” or “very much improved” at last study visit) was observed between treatment groups (51.1 vs 43.7%; P=0.15).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The change in the CGI-S from baseline decreased by 1.7±1.4 and 1.4±1.4 in the trazodone and placebo groups, which statistically favored treatment with trazodone (P=0.036). The CGI-I scores at the last study visit were comparable in both treatment groups (P=0.22). The PGI-I scores at the last study visit were comparable in both treatment groups (P=0.084). Four percent of patients in the trazodone group discontinued treatment due to lack of efficacy compared to 4.4% of patients in the placebo group (P>0.99). At the end of the study, patients treated with trazodone had statistically significant improvements compared to placebo in all quality of sleep parameters.
Lenox-Smith et al.[131] (2008) Venlafaxine ER 75 to 300 mg/day vs citalopram 20 to 60 mg/day	DB, MC, RCT Patients 18 to 65 years of age with MDD who had not experienced a treatment response to 8 weeks of monotherapy with an adequate regimen of an SSRI	N=406 12 weeks	Primary: HAM-D_{21} total score Secondary: MADRS, CGI-S, CGI-I	Primary: There was no significant difference between venlafaxine ER and citalopram on the HAM-D_{21} total score (-17.0 vs -16.5, respectively; P=0.4778). Secondary: There were no significant differences between venlafaxine ER and citalopram on the MADRS total scores (P=0.5002) or CGI-S (P=0.3014), or in the analyses of response (P=0.953). Significant differences between treatment groups were observed for one subscale analysis: more venlafaxine ER patients had a CGI-I score of 1 at week 12 (P=0.024).
Bielski et al.[132] (2004) Venlafaxine ER 225 mg/day vs	DB, RCT Patients with MDD	N=195 8 weeks	Primary: MADRS Secondary: Adverse effects	Primary: There were no significant differences in efficacy, remission rates, or response rates between venlafaxine ER and escitalopram. Mean changes from baseline to endpoint in MADRS total score for escitalopram and venlafaxine ER were –15.9 and –13.6, respectively. Remission (MADRS score of ≤10) rates at endpoint were 41.2% for

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escitalopram 20 mg/day				escitalopram and 36.7% for venlafaxine ER. Response (≥50% reduction from baseline MADRS score) rates for the escitalopram and venlafaxine ER groups were 58.8 and 48.0%, respectively. Secondary: More patients in venlafaxine ER group had treatment-emergent adverse effects compared to escitalopram (85.0 vs 68.4%) but this was not statistically significant and may have been due to rapid titration of the venlafaxine dose. Venlafaxine ER had a higher incidence of discontinuation due to adverse events (16.0 vs 4.1%; P<0.01).
Nemeroff et al.[133] (2007) Venlafaxine 75 to 225 mg/day vs fluoxetine 20 to 60 mg/day vs placebo	DB, MC, PC, RCT Outpatients ≥18 years of age with MDD	N=308 6 weeks	Primary: HAM-D Secondary: Not reported	Primary: On the HAM-D, overall differences among treatment groups at week six did not reach significance (P=0.051), though the difference between the venlafaxine and placebo groups was significant (P=0.016). The differences between fluoxetine and placebo (P=0.358) and between venlafaxine and fluoxetine (P=0.130) were not significant. The difference on the HAM-D depressed mood item was significant among treatment groups at week six (P<0.001); both active treatments were significantly more effective than placebo (venlafaxine; P<0.001, fluoxetine; P=0.024). The difference between the active treatments was not statistically significant (P=0.117). Secondary: Not reported
Rudolph et al.[134] (1999) Venlafaxine ER 75 to 225 mg/day vs fluoxetine 20 to 60 mg/day	DB, MC, PC, PG, RCT Outpatients ≥18 years of age with MDD	N=301 8 weeks	Primary: HAM-D, MADRS, CGI Secondary: Not reported	Primary: The percentages of patients who achieved full remission of their depression (HAM-D total score ≤7) at the end of treatment were 37, 22, and 18% for the venlafaxine ER, fluoxetine and placebo groups, respectively. The differences in remission rates between venlafaxine ER and the other groups were significant (P<0.05). Venlafaxine ER produced a significant lower mean total score on the MADRS analysis than did fluoxetine (P=0.048). The P value for the statistical test of center by center interaction was not significant, indicating

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vs placebo				that treatment outcomes did not differ significantly between individual investigational sites. Secondary: Not reported
Benkert et al.[135] (1996) Venlafaxine 150 to 375 mg/day vs imipramine 200 mg/day	DB, PG, RCT Hospitalized patients with major depression and melancholia	N=167 6 weeks	Primary: HAM-D, MADRS Secondary: Not reported	Primary: No differences in the response rates on the HAM-D or MADRS were observed between treatments. Among patients who demonstrated a response on the HAM-D, there was a significantly faster onset of response (P=0.036) and sustained response (P=0.018) in the venlafaxine group. The median time to response on the HAM-D among responders was 14 days with venlafaxine and 21 days with imipramine. However, no differences between treatments were observed among responders on the MADRS. Secondary: Not reported
Kok et al.[136] (2007) Venlafaxine ER 75 to 375 mg/day vs nortriptyline 25 to 200 mg/day	DB, RCT Inpatients ≥60 years of age with MDD	N=81 12 weeks	Primary: Remission (MADRS ≤10) Secondary: Remission on HAM-D and GDS, response rates	Primary: There was no significant difference in remission between the treatment groups as measured by a reduction in MADRS (venlafaxine, 27.5% vs nortriptyline, 36.6%; P=0.381). Secondary: There was no significant difference in remission rates between the treatment groups as measured by HAM-D and GDS (P=NS). There was no significant difference in response rates between the treatment groups as measured by MADRS, HAM-D, GDS, and CGI-I (P=NS).
Richard et al.[137] (2012) Venlafaxine ER, up to a maximum	DB, PC, RCT Patients ≥30 years of age with idiopathic PD,	N=115 12 weeks	Primary: HAM-D-17 total score Secondary:	Primary: Treatment effects relative to placebo, expressed as mean 12 week reduction in HAM-D-17 total score, were 6.2 points (97.5% CI, 2.2 to 10.3; P=0.0007) with paroxetine and 4.2 points (97.5% CI, 0.1 to 8.4; P=0.02) with venlafaxine ER. There was no difference noted between

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of 225 mg/day vs paroxetine, up to a maximum of 40 mg/day vs placebo	without dementia, and depressive disorder or operationally defined subsyndromal depression		MADRS, BDI-II, GDS, UPDRS, safety	paroxetine and venlafaxine ER (P=0.28). Secondary: Significant beneficial effects of paroxetine and venlafaxine ER relative to placebo were apparent for the secondary outcomes (MADRS, BDI-II, and GDS; P≤0.01 for all comparisons). UPDRS total and motor scores improved in all three treatment groups, but there were no significant group differences in mean response. There was no evidence of treatment-associated worsening of motor function. One hundred patients reported at least one adverse event during the trial: 86, 85, and 90% with paroxetine, venlafaxine ER, and placebo. Insomnia was reported significantly less frequently with paroxetine compared to venlafaxine ER and placebo. There were three serious adverse events.
Mazeh et al.[138] (2007) Venlafaxine 75 to 300 mg/day vs paroxetine 10 to 60 mg/day	RCT, SB Inpatients ≥65 years of age with MDD who did not respond to two adequate pharmacological treatments for depression during the current depressive episode	N=30 6 weeks	Primary: CGI, HAM-D, GDS Secondary: Not reported	Primary: Nine patients treated with venlafaxine (60%) and five patients treated with paroxetine (33%) remitted after eight weeks of treatment. Three patients from each group responded without achieving remission after eight weeks of treatment (20%). Four patients treated with venlafaxine (26.7%) and eight patients treated with paroxetine (53.3%) failed to respond. Mean score changes from baseline to endpoint for paroxetine were: HAM-D=-12.5, CGI=-2.3, and GDS=-3.2. Mean score changes from baseline to endpoint for venlafaxine were: HAM-D=-19.1, CGI=-2.3, and GDS=-6.0 in the venlafaxine group. Venlafaxine was more effective than paroxetine on CGI and HAM-D measures (P<0.0003). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
DeSilva et al.[139] (2012) Venlafaxine vs an SSRI	MA Published, randomized, DB, head-to-head trials, which compared venlafaxine and an SSRI in the treatment of MDD in adults	N=26 trials Duration varied	Primary: Remission, response, discontinuation Secondary: Not reported	Primary: MA using a random effect model showed that venlafaxine was more efficacious compared to SSRIs in achieving remission (OR, =1.13; 95% CI, 1.0 to 1.28; P=0.05) and response (OR, 1.17; 95% CI, 1.03 to 1.34; P=0.02). Subgroup analysis found that venlafaxine had a significantly better response rate than fluoxetine (OR, 1.28; 95% CI, 1.05 to 1.55; P=0.01). There were no significant differences in response or remission between venlafaxine and other individual SSRIs. There was no significant difference in all cause discontinuation between venlafaxine and SSRIs (OR, 1.10; 95% CI, 0.97 to 1.25; P=0.15). Venlafaxine had significantly higher discontinuation due to adverse events compared to SSRIs (OR, 1.41; 95% CI, 1.10 to 1.79; P=0.006). Secondary: Not reported
Reed et al.[140] (2012) Vilazodone 40 mg QD vs placebo	2 DP, PC, RCT Patients with MDD	N=410 (RCT-1), 481 (RCT-2) 8 weeks	Primary: Change from baseline to end of treatment MADRS total score; mixed-effects repeated-measures analyses were conducted in the PC trials; effectiveness analyses in the long-term study included mean MADRS score change over time Secondary; Not reported	Primary: Vilazodone-treated patients in both short-term studies showed greater improvement from baseline to end of treatment in mean MADRS scores than placebo-treated patients (LSM treatment difference, -3.2; P=0.00 RCT-1 and -2.5; P=0.009 RCT-2). CGI-I mean scores at end of treatment reflected greater improvement with vilazodone compared to placebo in both studies (LSM treatment difference, -0.4; P=0.001 RCT-1 and -0.3; P=0.004 RCT-2). MADRS response rates were significantly greater among patients receiving vilazodone vs those receiving placebo (RCT-1, 40.4 vs 28.1%, respectively; P=0.007 and RCT-2, 43.7 vs 30.3%, respectively; P=0.002). The greater efficacy of vilazodone vs placebo was consistent for the majority of demographic and MDD characteristic subgroups. In the long-term study, the mean MADRS score improved from 29.9 (baseline) to 11.4 (week eight), 8.2 (week 24), and 7.1 (week 52). Secondary; Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Khan et al.[141] (2011) Vilazodone 40 mg QD vs placebo	DB, MC, PC, RCT Patients 18 to 70 years of age with MDD (single episode or recurrent)	N=481 8 weeks	Primary: Change in MADRS total score Secondary: MADRS and HDRS-17 response, HDRS-21, HARS, CGI-S, CGI-I scores, CSFQ	Primary: Patients receiving vilazodone showed significantly greater improvements in mean MADRS scores compared to placebo (LSM treatment difference, -2.5; P=0.009). Secondary: Treatment with vilazodone resulted in significant improvements for the HDRS-17 (P=0.026), HDRS-21 (P=0.029), HARS (P=0.037) and CGI-S (P=0.004) scores. CGI-I scores at week eight showed significantly greater global improvement with vilazodone compared to placebo (P=0.004). The MADRS response rate was significantly greater among patients receiving vilazodone compared to placebo (43.7 vs 30.3%, respectively; P=0.002), as was the HDRS-17 response rate (44.2 vs 32.9%; P=0.013). Remission rates for vilazodone were not significantly different than placebo based on MADRS (27.3 vs 20.3%, respectively; P=0.066) or HDRS-17 (24.2 vs 17.7%, respectively; P=0.088). More patients receiving vilazodone (82.1%) experienced a treatment-related adverse event compared to placebo (64.4%). The most frequently reported adverse events with vilazodone compared to placebo were diarrhea (30.6 vs 10.7%), nausea (26.0 vs 5.6%) and headache (12.8 vs 10.3%). Most adverse events were considered mild-to-moderate in nature. Treatment-related effects on sexual function as measured by CSFQ were small and similar among the treatment groups. Effects on weight were similar to placebo.
Rickels et al.[142] (2009) Vilazodone 40 mg QD vs placebo	DB, MC, PC, RCT Patients 18 to 65 years of age with MDD (single episode or recurrent)	N=410 8 weeks	Primary: Change in MADRS total score, HAM-D_{17} total score, and HAM-A total score, CGI-S and CGI-I scores Secondary:	Primary: The mean change on the MADRS total score was significantly greater with vilazodone compared to placebo (-12.9 vs -9.6, respectively; P=0.001). The difference was evident by week one (P<0.001) and on each subsequent visit (P<0.05). The mean change on the HAM-D_{17} total score was significantly greater with vilazodone compared to placebo (-10.4 vs -8.6, respectively; P=0.022). The difference was evident by week one and on each subsequent visit (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Response (≥50% decrease in total score on MADRS, and HAM-D_{17} total scores, or a score of 1 or 2 on the CGI-I)	The mean score change on the CGI-S was significantly greater with vilazodone compared to placebo (-1.4 vs -1.0, respectively; P=0.001). The mean score change on the CGI-I was significantly improved with vilazodone compared to placebo (2.6 vs 3.0, respectively; P=0.001). The mean change on the HAM-A total score was significantly greater with vilazodone compared to placebo (-6.6 vs -5.1, respectively; P=0.045). Secondary: Response rates were significantly better with vilazodone than with placebo on the MADRS (P=0.007), HAM-D_{17} (P=0.011), and CGI-I (P=0.001). Treatment-emergent adverse events with vilazodone included diarrhea, nausea and somnolence. Most of the adverse events were mild-to-moderate in severity.
Heisenberg N, et. al.[143] (2012) Vortioxetine 1 mg QD or vortioxetine 5 mg QD or vortioxetine 10 mg QD vs placebo QD	DB, MC, PC, PG, RCT Patients 18 to 75 years of age, had a current MDE per DSM-IV-TR criteria, ambulatory and a baseline MADRS total score ≥26	N=556 (N=505 completed study) 8 weeks	Primary: Change from baseline in HAMD-24 after eight weeks of treatment Secondary: Decrease from baseline on SDS, CGI-I score and decrease from baseline on MADRS	Primary: At eight weeks, all treatment groups had a significantly greater decrease from baseline in HAMD-24 compared to placebo. Vortioxetine 1 mg had a decrease from baseline on the HAMD-24 of -14.82 (P<0.001). Vortioxetine 5 mg had a decrease from baseline of -15.42 (P<0.001), and vortioxetine 10 mg had a decrease from baseline on the HAMD-24 of -16.23 (P<0.001). Secondary: None of the vortioxetine treatment groups had statistically significant decrease from baseline on the SDS as compared to placebo for (P values not reported). Vortioxetine 1, 5 and 10 mg all met the secondary endpoint of CGI-I compared to placebo; 2.37, 2.37 and 2.29 respectively (P<0.001 for all comparators). Vortioxetine 1, 5, and 10 mg all met statistical significance for the endpoint of decrease from baseline on the MADRS total score; -14.89, -15.09 and -15.65, respectively (P<0.001 for all).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Jain et al.[144] (2013) Vortioxetine 5 mg QD vs placebo QD	DB, PC Patients 18 to 75 years of age with MDD and a baseline MADRS total score >30	N=600 8 weeks	Primary: Change from baseline in HAMD-24 total score at week six compared to placebo Secondary: Response and remission rates, CGI-I, HAMA, MADRS-S total score, adverse events	Primary: There were no significant differences in efficacy measures between subjects in the 5 mg vortioxetine and placebo groups at week six. Secondary: HAMD-24 total score in subjects with baseline HAMA >19 in the 5 mg vortioxetine group was improved at weeks three to six compared to the placebo group (P<0.05). The most common adverse events for the vortioxetine and placebo groups were nausea (19.1 and 9.4%), headache (17.1 and 15.1%) and diarrhoea (11.4 and 7.0%), respectively.
Katona C, et. al.[145] (2012) Vortioxetine 5 mg QD or duloxetine 60 mg QD vs placebo QD	AC, DB, MC, PC, PG, RCT Patients ≥65 years of age, with a primary diagnosis of MDD per DSM-IV-TR criteria and a MADRS score ≥26	N=453 (N=392 completed the study) 8 weeks	Primary: Change from baseline in HAMD-24 total score at weeks one, two, four, six, and eight. Secondary: Change in baseline from CGI-I, MADRS total score, HAMA and CGI-S at week eight. Cognitive changes from baseline assessed via the RAVLT and DSST at week eight	Primary: The vortioxetine treatment group did not meet the primary endpoint until week six of the study, and it was not reported when the duloxetine treatment group began to separate from placebo for the primary endpoint. The vortioxetine treatment group began to separate on the HAMD-24 scale from placebo at week six (P=0.024). At week eight, vortioxetine 5 mg had a mean change from baseline in HAMD-24 score of -13.7 (P<0.01), and duloxetine 60 mg had a mean change from baseline on the HAMD-24 of -15.8 (P<0.0001). Secondary: Vortioxetine 5 mg and duloxetine 60 mg both met all secondary endpoints at week eight. A change in CGI-I of -0.56 (P<0.001) was reported for the vortioxetine group, along with a decrease in MADRS total change of -4.29 (P<0.001), a decrease in HAMA scores of -2.35 (P<0.01) and a decrease of CGI-S of -0.60 (P<0.001). Duloxetine showed similar results for these secondary endpoints with a P<0.001 for all of these measures. The cognitive measures also showed positive results for both treatment groups. Vortioxetine 5 mg showed a difference from placebo on the DSST change of 2.79 (P>0.05), and vortioxetine showed a difference from placebo in RAVLT for acquisition change of 1.14 (P<0.05) and delayed

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				recall change of 0.47 (P<0.05). The duloxetine group did not show statistical significance for DSST change with a value of 0.77 (no P value reported). The duloxetine group did show statistical significance on the RAVLT for acquisition of change of 1.41 (P<0.01) and delayed recall change of 0.64 (P<0.01)
Mahableshwarkar, et. al.[146] (2013) Vortioxetine 2.5 mg QD or vortioxetine 5 mg QD vs duloxetine 60 mg QD vs placebo QD	DB, PC Adult patients with MDD	N=611 8 weeks	Primary: Change from baseline in the HAM-D24 Secondary: Responder rate, CGI-I), and remission rate; adverse events, ASEX	Primary: Both doses of vortioxetine were associated with declines in HAM-D24 total scores compared to placebo but were not statistically significant. At eight weeks, changes from baseline were [mean]: -10.50 (0.76) placebo, -12.04 (0.74) 2.5 mg vortioxetine, and -11.08 (0.74) 5 mg vortioxetine. Secondary: CGI-I and remission rate were not significantly different from placebo. Duloxetine treatment was associated with declines in HAM-D24 total score [-13.47(0.75); P=0.005] as well as significant improvements in secondary outcome measures vs placebo (P<0.05). The most common adverse events for vortioxetine were nausea, dry mouth, and headache. Rates of sexual dysfunction (ASEX) were 51.0, 37.5, 46.9, and 33.3% in the vortioxetine 2.5 mg, vortioxetine 5 mg, duloxetine, and placebo groups, respectively.
Robinson et al.[147] (2011) Vilazodone 40 mg QD	MC, OL Patients 18 to 70 years of age with MDD	N=616 52 weeks	Primary: Safety, sexual function (CSFQ), effectiveness (MADRS, CGI-S and CGI-I scales) Secondary: Not reported	Primary: A total of 93.8% of patients had ≥1 treatment-emergent adverse events. The most frequent treatment-emergent adverse events were diarrhea (35.7%), nausea (31.6%), and headache (20.0%). The incidence of severe adverse events was 14.9%. The incidence of severe gastrointestinal adverse events was 3.5% and the incidence of severe headache was 1.2%. Mean weight increase was 1.7 kg at week 52. At six months, mean weight change for patients with normal baseline weight was 1.3 kg; for overweight and obese patients, mean weight increases were 1.6 and 1.0 kg, respectively.

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				The mean CSFQ scores at baseline were 46.9 for men and 38.7 for women; both scores indicative of sexual dysfunction. The CSFQ mean scores improved and exceeded threshold values for sexual dysfunction at week four for men and week eight for women. Adverse events pertaining to impaired sexual desire or function were decreased libido (4.2%) and anorgasmia including abnormal orgasm (2.3%). Those pertaining to males only were erectile dysfunction (4.2%) and delayed ejaculation (3.1%). There were a total of eight patients who had adverse events of either suicidal ideation or behavior. The mean MADRS scores improved from 29.9 at baseline to 11.4 at week eight (change, -18.5), 8.2 at week 24 (change, -21.7), and 7.1 at one year (change, -22.8). The mean CGI-S improved from 4.3 at baseline to 2.5 at week eight (change, -1.9) and 1.7 at one year (change, -2.6). The CGI-I mean score decreased from 3.5 at week one to 1.9 at week eight and 1.4 at one year. Secondary: Not reported
Baldwin et al.[148] (2012) Vortioxetine 2.5 mg QD or vortioxetine 5 mg QD or vortioxetine 10 mg QD	OL Patients with MDD	N=535 52 weeks	Primary: Safety and tolerability, MADRS Secondary: Not reported	Primary: Adverse events reported by >10% of patients were nausea, headache, and nasopharyngitis. Six patients had eight adverse events related to sexual dysfunction. There were no clinically significant safety findings with respect to mean changes of vital signs, weight, ECG parameters, or clinical laboratory values. Patients entered the ES with a mean MADRS total score of 13.5+8.7. The mean MADRS total score decreased (improved) by approximately 8 points to 5.5+6.0 at week 52. By the end of the study, the proportion of responders had increased from 63 to 94%, as had the proportion in remission (MADRS <10), increasing from 42 to 83%. Patients in remission (n=226) at the start of this study had a relapse rate (MADRS >22) of 9.7%.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Cipriani et al.[149] (2009) New-generation antidepressants (bupropion, citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, milnacipran, mirtazapine, paroxetine, reboxetine, sertraline, venlafaxine)	MA (117 trials) Patients with MMD receiving acute treatment	N=25,928 6 to 12 weeks	Primary: Response (defined as the proportion of patients who had a reduction ≥50% from the baseline score on the HDRS or MADRS, or who scored much improved or very much improved on the CGI at eight weeks) and dropout rates Secondary: Not reported	Primary: *Direct Comparisons* Efficacy favored escitalopram over citalopram; citalopram over reboxetine and paroxetine; mirtazapine over fluoxetine and venlafaxine; sertraline over fluoxetine; and venlafaxine over fluoxetine and fluvoxamine. For dropouts, fluoxetine was better tolerated than reboxetine and citalopram than sertraline. *Multiple-treatments MA* Escitalopram, mirtazapine, sertraline, and venlafaxine were significantly more efficacious than duloxetine, fluoxetine, fluvoxamine, paroxetine, and reboxetine. Reboxetine was significantly less efficacious than all the other 11 antidepressants. Duloxetine and paroxetine were less well tolerated than escitalopram and sertraline; fluvoxamine was less well tolerated than citalopram, escitalopram, and sertraline; venlafaxine was less well tolerated than escitalopram; reboxetine was less well tolerated than many other antidepressants, such as bupropion, citalopram, escitalopram, fluoxetine, and sertraline; and escitalopram and sertraline were better tolerated than duloxetine, fluvoxamine, paroxetine, and reboxetine. Mirtazapine, escitalopram, venlafaxine, and sertraline were more efficacious than fluoxetine, and fluoxetine was more efficacious than reboxetine. Fluoxetine was better tolerated than reboxetine. Mirtazapine, escitalopram, venlafaxine, and sertraline were among the most efficacious treatments, and escitalopram, sertraline, bupropion, and citalopram were better tolerated than the other remaining antidepressants. The cumulative probabilities of being among the four most efficacious treatments were: mirtazapine (24.4%), escitalopram (23.7%), venlafaxine (22.3%), sertraline (20.3%), citalopram (3.4%), milnacipran (2.7%), bupropion (2.0%), duloxetine (0.9%), fluvoxamine (0.7%), paroxetine

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(0.1%), fluoxetine (0.0%), and reboxetine (0.0%). The cumulative probabilities of being among the four best treatments in terms of acceptability were escitalopram (27.6%), sertraline (21.3%), bupropion (19.3%), citalopram (18.7%), milnacipran (7.1%), mirtazapine (4.4%), fluoxetine (3.4%), venlafaxine (0.9%), duloxetine (0.7%), fluvoxamine (0.4%), paroxetine (0.2%), and reboxetine (0.1%). Secondary: Not reported
Moncrieff et al.[150] (2004) Antidepressants vs placebo	MA Patients with MDD	N=751 (9 trials) Variable duration	Primary: Efficacy Secondary; Not reported	Primary: TCAs were statistically better than active placebo in the pooled analysis (0.39, 95% CI, 0.24 to 0.54). Secondary; Not reported
Walsh et al.[151] (2002) Antidepressants vs placebo	MA Adult outpatients with MDD	N=not specified (75 trials) Variable duration	Primary: HAM-D, CGI Secondary: Not reported	Primary: The mean proportion of patients in the placebo group who responded was 29.7% (range, 12.5 to 51.8). Response was determined by a reduction of at least 50% in their score on the HAM-D and/or CGI rating of markedly or moderately improved. Both the proportion of patients responding to placebo and the proportion responding to medication were significantly positively correlated with the year of publication (for placebo P<0.001; for medication P=0.02). The association between year of publication and response rate was more statistically robust for placebo than medication. Secondary; Not reported
Geddes et al.[152] (2003) Antidepressants	MA Studies evaluating relapse prevention	N=4,410 (31 trials) 6 to 36 months	Primary: Proportion of patients relapsing; withdrawal from	Primary: Continuing treatment with antidepressants reduced the odds of relapse by 70% (95% CI, 62 to 78; P<0.00001) compared to treatment discontinuation. The average rate of relapse on placebo was 41%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	of depression		the trial Secondary: Not reported	compared to 18% on active treatment. The treatment effect seemed to persist for up to 36 months, although most trials were of 12 months duration, and so the evidence on longer-term treatment requires confirmation. Significantly more participants allocated antidepressants withdrew from the trials than did those allocated to placebo (18 vs 15%, respectively; OR, 1.30; 95% CI, 1.07 to 1.59). Secondary: Not reported
Thase et al.[153] (1995) Phenelzine (PHZ) vs isocarboxazid (ISO) vs tranylcypromine (TRP) vs placebo	MA Patients with MDD	Review of Medline and Psychological abstracts from 1959 to 1992	Primary: Efficacy Secondary; Not reported	Primary: For outpatients using ITT samples, all three agents appear to be equally effective (PHZ=57.9%±4.0%; ISO=60.1%±7.1%; TRP=52.6%±12.4%). When compared to placebo in outpatients, ISO (41.3%±18.0%) had a larger relative advantage compared to either PHZ (29.5% ±11.1%) or TRP (22.1%±25.4%) in the doses studied. For inpatients, PHZ was somewhat more effective (22.3%±30.7%) than placebo, whereas the ISO-placebo difference was smaller (15.3%±12.6%). Secondary; Not reported
Cipriani et al.[154] (2005) Fluoxetine, sertraline, nortriptyline, amitriptyline, venlafaxine,	MA (132 trials) Patients with depression	N=9,311 Duration varied	Primary: Number of patients who responded to treatment (HAM-D, MADRS) Secondary: Tolerability	Primary: On a dichotomous outcome fluoxetine was less effective than sertraline (PetoOR, 1.40; 95% CI, 1.11 to 1.76), mirtazapine (PetoOR, 1.64; 95% CI, 1.01 to 2.65) and venlafaxine (PetoOR, 1.40; 95% CI, 1.15 to 1.70; P values not reported). On a continuous outcome, fluoxetine was less effective than venlafaxine (SMD random effect, 0.11; 95% CI, 0.00 to 0.23; P value not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
imipramine, nefazodone, citalopram, desipramine, paroxetine, pramipexole, fluvoxamine, trazodone, bupropion, clomipramine, duloxetine, mirtazapine, doxepin				Secondary: Fluoxetine was better tolerated than TCAs considered as a group (PetoOR, 0.78; 95% CI, 0.68 to 0.89), and was better tolerated in comparison with individual antidepressants, in particular than amitriptyline (PetoOR, 0.64; 95% CI, 0.47 to 0.85) and imipramine (PetoOR, 0.79; 95% CI, 0.63 to 0.99), and among newer antidepressants than pramipexole (PetoOR, 0.20; 95% CI, 0.08 to 0.47; P values not reported).
Stahl et al.[155] (1997) Mirtazapine up to 35 mg daily vs amitriptyline up to 280 mg daily vs placebo up to 7 capsules daily	MA Patients with MDD	N=580 (4 trials) 6 weeks	Primary: HAM-D, HDRS, responder rate (percentages of patients with ≥50% decrease in baseline 17-item HDRS score), remitter rate (patients with a total 17-item HDRS score ≤7), MADRS, CGI Secondary: Change from baseline in the "depressed mood" item on the HDRS scale, anxiety/ somatization factor, sleep disturbance factor, melancholia factor,	Primary: Compared to placebo, both mirtazapine and amitriptyline therapy significantly improved patient HDRS, MADRS, and CGI scores from baseline (P<0.05). Significantly greater percentages of patients responded to mirtazapine or amitriptyline therapy, assessed with the HDRS criteria, compared to placebo (P<0.05). Significantly greater percentages of patients randomized to mirtazapine or amitriptyline therapy exhibited remission compared to placebo (P<0.05). There were no statistically significant differences between mirtazapine and amitriptyline in any of the primary endpoints. Secondary: Significantly greater improvement from baseline in the "depressed mood" item was seen in the mirtazapine and amitriptyline groups compared to placebo (P<0.05). Significantly greater improvement from baseline in the anxiety/soma-tization, sleep disturbance, and melancholia factors was seen in the mirtazapine and amitriptyline groups compared to placebo (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			tolerability	There were no statistically significant differences between mirtazapine and amitriptyline in the "depressed mood", anxiety, somatization, sleep disturbance, or melancholia factors on the HDRS scale. Patients on amitriptyline therapy experienced a significantly higher incidence of restlessness (14.0 vs 2.1%), vertigo (2.1 vs 0), blurred vision (6.2 vs 0.5%), dyspepsia (10.4 vs 0.5%), dry mouth (80.8 vs 34.0%), constipation (31.1 vs 18.0%), palpitations (8.8 vs 3.6%), and tachycardia (4.7 vs 0.5%) compared to patients receiving mirtazapine therapy (P<0.05). Patients on mirtazapine therapy experienced a significantly higher incidence of weight gain compared to the amitriptyline group (14.4 vs 6.7%; P<0.05). Drowsiness and sedation were more common in the active groups compared to the placebo group (P<0.05). Hypotension was more common in the amitriptyline group compared to the placebo (3.6 vs 0.5%; P<0.05). Increased appetite was more common in the mirtazapine group compared to the placebo group (3.6 vs 0; P<0.05).
Bull et al.[156] (2002) Continuation of an SSRI vs discontinuation of an SSRI vs switching of an	RETRO Adult patients diagnosed with a depressive disorder, taking an SSRI for at least 6 months were interviewed over the phone; prescribing physicians were asked to complete a survey	N=137,401 6 months	Primary: Patient-physician communication about therapy duration and adverse effects, therapy discontinuation or switching of medication within three months of SSRI use, BDI-FS, depression symptoms	Primary: While 72% of physicians reported instructing their patients on taking SSRIs for a minimum of 6 months, only 34% of patients acknowledged receiving this information from their physician and 56% reported receiving no instructions at all. Patients instructed to continue therapy for less than 6 months were 3 times more likely to discontinue therapy prematurely compared to those told to continue therapy for a longer duration (OR, 3.12; 95% CI, 1.21 to 8.07; P<0.001). Patients who were informed about adverse effects common with their medication were less likely to discontinue therapy than patients who did not have this discussion with their physician (OR, 0.49; 95% CI, 0.25 to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
SSRI			Secondary; Not reported	0.95). Patients who discussed adverse effects with their physicians were more likely to switch medications (RR, 5.60; 95% CI, 2.31 to 13.60). Patients experiencing adverse effects were 3 times more likely to switch their medication (OR, 3.09; 95% CI, 1.30 to 7.31). Less than three follow-up visits, and lack of therapeutic response to medication at three months were also associated with a higher incidence of therapy discontinuation (P=0.002, P<0.001, respectively). Patients who continued to have severe symptoms, based on the BDI-FS scale, were six times more likely to switch their medication (OR, 6.15; 95% CI, 2.11 to 17.89). Secondary; Not reported
Anderson et al.[157] (2000) TCAs vs SSRIs	MA Patients with MDD	N=10,706 (102 trials) Variable duration	Primary: HAM-D, MADRS Secondary: Adverse events	Primary: Efficacy was based on 102 studies (5,533 SSRI patients and 5,173 TCA patients). Efficacy was determined by comparing the mean reduction in depression scores based upon the HAM-D or the MADRS. There was no statistical difference in efficacy between the two groups (effect size, –0.03; 95% CI, –0.09 to 0.03). TCAs did appear more effective for inpatients (–0.23; 95% CI, –0.4 to -0.05). 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.[158] (2003) TCAs vs	MA Patients with MDD	N=2,951 (11 trials) Variable duration	Primary: HAM-D; MADRS Secondary: Tolerability	Primary: Efficacy between SSRI and tricyclics did not differ significantly (standardized weighted mean difference, fixed effects 0.07; 95% CI, –0.02 to 0.15; P<0.11). Secondary: Significantly more patients receiving a tricyclic withdrew from treatment (RR, 0.78; 95% CI, 0.68 to 0.90; P<0.0007) and withdrew specifically

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
SSRIs				because of side effects (RR, 0.73; 0.60 to 0.88; P<0.001).
Steffens et al.[159] (1997) TCAs vs SSRIs	MA Patients with MDD	N=not specified (34 trials) Variable duration	Primary: HAM-D Secondary: Frequency of side effects	Primary: Overall, the response rate to treatment for patients who completed a trial was 63.2% for SSRIs and 68.2% for TCAs (P=0.038). For the ITT groups, these rates dropped to 48.0 and 48.6% (P=NS), respectively. Significantly more TCA-treated than SSRI-treated patients dropped out due to either lack of efficacy or adverse reactions (30.0 vs 24.7%; P=0.01). Secondary: Patients taking SSRIs experienced more gastrointestinal problems and sexual dysfunction, whereas treatment with TCAs produced significantly more complaints of sedation, dizziness, and anticholinergic symptoms.
Diabetic Neuropathy				
Yan et al.[160] (2010) Duloxetine 60 to 120 mg daily vs placebo	DB, PC, RCT Adult Chinese patients with diabetic peripheral neuropathic pain and BPI 24-hour average pain severity rating ≥4	N=215 12 weeks	Primary: Change from baseline to endpoint in BPI average pain score Secondary: BPI-S and BPI-I, PGI-I, CGI-S, EQ-5D, Athens Insomnia Scale	Primary: Mean change from baseline to endpoint in BPI pain score was not significantly different between treatments (-2.31±0.18 vs -2.69±0.19; P=0.124). Duloxetine-treated patients showed significantly greater pain reduction compared to placebo-treated patients at weeks one, two, and four (P=0.004, P=0.009, and P=0.006), but not at week eight (P=0.125) and 12 (P=0.107). Secondary: Duloxetine-treated patients experienced significant improvement in PGI-I (2.32±0.11 vs 2.64±0.10; P=0.028), CGI-S (-1.24±0.11 vs -0.99±0.11; P=0.036), AUC for pain relief, BPI-S pain right now (-2.72±0.26 vs -1.99±0.25; P=0.012), and BPI-I walking ability (-2.45±0.24 vs -1.82±0.23; P=0.016). Patients receiving duloxetine had numerically higher 30 and 50% response rates on BPI average pain compared to placebo-treated patients. A higher proportion of patients receiving duloxetine (62.5%) met the criteria for sustained response compared to patients receiving placebo (50.5%). All other secondary efficacy measures, including health outcomes measures, were numerically but not significantly improved in patients receiving duloxetine compared to patients receiving placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Armstrong et al.[161] (2007) Duloxetine 20 or 60 mg QD, or 60 mg BID vs placebo	3 DB, MC, PC, RCT Patients with diabetic peripheral neuropathic pain	N=1,139 12 weeks	Primary: Patient-reported functional outcomes (SF-36, BPI, EQ-5D) Secondary: Not reported	Primary: Diabetic peripheral neuropathic pain patients treated with duloxetine 60 mg QD or BID had greater improvement, compared to placebo, in all SF-36 domains of physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. Within treatment group changes among the domain scores ranged from 0.9 to 23.5 points. Duloxetine 60 mg BID showed some advantage over duloxetine 60 mg QD on general health (P=0.02) and mental health (P=0.04) status. Consistent results were seen in the ITT population with the exception that the above indicated advantages of duloxetine 60 mg BID over 60 mg QD in the domains of general and mental health were not significant. Duloxetine 60 mg QD and 60 mg BID were significantly more efficacious to placebo at reducing scores in all BPI-I items thereby indicating improvements in all seven items, with similar results demonstrated for the ITT population. In the analysis of the EQ-5D, patients on duloxetine 60 mg QD (P=0.004) and 60 mg BID (P<0.001) were both significantly better compared to placebo for the trial completers. Results for the ITT analysis were consistent, thus demonstrating the superiority of duloxetine 60 mg QD and BID compared to placebo with regard to changes in all included function and QOL measures. Secondary: Not reported
Kajdasz et al.[162] (2007) Duloxetine 20 or 60 mg QD, or 60 mg BID vs placebo	Post-hoc analysis of 3 DB, MC, PC, RCT Patients with diabetic peripheral neuropathic pain	N=1,139 12 weeks	Primary: Response rate (defined as ≥30 and ≥50% reductions from baseline in weekly mean of the 24-hour average pain severity scores)	Primary: NNTs based on 50% reduction for patients receiving duloxetine 60 mg QD and 60 mg BID were 5.2 (95% CI, 3.8 to 8.3) and 4.9 (95% CI, 3.6 to 7.6), respectively, based on LOCF. Similarly, NNTs of 5.3 (95% CI, 3.8 to 8.3) for 60 mg QD and 5.7 (95% CI, 4.1 to 9.7) for 60 mg BID observed based on baseline observation carried forward. Secondary: The NNHs based on discontinuation due to adverse events were 17.5 (95% CI, 10.2 to 58.8) with duloxetine 60 mg QD and 8.8 (95% CI, 6.3 to 14.7)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Secondary: NNH (based on rates of dis-continuation due to adverse events)	with duloxetine 60 mg BID.
Lunn et al.[163] (2009) Duloxetine vs placebo or control Only outcomes for painful peripheral neuropathy are reported.	SR (6 RCTs) Patients with painful peripheral neuropathy or chronic pain conditions	N=2,200 ≥8 weeks	Primary: Short term (≤12 weeks) improvement in pain Secondary: Long term (>12 weeks) improvement in pain, improvement in short and long term pain ≥30%, improvement in any validated QOL score ≥30%	Primary: Three trials in painful diabetic neuropathy reported data on the primary outcome measure of 50% improvement of pain compared to baseline at <12 weeks. Patients were treated with duloxetine 20, 60, or 120 mg/day. Combining data from all doses from the three trials together, the RR of 50% improvement with any dose was 1.63 (95% CI, 1.35 to 1.97) greater than placebo. The RR of improvement was significantly greater compared to placebo for the 60 and 120 mg/day doses, but not 20 mg/day, for which it was 1.43 (95% CI, 0.98 to 2.09). The RR of improvement with 120 mg/day (1.66; 95% CI, 1.35 to 2.04) was not significantly greater compared to 60 mg/day (1.65; 95% CI, 1.34 to 2.03). The mean improvement in pain at <12 weeks on an 11-point Likert scale was significantly greater compared to placebo with 60 (-1.04; 95% CI, -1.37 to -0.71) and 120 mg/day (-1.16; 95% CI, -1.49 to -0.83) of duloxetine. Secondary: None of the included trials of painful diabetic neuropathy included outcomes >12 weeks. Two trials included data on >30% improvement of pain at ≤12 weeks. The results were similar to those for ≥50% improvement. Relative rates of improvement were significantly greater compared to placebo with duloxetine for the 60 mg/day (1.53; 95% CI, 1.27 to 1.83), 120 mg/day (1.55; 95% CI, 1.30 to 1.86), and for both doses combined (1.54; 95% CI, 1.30 to 1.82). Trials that included QOL information used the SF-36. In painful diabetic neuropathy, the effect of duloxetine 20 mg was not significant on any of the selected SF-36 subscores at up to 12 weeks (relevant physical, mental, and bodily pain subsections). The WMD of improvement on the physical

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				summary component was significantly greater with 60 mg/day (2.51; 95% CI, 1.00 to 4.01) and 120 mg/day (2.80; 95% CI, 1.04 to 4.55). The WMD on the mental summary component was significantly greater only with 120 mg/day (2.23; 95% CI, 0.69 to 3.77). The WMD on the bodily pain subscale showed significantly more improvement compared to placebo with 60 mg/day (5.58; 95% CI, 1.74 to 9.42) and with 120 mg/day (8.19; 95% CI, 4.33 to 12.05). Three trials reported the PGI-C and pain at rest, and two reported the bodily pain index. The WMD for each outcome was significant and similar in magnitude for 60 and 120 mg/day. However, a clinically meaningful differences in the PGI-C is suggested as one point and hence the change associated with 60 mg/day (-0.59; 95% CI, -0.78 to -0.41) may not be clinically significant. The RR for the bodily pain index is significantly reduced by -0.97 (95% CI, -1.38 to -0.57) but again this borders on a change considered clinically significant.
Kaur et al.[164] (2011) Duloxetine 20 to 60 mg QD for 6 weeks vs amitriptyline 10 to 50 mg QD at bedtime for 6 weeks	AC, DB, RCT, XO Patients 18 to 75 years of age with type 2 diabetes who had painful diabetic neuropathy for ≥1 month	N=58 14 weeks	Primary: Reduction in the median pain score from baseline Secondary: Assessment of pain by McGill Pain Questionnaire, overall improvement score, 24-point HAM-D, change in sleep pattern, and patient self-evaluation of change in PGI-C scale	Primary: There was a significant improvement in pain at six weeks with both treatments compared to their baseline values (P<0.001 for both). For duloxetine, 59% of patients showed good improvement, 22% showed moderate improvement, and 9% showed mild improvement. For amitriptyline, 55% of patients showed good improvement, 24% showed moderate improvement, and 16% showed mild improvement. Overall pain relief of >30% was observed in 64% of patients receiving duloxetine and 62% of patients receiving amitriptyline. A >50% improvement was seen in 50% of patients receiving duloxetine and 55% of patients receiving placebo. Secondary: There was no significant difference in efficacy among the treatment groups as assessed by the McGill Pain Questionnaire and Likert scale. Significant improvement in sleep and overall well being was observed with both drugs (P<0.001 for both). Overall, 48% of patients preferred duloxetine compared to 36% of patients who preferred amitriptyline (P=0.18). Based on pain relief and tolerability,

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				5, 14 and 30% of patients preferred duloxetine 20, 40, and 60 mg, respectively. A total of 5, 22, and 9% of patients preferred amitriptyline 10, 25, and 50 mg. The number of mild treatment-emergent adverse effects was higher with duloxetine compared to amitriptyline (P<0.02). The number of moderate to severe treatment emergent adverse event was higher with amitriptyline (P<0.01). Dry mouth was significantly more common with amitriptyline that duloxetine (55 vs 24%, respectively; P<0.01).
Boyle et al.[165] (abstract) (2012) Duloxetine 60 mg/day vs amitriptyline 50 mg/day vs pregabalin 300 mg/day	AC, DB, PG, RCT Patients ≥18 years of age with diabetes (type 1 or type 2) for ≥1 year and neuropathic pain of diabetic origin (≥1 of the following: dysesthesia, burning pain, cold or heat allodynia, shooting or lancinating pains and hyperalgesia affecting both lower extremities at any level below the mid-thighs) and LANSS score >12	N=83 4 weeks	Primary: BPI Secondary: SF-36, sleep, mood and daytime sleepiness	Primary: All three treatments significantly reduced pain compared to placebo. No one treatment was "superior" to the others with regard to pain. Secondary: For sleep, pregabalin improved sleep continuity (P<0.001), whereas duloxetine increased wake and reduced TST (P<0.01 and P<0.001). Despite negative effects on sleep, duloxetine enhanced central nervous system arousal and performance on sensory motor tasks. There were no significant safety findings; however, there were a significantly higher number of adverse events in the pregabalin treatment group.
Tanenberg et al.[166] (2011) Duloxetine 60 mg/day vs pregabalin 300	MC, NI, OL, RCT Adult patients with type 1 or 2 with HbA_{1c} ≤12%, and diabetic peripheral neuropathic pain who had been treated with	N=407 12 weeks	Primary: Reduction from baseline in the weekly mean of the daily 24-hour pain diary ratings at week 12 Secondary:	Primary: The estimated mean change in the daily pain severity score at 12 weeks was -2.6 for duloxetine and -2.1 for pregabalin, representing an observed 0.49 advantage of duloxetine; therefore, NI was established. Significant superiority vs pregabalin in the mean daily pain diary ratings was observed at weeks, two, three, and five through 11 with duloxetine and with duloxetine plus gabapentin at weeks two and eight, but between-treatment differences at the 12 week end point met NI criteria, not

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/day vs duloxetine 60 mg/day and gabapentin ≥900 mg/day (existing therapy)	gabapentin (900 mg/day) and had an inadequate response		Worst pain and night pain ratings, Clinician Global Impression of Severity, BPI-S and BPI-I, BDI-II, PGI-I, SDS, response rate	statistical superiority. The NI comparison between duloxetine and combination therapy on the differences between end point mean changes in daily pain diary ratings in the ITT patient population was also met. Secondary: Reduction from baseline in BPI average pain and BPI worst pain severity ratings was significantly greater with duloxetine vs pregabalin, but differences between treatments were not significant for the other BPI pain measures, CGI-S, depressive symptoms, or the SDS global measure. Also, no significant between-treatment differences were found among the various response outcomes.
Quilici et al.[167] (2009) Duloxetine vs pregabalin and gabapentin Placebo was used a common comparator.	MA (11 RCTs; duloxetine, 3 trials; pregabalin, 6 trials; gabapentin, 2 trials) Patients with diabetic peripheral neuropathic pain	N=not specified ≥5 to 13 weeks	Primary: Reduction in 24-hour pain severity, response rate (≥50% pain reduction), overall health improvement (PGI-I and PGI-C) Secondary: Not reported	Primary: Direct comparisons All three agents were more efficacious to placebo for all efficacy parameters. For 24-hour pain severity effect values were -1.13 (95% CI, -1.36 to -0.89), -0.90 (95% CI, -1.23 to -0.57), and -1.44 (95% CI, -2.21 to -0.66) with duloxetine, pregabalin, and gabapentin. Corresponding effect values for response rates were 0.86 (95% CI, 0.63 to 1.09; NNT, 5; 95% CI, 3 to 7) and 0.84 (95% CI, 0.52 to 1.16; NNT, 5; 95% CI, 4 to 8) with duloxetine and pregabalin, and for PGI-I/C were -0.76 (95% CI, -1.00 to -0.51) and -1.29 (95% CI, -1.72 to -0.86) with duloxetine and pregabalin. Indirect comparisons For the primary efficacy outcome of 24-hour reduction in pain severity, a difference of -0.248 (95% CI, -0.677 to 0.162) was observed in favor of duloxetine over pregabalin. Duloxetine was not inferior to pregabalin on this outcome. For response rates, the difference between duloxetine and pregabalin was close to zero and not significant. For PGI-I/C outcomes, pregabalin showed an improvement of 0.542 points over duloxetine, a difference that reached significant (95% CI, 0.016 to 1.060). Secondary: Not reported

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Wernicke et al.[168] (2007) Duloxetine 60 mg BID vs routine care (gabapentin, amitriptyline, and venlafaxine)	ES, OL, RCT Adult patients who presented with pain due to bilateral peripheral neuropathy caused by type 1 or 2 diabetes	N=293 52 weeks	Primary: Not reported Secondary: Health outcomes	Primary: Not reported Secondary: There were significant treatment-group differences observed in favor of duloxetine in the SF-36 physical component summary score, and subscale scores of physical functioning, bodily pain, mental health, and vitality. A significant treatment-by-investigator interaction was seen for general health perceptions (P=0.073), mental health (P=0.092), and social functions (P=0.003) subscales. There were no significant treatment-group differences observed on the EQ-5D questionnaire. During the trial, four deaths occurred. Deaths were considered to be unrelated to the study drug or protocol procedures. During the trial, 22 (11.2%) duloxetine vs 16 (16.7%) routine care-treated patients experienced at least one serious adverse event. The most frequently reported serious adverse events for both treatments together were cerebrovascular accident and diabetes, and these events were not considered to be drug-related. Fourteen (4.8%) patients discontinued due to any adverse event; which included 11 and three duloxetine- and routine care-treated patients (P=0.560). A total of 157 (53.6%) patients reported at least one treatment-emergent adverse event, and there were no treatment-group differences in the overall incidence of these events. There was a significant increase in mean uric acid levels in routine care-treated patients compared to duloxetine-treated patients with regard to chemistry/urinalysis. Both treatments experienced a slight increase in HbA_{1c}, with duloxetine-treated patients experiencing a larger increase in the mean change from baseline to endpoint (P<0.001). No significant treatment-group differences were observed in low density lipoprotein cholesterol, high density lipoprotein cholesterol, and triglyceride levels. There were no significant treatment-group differences observed in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				mean change in the Michigan Neuropathy Screening Instrument score from baseline to endpoint. There were no significant treatment-group differences observed in either subset of patients in the ulnar F-wave, ulnar distal sensory latency, and peroneal compound muscle action potential from baseline to endpoint for all patients. There was a significant increase observed in the peroneal F-wave measure for routine care-treated patients (P=0.05). There were no significant treatment-group differences observed for any of the ophthalmologic exam measures. There was a significant treatment-group difference observed in the mean change in microalbumin/creatinine ratio from baseline to endpoint (P=0.031), with duloxetine-treated patients experiencing a bigger mean decrease compared to routine care-treated patients. There was no significant treatment-group difference observed in the mean change from baseline to endpoint vital signs and weight. One duloxetine-treated patient and one routine care-treated patient met the definition for sustained elevation in SBP, and there were no significant differences between treatments. There were no ECG parameters that were significantly different between treatments. Significantly more routine-care patients had potentially clinically significant Fridericia-corrected QT interval increases (P=0.034).
Raskin et al.[169] (2006) Duloxetine 60 mg BID vs routine care (gabapentin,	ES, OL, RCT Adult patients who presented with pain due to bilateral peripheral neuropathy caused by type 1 or 2 diabetes	N=237 52 weeks	Primary: Not reported Secondary: SF-36, EQ-5D	Primary: Not reported Secondary: No significant treatment-group differences were observed in the SF-36 subscales or in the EQ-5D questionnaire.

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amitriptyline, and venlafaxine)				
Fibromyalgia				
Arnold et al.[170] (2012) Duloxetine 30 mg/day	DB, PC, RCT Patients meeting the criteria for primary fibromyalgia as defined by the American College of Rheumatology	N=308 12 weeks	Primary: Average pain severity item from the BPI-Modified Short Form, Secondary: PGI-I, FIQ total score and those measuring pain, depression, anxiety, health outcomes, and safety	Primary: Duloxetine-treated patients did not have a statistically significant BPI-Modified Short Form average pain severity reduction vs placebo-treated patients (-2.04 vs -1.70; P=0.202). Secondary: There was a significant difference between duloxetine-treated and placebo-treated patients (P<0.05) for the PGI-I endpoint score (2.97 vs 3.35) and the changes in FIQ total score (-14.62 vs -9.75) and the SF-36 mental component score. Discontinuations due to adverse events did not differ significantly between treatment groups; nausea and dry mouth were the only adverse events with a significantly higher incidence with duloxetine vs placebo.
Arnold et al.[171] (2009) Duloxetine 60 to 120 mg/day vs placebo	DB, MC, PC, RCT (pooled analysis of 4 trials) Outpatients ≥18 years of age with fibromyalgia and a score ≥4 on the average pain severity item of the BPI	N=1,332 12 to 15 weeks	Primary: Pain severity (BPI) Secondary: BPI pain interference items, FIQ, CGI-S, PGI-I, HAM-D, SF-36, SDS, MFI	Primary: In both depressed and nondepressed patients, significantly more duloxetine-treated patients achieved ≥30% reduction in BPI average pain score from baseline compared to placebo-treated patients (P<0.001). The treatment-by-MDD status interaction was not significant (P=0.34). In both depressed and nondepressed patients, significantly more duloxetine-treated patients achieved ≥50% reduction in BPI average pain score from baseline compared to placebo-treated patients (P<0.001). The treatment-by-MDD status interaction was not significant (P=0.39). Secondary: For both depressed and nondepressed patients, mean changes from baseline to endpoint on the FIQ, SDS, and CGI-S were significantly greater for duloxetine-treated patients compared to placebo-treated patients (P<0.05). All treatment-by-MDD status interactions were not significant for these assessments (P value not significant). In patients with MDD, significant differences in baseline to endpoint mean changes between duloxetine-treated and placebo-treated patients were observed for the following SF-36 domains: mental component score,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				mental health score, bodily pain, physical role functioning, social functioning score, and vitality score. In patients without MDD, significant differences in baseline to endpoint mean changes between duloxetine-treated and placebo-treated patients were observed for the following SF-36 domains: mental component score, mental health score, general health score, bodily pain, physical functioning, emotional role functioning score, and vitality score. With the exception of the mental health subscale, for all SF-36 domains and composite scales, the treatment-by-MDD status interactions were not significant. In patients with MDD, significant differences in baseline to endpoint mean changes between duloxetine-treated and placebo-treated mental fatigue and reduced motivation; whereas in patients without MDD, the only significant difference between the duloxetine-treated and placebo-treated groups was observed for the mental fatigue score. For all MFI domains, the treatment-by-MDD status interactions were not significant. In the MDD subgroup, the mean improvement on the clinician-rated HAM-D-17 total score from baseline to endpoint was significantly greater for duloxetine-treated patients compared to placebo-treated patients. In patients without MDD, the mean improvement on the HAM-D-17 total score from baseline to endpoint was not significantly different between the treatment groups. The treatment by- MDD status interaction was not significant (P=0.14). For both depressed and nondepressed patients, significantly more duloxetine-treated patients rated themselves as ‘‘much improved’’ or ‘‘very much improved’’ compared to placebo-treated patients (P<0.001). The treatment-by-MDD status interaction was not significant (P=0.45).
Russell et al.[172] (2008) Duloxetine 20 mg/day vs	DB, MC, PC, RCT Patients ≥18 years of age with fibromyalgia	N=502 6 months	Primary: Pain severity (BPI), PGI-I Secondary: FIQ, CGI-S, tender-point pain assessments, MFI,	Primary: After three months of therapy, patients treated with duloxetine 60 and 120 mg/day experienced significantly greater improvements in average pain severity score compared to patients treated with placebo (-1.99, -2.31, -1.39, respectively; P≤0.05 and P≤0.001 vs placebo, respectively). There was no significant difference in pain severity with duloxetine 20 mg/day. At the six-month endpoint, patients treated with duloxetine experienced greater improvements in average pain severity score compared to patients

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
duloxetine 60 mg/day vs duloxetine 120 mg/day vs placebo			HAM-D-17, SDS, SF-36, EQ-5D	treated with placebo (duloxetine 20/60 mg/day, -2.22 [P≤0.05]; duloxetine 60 mg/day, -1.98 [P≤0.05]; duloxetine 120 mg/day, -2.26 [P≤0.01]). After three months of therapy, the mean endpoint PGI-I score was significantly lower in patients treated with duloxetine 20 and 120 mg/day compared to patients treated with placebo (2.79, 2.93, 3.37, respectively; P≤0.01 and P≤0.05 vs placebo, respectively). There was no significant difference in PGI-I scores with duloxetine 60 mg/day compared to placebo. After six months of therapy, the mean endpoint PGI-I score was significantly lower in the duloxetine 20/60 mg/day (2.79; P≤0.01) and duloxetine 120 mg/day groups (2.93; P≤0.05), but not the duloxetine 60 mg/day group (3.08; P value not significant) compared to the placebo group (3.37). Secondary: After three months of therapy, duloxetine-treated patients demonstrated greater improvements in the CGI-S score (60 and 120 mg; P≤0.01 and P≤0.001, respectively), SF-36 mental component score (120 mg; P≤0.05), and some of the MFI domains (20, 60, 120 mg; P≤0.05, P≤0.01, and P≤0.001) compared to placebo-treated patients. There were no differences between duloxetine and placebo on other secondary efficacy and health outcome measures. After six months of therapy, duloxetine-treated patients demonstrated greater improvements in the CGI-S score (20/60 mg/day; P≤0.05, 60 mg/day; P≤0.01, 120 mg/day; P≤0.001) and MFI mental fatigue domain (20/60 mg/day; P≤0.05, 60 mg/day; P≤0.05, 120 mg/day; P≤0.01). The other efficacy and health outcome measures that achieved significance in the duloxetine treatment groups compared to the placebo group included the MFI physical fatigue domain and EQ-5D (duloxetine 20/60 mg/day) and the MFI physical fatigue, reduced motivation, and reduced activity domains, as well as SF-36 mental component score (duloxetine 120 mg/day). Response rates (defined as a ≥50% improvement from baseline to the three-month endpoint in the average pain severity score) were significantly greater for duloxetine 120 mg/day (40.1%; P=0.003), but not for

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				duloxetine 60 mg/day (34.0%; P=0.067) or for duloxetine 20 mg/day (32.5%; P=0.200) compared to placebo (23.7%). Response rates from baseline to the six-month endpoint were significantly greater for duloxetine 20/60 mg/day (36.4%; P=0.025), duloxetine 60 mg/day (32.6%; P=0.045), and duloxetine 120 mg/day (35.9%; P=0.009) compared to placebo (21.6%). In patients diagnosed with MDD at study entry, least squares mean changes in HAM-D-17 total score at six months were -4.8 for placebo, -5.2 for duloxetine 20/ 60 mg/day, -6.9 for duloxetine 60 mg/day, and -7.2 for 120 mg/day. Treatment group differences were not statistically significant when compared to placebo.
Mease et al.[173] (2010) Duloxetine 60 to 120 mg/day	ES Patients ≥18 years of age with fibromyalgia	N=278 6 months	Primary: Safety, efficacy Secondary: Not reported	Primary: Overall study drug compliance during the six-month ES was 81% in Study 1 and 79% in Study 2. The most common adverse events leading to discontinuation were fatigue and insomnia in Study 1, and diarrhea and nausea in Study 2. The most common treatment-emergent adverse events in Study 1 were nausea, dry mouth, and insomnia. The most common treatment-emergent adverse events in Study 2 were dry mouth, nausea, headache, hyperhidrosis, and muscle spasm. The majority of the treatment groups showed small mean change improvements in the BPI average pain severity score over the final six-month period. The placebo/duloxetine groups in both studies showed significant improvement in the PGI-I, as well as improvement in nearly all other efficacy and health outcome measures, including significant improvement in several SF-36 measures. The maintenance of efficacy analysis in Study 2 did not demonstrate statistical significance (90% CI, -0.39 to 0.77; P=0.580). The mean change in the BPI average pain severity score increased by 0.19 point during the extension phase. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Hauser et al.[174] (2013) Duloxetine or milnacipran vs placebo	MA, SR (10 RCTs) Adult patients >18 years of age with clinical diagnosis of fibromyalgia syndrome by any published, recognized and standardized criteria	N=6,038 Study duration had to be >4 weeks	Primary: Reduction in pain (50%), fatigue, sleep problems, disease-related QOL as measured by total score of FIQ, safety Secondary: 30% reduction in pain, depression, anxiety, disability, sexual function, PGI-C or CGI, cognitive disturbances, tenderness	Primary: Duloxetine and milnacipran had a small effect over placebo in reducing pain (SMD, -0.23; 95% CI, -0.29 to -0.18; 6.1% relative improvement; P<0.001). One-hundred and ninety-two participants per 1,000 on placebo reported an at least 50% pain reduction compared to 286 per 1,000 on duloxetine or milnacipran (RR, 1.49; 95% CI, 1.35 to 1.64; NNT, 11; 95% CI, 9 to 15; P<0.0001). Duloxetine and milnacipran did not reduce fatigue substantially (SMD, -0.14; 95% CI, -0.19 to -0.08; 2.5% relative improvement; NNT, 17; 95% CI, 12 to 29; P<0.001), and did not improve QOL substantially (SMD, -0.20; 95% CI, -0.25 to -0.14; 4.6% relative improvement; NNT, 12; 95% CI, 9 to 17; P<0.001) compared to placebo. There were no statistically significant differences between either duloxetine or milnacipran and placebo in reducing sleep problems (SMD, -0.07; 95% CI, -0.16 to 0.03; 2.5% relative improvement; P=0.15). Secondary: Duloxetine and milnacipran had a significant effect over placebo in 30% pain reduction (RR, 1.36; 95% CI, 1.26 to 1.46; P<0.0001). Duloxetine and milnacipran did not reduce depression substantially (SMD, -0.15; 95% CI, -0.21 to -0.10; P<0.001), and did not improve disability substantially (SMD, -0.22; 95% CI, -0.28 to -0.16; P<0.001) compared to placebo. There were no statistically significant differences between either duloxetine or milnacipran and placebo in reducing anxiety (P=0.54). Out of two studies that reported on sexual function, one study lacked data for reporting and the other study found no difference in reducing sexual problems between milnacipran and placebo. Duloxetine and milnacipran did not improve PGI-C substantially (SMD, -0.27; 95% CI, -0.33 to -0.21; P<0.001), did not have a substantial effect on cognitive disturbances (SMD, -0.15; 95% CI, -0.21 to -0.10; P<0.001), and did not substantially raise the tender point pain threshold (SMD, -0.23; 95% CI, -0.35 to -0.12; P<0.001), compared to placebo. Dropout rates due to adverse events were significantly higher in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				duloxetine or milnacipran groups at 20.6% compared to 10.9% in the placebo groups (RR, 1.83; 95% CI, 1.53 to 2.18; NNH, 11; 95% CI, 9 to 13; P<0.001). There was no statistically significant difference in serious adverse events between either duloxetine or milnacipran and placebo (RR, 0.78; 95% CI, 0.55 to 1.12; P=0.15). The most frequently reported symptoms leading to stopping medication were nausea, dry mouth, constipation, headache, somnolence/dizziness and insomnia.
Hauser et al.[175] (abstract) (2010) Duloxetine, milnacipran or pregabalin vs placebo	MA (17 RCTs) Patients with fibromyalgia syndrome	N=7,739 Not noted (efficacy noted up to 6 months)	Primary: Symptom reduction (pain, fatigue, sleep disturbance, depressed mood, reduced HRQoL) and adverse events Secondary: Not reported	Primary: Duloxetine, milnacipran and pregabalin were superior to placebo for the outcomes noted except for the following: duloxetine for fatigue, milnacipran for sleep disturbance, and pregabalin for depressed mood were not more efficacious to placebo. There were no significant differences between duloxetine, milnacipran, or pregabalin for 30% pain relief per adjusted indirect comparisons. Differences in average symptom reduction were noted as follows: duloxetine and pregabalin were more efficacious to milnacipran in reduction of pain and sleep disturbances; duloxetine was more efficacious to milnacipran and pregabalin in reducing depressed mood; and milnacipran and pregabalin were more efficacious to duloxetine in reducing fatigue. Secondary: Not reported.
Generalized Anxiety Disorder (GAD)				
Rynn et al.[176] (2008) Duloxetine 60 or 120 mg/day vs placebo	DB, PC, RCT Adult patients with GAD	N=327 10 weeks	Primary: HAMA total score Secondary: Response rate (HAMA total score reduction ≥50% from baseline), CGI-I, SDS, safety	Primary: Duloxetine resulted in significantly greater improvement in HAMA total scores compared to placebo (P=0.023); mean decrease for duloxetine was 8.12 (36% improvement from baseline) compared to a mean decrease of 5.89 (25% improvement from baseline). Significant differences between the two treatments were observed at week two of treatment and remained significant at each subsequent visit (P≤0.001). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Response and sustained improvement rates were significantly greater for duloxetine-treated patients compared to placebo-treated patients (P<0.05). With duloxetine, the response rate was 40% and sustained improvement was 43.7% compared to 32.0 and 33.1% with placebo. There was no difference in the proportion of patients meeting the criteria for remission (28 vs 23%; P=0.27). Duloxetine resulted in a significantly greater functional improvement based on CGI-I scores compared to placebo (2.68 vs 2.97; P=0.04). Duloxetine-treated patients were significantly more improved compared to placebo-treated patients on SDS global functioning (P<0.01), and work, social, and family/home improvement scores (P<0.05). The rate of discontinuation due to an adverse event was significantly higher with duloxetine compared to placebo (P=0.002). The most commonly reported adverse events with duloxetine treatment were nausea, dizziness, and somnolence.
Koponen et al.[177] (2007) Duloxetine 60 or 120 mg/day vs placebo	DB, MC, PC, PG, RCT Patients ≥18 years of age with GAD of at least moderate severity	N=513 9 weeks	Primary: HAMA total score Secondary: SDS; HAMA psychic and somatic anxiety factor scores; HAMA response, remission, and sustained improvement rates, safety	Primary: Both doses of duloxetine demonstrated significantly greater improvements in HAMA total scores compared to placebo (P≤0.001 for both). Both doses of duloxetine resulted in mean decreases in HAMA total score that were more than four points greater than the decreases achieved with placebo; the mean change represents a 49% decrease from baseline with duloxetine. Significant differences between duloxetine and placebo were observed as early as two weeks after treatment initiation, and remained significant at each subsequent visit. Secondary: Both doses of duloxetine demonstrated significantly greater functional improvements in SDS global and specific domain scores compared to placebo (P≤0.001). Both doses of duloxetine achieved a mean decrease of more than three points greater than the decreases achieved with placebo; the mean change represents a 47% improvement from baseline with duloxetine. Both doses of duloxetine demonstrated significantly greater improvements

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				in HAMA psychic and somatic anxiety factor scores compared to placebo (P≤0.001 for all comparisons). Both doses of duloxetine resulted in significantly greater HAMA response (58, 56, and 31% with duloxetine 60 mg/day, duloxetine 120 mg/day, and placebo; P≤0.001 for both), remission (31, 38, and 19%; P≤0.01 for duloxetine 60 mg/day vs placebo and P≤0.001 for duloxetine 120 mg/day vs placebo), and sustained improvement rates (64, 67, and 43%; P≤0.001 for both) compared to placebo. There were no significant differences between the two doses of duloxetine on any of the efficacy outcome measures. Approximately 20% of patients receiving duloxetine had their dose decreased during the first two weeks of acute treatment. The rate of study discontinuation due to an adverse event was 11.3, 15.3, and 2.3% with duloxetine 60 mg/day, duloxetine 120 mg/day, and placebo (P≤0.001). Overall, nausea was the most frequent adverse event, which resulted in study discontinuation for 6.0 and 2.4% of duloxetine 60- and 120 mg/day-treated patients.
Davidson et al.[178] (2008) Duloxetine vs placebo All patients received OL duloxetine for 26 weeks. Treatment responders (≥50% reduction in	DB, PC, RCT Patients ≥18 years of age with moderate to severe GAD	N=533 (N=887 OL phase) 26 weeks	Primary: Time to relapse (increase in CGI-S rating ≥2 points from randomization to a score ≥4 while meeting criteria for GAD or by discontinuation due to lack of efficacy) Secondary: HAMA total score, HAMA psychic factor score,	Primary: Significantly more placebo-treated patients (41.8%) met relapse criteria compared to duloxetine-treated patients (13.7%; P≤0.001). Among patients who did relapse, duloxetine-treated patients had a longer time to relapse compared to patients who were switched to placebo (P≤0.001). Secondary: Patients who continued duloxetine maintained the improvements that were demonstrated during the OL phase. Patients who were switched to placebo significantly worsened on each of the secondary outcomes, including HAMA total score, HAMA psychic factor score, HAMA somatic factor scores, and HADS-A (P≤0.001 for all comparisons). The remission rate for duloxetine-treated patients at endpoint was 68.1 and 39.3% for placebo-treated patients (P≤0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
HAMA total score to ≤11 and "much"/"very much improved" ratings for the last 2 visits of the OL phase.			HAMA somatic factor scores, HADS-A, CGI-I, PGI-I, SDS, EQ-5D VAS, safety	Patients receiving placebo were rated as overall less improved by the CGI-I and PGI-I mean endpoint scores compared to patients receiving duloxetine (P≤0.001 for both). Patients treated with placebo also had worsening of their role functioning in all SDS domains of work/school, social life, and family/home management compared to patients who continued with duloxetine (P≤0.001). By endpoint, mean SDS global functioning impairment score with placebo had significantly increased into the range indicating mild to moderate impairment (P≤0.001). The switch to placebo was also associated with decreased life satisfaction and poorer perceived health, as measured by changes in EQ-5D VAS scores (P≤0.001 for all comparisons) compared to patients who continued duloxetine. During the OL phase, 15 treatment-emergent adverse events occurred at a frequency of ≥5%: nausea (28.3%), headache (18.7%), dry mouth (14.3%), diarrhea (14.2%), dizziness (13.4%), constipation (12.5%), fatigue (11.5%), hyperhidrosis (10.0%), insomnia (9.8%), somnolence (8.2%), decreased appetite (6.1%), upper respiratory tract infection (5.5%), decreased libido (5.4%), vomiting (5.4%), and nasopharyngitis (5.0%). Most adverse events were mild to moderate in severity. During the DB, continuation phase patients experienced discontinuation-emergent adverse events as the study medication was being withdrawn. Compared to patients receiving duloxetine, dizziness was the only adverse event to occur significantly more often with patients receiving placebo (9.9 vs 3.7%; P≤0.05). No significant increases in pulse rate, DBP, or SBP were observed in duloxetine-treated patients compared to placebo-treated patients. Most events were mild to moderate in severity. Discontinuation from study due to adverse events occurred in four and two patients receiving duloxetine and placebo.
Hartford et al.[179] (2007) Duloxetine 60 to	DB, MC, PC, RCT Outpatients ≥18 years of age with	N=487 10 weeks	Primary: HAMA total score Secondary:	Primary: Patients receiving duloxetine or venlafaxine ER experienced greater improvements in anxiety symptom severity (as measured by HAMA) compared to patients receiving placebo (duloxetine; P=0.007 and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
120 mg/day vs venlafaxine ER 75 to 225 mg/day vs placebo	GAD		HAMA psychic anxiety factor score, somatic anxiety factor score, mood item, and tension item; HADS anxiety and depression subscales scores; CGI-I, PGI-I; SDS	venlafaxine ER; P<0.001). The mean decrease in the HAMA total scores was 11.8 for duloxetine and 12.4 for venlafaxine ER compared to 9.2 for placebo. Secondary: Patients treated with duloxetine and venlafaxine ER demonstrated greater improvements in HAMA psychic anxiety factor score, HAMA anxious mood, HAMA tension, and HADS anxiety and depression subscales compared to patients treated with placebo (P<0.01 for all comparisons). Patients treated with both duloxetine and venlafaxine ER had greater improvement ratings at endpoint on the CGI-I and PGI-I compared to patients treated with placebo (P<0.01 for all comparisons). Treatment response was seen in 47% of patients receiving duloxetine, 54% of patients receiving venlafaxine ER, and 37% of patients receiving placebo (P<0.001 for venlafaxine ER vs placebo). Using the CGI-I endpoint score, the percentage of responders was greater for duloxetine (55.7%; P=0.007) and venlafaxine ER (60.4%; P<0.001) compared to placebo (41.8%). More venlafaxine ER-treated patients met remission criteria (30%) than placebo-treated patients (19%; P<0.05). The difference was not significant for duloxetine compared to placebo (23%; P value not significant). Sustained improvement rates were greater with duloxetine (55%) and venlafaxine ER (54%) compared to placebo (39%; P<0.01). Duloxetine and venlafaxine ER-treated patients experienced greater improvements in their functioning (SDS global improvement score) from baseline to endpoint compared to placebo (duloxetine, -8.03; venlafaxine ER, -7.97; placebo,-5.42; P<0.01).
Nicolini et al.[180] (2009) Duloxetine 20	DB, MC, PC, RCT Outpatients ≥18 years of age with	N=581 10 weeks	Primary: HAMA total score Secondary:	Primary: For the HAMA total score, all three treatment groups demonstrated significant improvements from baseline compared to treatment with placebo (duloxetine 20 mg/day, -14.7 [P≤0.01]; duloxetine 60 to 120

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/day vs duloxetine 60 to 120 mg/day vs venlafaxine ER 75 to 225 mg/day vs placebo	GAD		HAMA psychic and somatic factor scores, SDS, HAMA, CGI-I, PGI-I	mg/day, -15.3 [P≤0.001]; venlafaxine ER, -15.5 [P≤0.001]; placebo -11.6). Secondary: For the HAMA psychic factor scores, all three treatment groups demonstrated significant improvements from baseline compared to treatment with placebo (duloxetine 20 mg/day, -8.1 [P≤0.01]; duloxetine 60 to 120 mg/day, -8.7 [P≤0.001]; venlafaxine ER, -8.6 [P≤0.001]; placebo -6.0). For the HAMA somatic factor score, all three treatments led to improvements from baseline compared to placebo (duloxetine 20 mg/day, -6.6 [P=0.07]; duloxetine 60 to 120 mg/day, -6.6 [P≤0.05]; venlafaxine ER, -7.0 [P≤0.01]; placebo -5.5). Response rates were 60% for duloxetine 20 mg/day (P<0.01), 65% for duloxetine 60 to 120 mg/day (P<0.001), 61% for venlafaxine ER (P<0.001), and 42% for placebo. Remission rates were 42% for duloxetine 20 mg/day, 44% for duloxetine 60 to 120 mg/day, 44% for venlafaxine ER, and 20% for placebo (P<0.001 for each comparisons vs placebo). Overall improvement ratings at endpoint were greater for duloxetine-treated patients (20 or 60 to120 mg/day) and venlafaxine ER-treated patients compared to placebo-treated patients by the CGI-I scores (P<0.001 for all comparisons). All three treatments demonstrated significant improvement on the mean HADS anxiety subscale scores compared to placebo (duloxetine 20 mg/day, -7.0 points; duloxetine 60 to 120 mg/day, -7.7 points; venlafaxine ER, -6.9 points; placebo, -4.9 points; P<0.001 for all comparisons). All three treatments demonstrated significant improvement on the mean HADS depression subscale score compared to placebo (duloxetine 20 mg/day, -3.3 points; duloxetine 60 to 120 mg/day, -3.5 points; venlafaxine ER, -3.6 points; placebo, -1.9 points; P<0.001 for all comparisons).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				For the SDS global functioning improvement score, all three treatment groups demonstrated significant improvements from baseline compared to treatment with placebo (duloxetine 20 mg/day group, -8.5 [P<0.05]; duloxetine 60 to 120 mg/day, -8.9 [P<0.01]; venlafaxine ER, -9.1 [P<0.001]; placebo, -6.2).
Davidson et al.[181] (2005) Escitalopram 10 to 20 mg daily	MC, OL Patients who completed an 8-week, DB, PC, lead-in and were diagnosed with GAD were eligible to enter extension trial	N=526 24 weeks	Primary: CGI-I, HAMA core ≤7 Secondary: Safety	Primary: Ninety two percent of the patients were considered responders. Secondary: Adverse events led to study withdrawal in 9.9% of patents. The most frequent adverse events leading to study withdrawal were ejaculations disorder (1.6%), insomnia (1.3%), and nausea (1%). Serious adverse events were reported by 2.1% of patients, including one completed suicide.
Goodman et al.[182] (2005) Escitalopram 10 to 20 mg daily vs placebo	DB, MC, PC Patients 18 to 80 years of age with DSM-IV defined GAD	N=850 8 weeks	Primary: HAMA Secondary: CGI-S, CGI-I	Primary: Escitalopram significantly improved mean HAMA total scores (the primary efficacy measure) relative to placebo with the mean change from baseline to week eight in HAMA total score –10.1±0.3 for escitalopram and –7.6±0.3 for placebo (P<0.001). Secondary: Escitalopram led to statistically significant improvements compared to placebo in both HAMA subscales: psychic anxiety (–5.8+0.2 vs –3.9±0.2; P<0.001; and somatic anxiety (–4.3±0.2 vs –3.7±0.2; P=0.02). At endpoint, 47.5% of escitalopram-treated patients and 28.6% of placebo-treated patients were responders (P<0.001), and 26.4% of escitalopram-treated patients and 14.1% of placebo-treated patients were remitters (P<0.001). CGI-I response rates at endpoint were 52% for escitalopram and 37% for placebo (P<0.001).
Bielski et al.[183] (2005) Escitalopram 10 to	DB, RCT Patients with GAD	N=121 24 weeks	Primary: Mean change from baseline in the HAMA scores at	Primary: After 24 weeks of treatment, patients receiving escitalopram had significantly greater improvement in the HAMA scores compared to the paroxetine group (–15.3 vs –13.3; P=0.13).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
20 mg/day vs paroxetine 20 to 50 mg/day			week 24, treatment-emergent adverse effects Secondary; Not reported	Significantly fewer patients withdrew from escitalopram than paroxetine treatment due to adverse events (6.6 vs 22.6%; P=0.02). Significantly more patients on paroxetine than on escitalopram experienced treatment-related adverse events (88.7 vs 77.0%). The following adverse events were noted to occur more frequently in the paroxetine group compared to the escitalopram-treated patients: insomnia (25.8 vs 14.8%), constipation (14.5% vs 1.6%), ejaculation disorder (30.0 vs 14.8%), anorgasmia (26.2 vs 5.9%), and decreased libido (22.6 vs 4.9%). In contrast, diarrhea and upper respiratory tract infection were reported more frequently with escitalopram than paroxetine (21.3 vs 8.1%, and 14.8 vs 4.8%, respectively). Secondary; Not reported
Bose et al.[184] (2008) Escitalopram 10 to 20 mg/day vs venlafaxine ER 75 to 225 mg/day vs placebo	DB, PC, RCT Outpatients 18 to 65 years of age with GAD	N=404 8 weeks	Primary: Change from baseline to week eight in the HAMA total score Secondary: HAMA psychic anxiety subscale, CGI-I, CGI-S, VAS, HADS QOL, SDS	Primary: The mean change in HAMA total score (LOCF) for escitalopram and venlafaxine ER vs placebo was -1.52 (P=0.09) and -2.27 (P=0.01), respectively at week eight. The mean change in HAMA total score for escitalopram and venlafaxine ER vs placebo was -1.92 (P=0.033) and -3.02 (P=0.001), respectively at week eight. Secondary: Neither escitalopram nor venlafaxine produced greater HAMA response or remission than placebo (response: 52.8 and 52.0% for escitalopram and venlafaxine, respectively vs 42.2% for placebo; remission: 31.2% for both escitalopram and venlafaxine vs 23.7% for placebo; P>0.05 vs placebo, LOCF). Both escitalopram and venlafaxine had significantly higher CGI-I response rates than the placebo (escitalopram 60.0%, venlafaxine 65.6%, placebo 45.9%, P<0.05, LOCF). Both groups had higher CGI-S and HADS response rates compared to placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There was no significant difference in VAS, QOL or SDS for escitalopram compared to placebo (LOCF). There was no significant difference in VAS or QOL for venlafaxine compared to placebo (LOCF).
Ball et al.[185] (2005) Paroxetine 10 to 40 mg daily vs sertraline 25 to 100 mg daily	DB, FD, PG Patients with GAD	N=55 8 weeks	Primary: HAMA scores as well as responder and remission rates based on the CGI scale Secondary: Improvement in IU-GAM	Primary: Both sertraline and paroxetine groups displayed significant reductions in HAMA scores from baseline to end of treatment (P<0.001). The mean percent reduction in HAMA scores was 57.3% for the paroxetine group and 55.9% for the sertraline group. The percent of treatment responders was 68% in the paroxetine group and 61% in the sertraline group. Secondary: Both sertraline and paroxetine groups displayed significant reductions in IU-GAMS scores from baseline to end of treatment (P<0.001). With treatment response defined as a reduction of greater than 50% in IU-GAMS scores from baseline to posttreatment, 40% of the paroxetine group responded compared to 25% of the sertraline group.
Dahl et al.[186] (2005) Sertraline 50 to 150 mg daily vs placebo	MC, RCT Outpatients with GAD	N=373 12 weeks	Primary: Change from baseline to endpoint in HAMA total score of the ITT population Secondary: CGI-S, CGI-I, MADRS, Q-LES-Q	Primary: Sertraline treatment was associated with significant improvement (P<0.001) in the HAMA psychic anxiety factor. Significant separation from placebo in primary endpoint was significant by week 4 for sertraline (52%) compared to placebo (34%; P=0.001). Clinically meaningful improvement (≥30% reduction in psychic symptom severity) was achieved by week four in the majority of patients (P=0001). Secondary: Global improvement was modestly but consistently better correlated with improvement in psychic anxiety. The degree of correlation was similar, regardless of study treatment.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				QOL was significantly improved in the sertraline group compared to placebo with improvement seen in 51% of patients on sertraline compared to 35% on placebo (P<0.01).
Schmitt et al.[187] (2005) Venlafaxine, paroxetine, imipramine, trazodone, diazepam, sertraline	MA RCTs evaluating antidepressants in GAD	N=2,238 8 to 28 weeks	Primary: Absence of treatment response (defined as absence of sufficient symptoms to meet diagnostic criteria for GAD) Secondary: Acceptability of the treatment as measured by the number of people dropping out during the trial	Primary: Antidepressants (imipramine, venlafaxine, and paroxetine) were found to be more effective when compared to placebo in treating GAD. The calculated NNT for antidepressants as a group in GAD was 5.15. Considering all trials, the pooled RR for nontreatment response was 0.70 (95% CI, 0.62 to 0.79), favoring antidepressant treatment. The calculated NNT was 5.5 (95% CI, 4.1 to 8.4). For imipramine the calculated RR was 0.67 (95% CI, 0.50 to 0.91) and the NNT was 4.0 (95% CI, 2.4 to 13.7). For venlafaxine the calculated RR for nontreatment response was 0.68 (95% CI, 0.46 to 0.99), and the calculated NNT was 5.00 (95% CI, 3.58 to 8.62). For paroxetine the calculated RR was 0.72 (95% CI, 0.56 to 0.92), and the calculated NNT was 6.72 (95% CI, 3.90 to 24.70). For paroxetine vs imipramine the calculated RR was 1.73 (95% CI, 0.31 to 9.57). Secondary: No significant differences were found between antidepressants and placebo with regard to drop out rate. The RR for dropout for any antidepressant was 0.95 (95% CI, 0.84 to 1.09). Similarly, when individual antidepressants were considered, no differences were found between individual treatments and the placebo group: imipramine: RR, 0.71 (95% CI, 0.41 to 1.24); venlafaxine: RR, 0.86 (95% CI, 0.72 to 1.02); sertraline: RR, 0.45 (95% CI, 0.03 to 5.84); paroxetine: RR, 1.15 (95% CI, 0.74 to 1.78); and paroxetine vs imipramine: RR, 1.62

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(95% CI, 0.58 to 4.48).
Insomnia				
Roth et al.[188] (2007) Doxepin 1 mg vs doxepin 3 mg vs doxepin 6 mg vs placebo	DB, PC, RCT, XO Patients 18 to 64 years of age with chronic primary insomnia	N=67 2 nights	Primary: WTDS Secondary: WASO, sleep efficiency, TST, LPS, number of awakenings after sleep onset, WTAS, and sleep architecture	Primary: WTDS was significantly reduced with doxepin 3 mg (P<0.0001) and doxepin 6 mg (P<0.0001) compared to placebo. There was no significant difference in WTDS with doxepin 1 mg compared to placebo (P=0.0918). Secondary: WASO was significantly decreased with doxepin (all doses) compared to placebo (1 mg; P=0.0090, 3 mg; P<0.0001, and 6 mg; P<0.0001). There were no significant differences in NAASO with doxepin (all doses) compared to placebo. There was no significant difference in LPS with doxepin (all doses) compared to placebo. TST and overall sleep efficiency were significantly increased with doxepin (all doses) compared to placebo (all P≤ 0.0005). WTAS was significantly reduced with doxepin 6 mg compared to placebo (P=0.0088). There was no significantly difference with doxepin 1 mg (P=0.1421) or doxepin 3 mg (P=0.0697) compared to placebo. WASO was not significantly decreased with doxepin 1 mg (56.4; P=0.8915), doxepin 3 mg (49.4; P=0.8789), or doxepin 6 mg (45.1; P=0.1168) compared to placebo (54.4). Number of awakenings after sleep onsest was significantly decreased with doxepin 3 mg (2.8; P=0.0207) compared to placebo (3.2). LSO was significantly decreased with doxepin 6 mg (43.0; P=0.0244), but not significantly decreased with doxepin 1 mg (46.5; P=0.1944) or doxepin 3 mg (45.3; P=0.0905) compared to placebo (49.6). TST was significantly increased with doxepin 6 mg (380.7; P=0.0190), but not with doxepin 1 mg (364.8; P=0.9992) or doxepin 3 mg (380.0;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				P=0.0562) compared to placebo (364.2). Sleep quality was significantly improved with doxepin 6 mg (0.8; P=0.0071) compared to placebo (0.4). There were no significant differences among doxepin doses for percentage or min of Stage 1 sleep. There was a significant increase in percentage of Stage 2 sleep (3 mg, 57.8%; P=0.0003, 6 mg, 58.7%; P<0.0001; placebo, 54.7%). There was a significant increase in min of Stage 2 sleep (1 mg, 228.5 min; P=0.0008, 3 mg, 240.4 min; P<0.0001, 6 mg, 245.8 min; P<0.0001; placebo, 212.9 min). There was a significant decrease in percentage of REM sleep (3 mg, 18.3%, P=0.0046; 6 mg, 17.8%, P=0.0002; placebo, 20.0%). The number of min spent in REM sleep was not significantly different among the doxepin doses. There were no significant differences among doxepin doses for either percentage or min of Stage 3/4 sleep. There were no significant differences among the treatment groups on any of the measures assessing either psychomotor function (DSST) or next-day alertness (VAS). Adverse events were comparable to placebo, with no reported anticholinergic effects, no memory impairment, and no significant hangover/next-day residual effects.
Scharf et al.[189] (2008) Doxepin 1 mg vs doxepin 3 mg vs doxepin 6 mg	DB, PC, RCT, XO Elderly patients with primary insomnia	N=76 2 nights	Primary: WTDS Secondary: WASO, TST, sleep efficiency, latency to sleep onset	Primary: Compared to placebo, treatment with doxepin (all doses) led to significant improvements WTDS (P<0.0001). Secondary: Compared to placebo, treatment with doxepin (all doses) led to significant improvements in WASO (P<0.0001). Compared to placebo, treatment with doxepin (all doses) led to significant improvements in TST (P<0.0001). Compared to placebo, treatment with doxepin (all doses) led to significant improvements in overall sleep efficiency (P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				Sleep efficiency was significantly improved during all thirds of the night with doxepin 3 and 6 mg compared to placebo (P<0.05). Treatment with doxepin 6 mg led to significant improvements in latency to sleep onset compared to placebo (P=0.0181). The incidence of adverse events with doxepin was comparable to placebo.
Krystal et al.[190] (2010) Doxepin 1 mg vs doxepin 3 mg vs placebo	DB, PC, RCT Patients ≥65 years of age with primary insomnia	N=240 12 weeks	Primary: WASO on night one Secondary: WASO at other time points, LPS, number of awakenings after sleep onset, TST, sleep efficiency, and WTAS, CGI-S, CGI-I	Primary: WASO was significantly improved on night one for doxepin 3 mg (P<0.0001) and doxepin 1 mg (P=0.0053) compared to placebo. Secondary: WASO was significantly improved on night 29 (P=0.0005) night 85 (P<0.0001) for doxepin 3 mg, and on night 85 (P=0.0330) for doxepin 1 mg compared to placebo. Mean change from night one to 85 were: placebo, 0.4 (P=0.96); doxepin 1 mg, 3.0 (P=0.57); doxepin 3 mg, 0.9 (P=0.62). TST and overall sleep efficiency were significantly improved on night one (P<0.0001), night 29 (P=0.0161), and night 85 (P=0.0007) for doxepin 3 mg, and on night one (P=0.0119) and night 85 (P=0.0257) for doxepin 1 mg compared to placebo. There was a significant improvement in sTST at weeks one (P=0.0043), four (P=0.0035), and 12 (P=0.0001) for doxepin 3 mg, and at weeks four (P=0.0343) and 12 (P=0.0027) for doxepin 1 mg compared to placebo. Sleep efficiency in the last quarter of the night was significantly increased on night one1 (P<0.0001), night 29 (P=0.0004), and night 85 (P=0.0014) for doxepin 3 mg compared to placebo. For doxepin 1 mg, sleep efficiency in the last quarter of the night was significantly increased on night one (P=0.0011) compared to placebo. Sleep efficiency in hour eight was significantly increased on night one (P<0.0001) and night 29 (P=0.0029) for doxepin 3 mg compared to placebo. For doxepin 1 mg, sleep efficiency in hour eight was significantly increased on night one compared to placebo

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(P=0.0211). WTAS was significantly decreased on N85 (P=0.0284) for doxepin 3 mg compared to placebo. LPS was not significantly reduced at any time point when compared to placebo. Sleep quality was significantly increased at weeks one (P=0.0039), four (P=0.0049), and 12 (P=0.0100) for doxepin 3 mg, and at weeks four (P=0.0464) and 12 (P=0.0107) for doxepin 1 mg compared to placebo. There was significant improvement after two weeks (P=0.0047), after four weeks (P=0.0356), and after 12 weeks (P=0.0005) on the CGI-S scale score for doxepin 3 mg, and after 12 weeks (P=0.0101) for doxepin 1 mg compared to placebo. There was significant improvement after two weeks (P=0.0060), after four weeks (P=0.0334), and after 12 weeks (P=0.0008) on the CGI-I scale score for doxepin 3 mg, and after 12 weeks (P=0.0082) for doxepin 1 mg compared to placebo. Daytime function ratings were significantly improved on night one for doxepin 3 mg (P=0.0282) and 1 mg (P=0.0192) and on night 85 for doxepin 3 mg (P=0.0028) and 1 mg (P=0.0102) compared to placebo. Sleep stages were preserved compared to placebo, with no apparent evidence of suppression of REM duration. There were no significant differences between placebo and either dose of doxepin on any of the measures assessing objective psychomotor function (DSST) or subjective next-day alertness (VAS) or drowsiness at any time point during the trial. Rates of treatment-emergent adverse events were lower in patients treated with doxepin 1 mg (40%) and doxepin 3 mg (38%) compared to placebo (52%). The most common adverse events were headache and somnolence.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Krystal et al.[191] (2011) Doxepin 3 mg vs doxepin 6 mg vs placebo	DB, PC, RCT Patients 18 to 64 years of age with primary insomnia	N=229 35 days	Primary: WASO on night one Secondary: WASO at other time points, LPS, number of awakenings after sleep onset, TST, sleep efficiency, and	Primary: WASO was significantly improved on night one for doxepin 3 mg (P<0.0001) and doxepin 6 mg (P<0.0001) compared to placebo. Secondary: WASO was significantly improved on night 15 (P=0.0053) and night 29 (P=0.0299) for doxepin 3 mg, and on night 15 (P=0.0023) and night 29 (P=0.0012) for doxepin 6 mg compared to placebo. There were no significant differences between doxepin groups on WASO. TST and sleep efficiency were significantly improved on night one (P<0.0001) and night 29 (P=0.0262) for doxepin 3 mg, and on night one (P<0.0001), night 15 (P=0.0157), and night 29 (P=0.0003) for doxepin 6 mg compared to placebo. There were no significant differences in number of awakenings after sleep onset for any dose at any time point. Sleep efficiency in the last quarter of the night was significantly improved on night one (P=0.0008) and night 15 (P=0.0220) for doxepin 3 mg, and on night one (P<0.0001), night 15 (P=0.0239), and night 29 (P=0.0029) for doxepin 6 mg compared to placebo. Sleep efficiency in hour eight was significantly improved on night one (P<0.0001) and night 29 (P=0.0315) for doxepin 3 mg, and on night one (P<0.0001), night 15 (P=0.0162), and night 29 (P=0.0020) for doxepin 6 mg compared placebo. WTAS was significantly improved on night one (P=0.0001) for doxepin 3 mg, and also on night one (P=0.0016) for doxepin 6 mg compared to placebo. LPS was significantly improved on night one (P=0.0047) for doxepin 3 mg, and on night one (P=0.0007) for doxepin 6 mg compared to placebo. There were significant improvements in patient-reported WASO for both doses of doxepin on night one compared to placebo (3 mg; P=0.0003, 6 mg; P=0.0004). There were significant improvements in patient-reported TST for both doses of doxepin at night one compared to placebo (3 mg;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				P=0.0088, 6 mg; P=0.0135). Sleep quality was significantly improved for both doses of doxepin at night one compared to placebo (3 mg; P=0.0068, 6 mg; P<0.0001). Subjective LSO was significantly improved on night one with doxepin 6 mg compared to placebo (P=0.0492). There was no evidence of tolerance to the sleep maintenance effects. There is evidence to suggest the development of tolerance to the sleep onset effects. There were increases in the duration of stage two sleep for both doses of doxepin, which were significant at most time points. There were no significant differences between the two doxepin groups vs placebo in minutes of stage one sleep, stage 3/4 sleep, or REM sleep. Across two nights, rebound insomnia was experienced by 1% of the placebo group, 1% of the doxepin 3 mg group, and 4% of the doxepin 6 mg group.
Roth et al.[192] (2010) Doxepin 6 mg vs placebo	DB, PC, MC, RCT Healthy adults 25 to 55 years of age with normal sleep habits	N=565 Single dose	Primary: LPS Secondary: WASO, TST, WTDS, WTAS, sleep efficiency, and number of awakenings after sleep onset, sleep architecture measurements, DSST, symbol copying test, and VAS	Primary: LPS was significantly lower for doxepin compared to placebo (21 vs 34 minutes, respectively; P<0.0001). Secondary: WASO was significantly lower for doxepin compared to placebo (38 vs 78 minutes, respectively; P<0.0001). WTDS was significantly lower for doxepin compared to placebo (P value not reported). There were no significant differences among the treatment groups in number of awakenings after sleep onset (P value not reported). TST was significantly higher for doxepin compared to placebo (425.2 vs 374.1 minutes, respectively; P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Overall sleep efficiency was significantly higher for doxepin compared to placebo (P value not reported). WTAS, sleep efficiency in the final quarter of the night, and sleep efficiency at hours seven and eight were significantly improved for doxepin compared to placebo (all P<0.0001). Doxepin had significantly higher sleep efficiency at each hour compared to placebo (P<0.0001). Subject- reported LSO was significantly lower for doxepin compared to placebo. WASO and sNAASO were significantly lower for doxepin compared to placebo. TST was significantly higher for doxepin compared to placebo. Sleep quality was significantly improved for doxepin compared to placebo. There were no significant differences between doxepin and placebo in the mean change in DSST score from predose to postdose. There were no significant differences in sleepiness with doxepin compared to placebo (symbol copying test; P=0.0228, VAS; P=0.0241). The incidence of adverse events with doxepin was comparable to placebo.
Musculoskeletal Pain				
Skljarevski et al.[193] (2010) Duloxetine 60 mg QD vs placebo	DB, PC, RCT Patients ≥18 years of age with chronic low back pain	N=401 12 weeks	Primary: Reduction of pain severity (BPI 24-hour average pain rating) Secondary: PGI-I, RMDQ-24, CGI-S, BPI-S, BPI-I, response rates, health outcomes (EQ-5D and SF-36)	Primary: There was a significantly greater reduction in the BPI 24-hour average pain in patients treated with duloxetine compared to patients treated with placebo (P≤0.001). Secondary: Duloxetine-treated patients reported significantly greater improvements in PGI-I scores compared to placebo-treated patients (2.88 vs 3.19, respectively; P=0.011). There was no significant difference in RMDQ-24 scores with duloxetine compared to placebo (-2.69 vs -2.22, respectively; P=0.255). There was no significant difference in CGI-S among the treatment groups. There was a significant reduction in all four domains of BPI-S (average

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				pain, worst pain, least pain, and pain right now) pain scores reported with duloxetine compared to placebo. All seven domains of the BPI-I (general activity, mood, walking ability, normal work, relations with others, sleep, enjoyment of life) were significantly better with duloxetine compared to placebo. A greater percentage of patients receiving duloxetine reported ≥50% pain reduction compared to patients receiving placebo (P=0.006). There was no significant difference in the 30% pain response rates among the treatment groups. There were significant differences in changes on four of six mood states on the POMS-Brief Form, along with the total mood disturbance score, between the two treatment groups: tension-anxiety (P≤0.001), anger-hostility (P≤0.001), vigor-activity (P=0.003), confusion-bewilderment (P=0.006), and total mood disturbance (P≤0.001). Changes in depression-dejection and fatigue-inertia states were not significant. The change in EQ-5D was significantly different between duloxetine and placebo with the United Kingdome index (P≤0.001) and United States index (P=0.002). In the SF-36 domains, the differences between duloxetine and placebo treatments were significant with regard to mental component summary (P=0.010), bodily pain (P=0.016), mental health transformed (P≤0.001), social functioning (P=0.030), and vitality transformed (P=0.022). There was no significant difference among the treatment groups in other domains. The WPAI questionnaire demonstrated a significant difference between the treatment groups with regard to activity impairment (P=0.007). There was no significant difference among the treatment groups in other domains. Significantly more patients in the duloxetine group (15.2%) than patients in the placebo group (5.4%) discontinued because of adverse events (P=0.002). Nausea and dry mouth were the most common treatment-emergent adverse events with rates significantly higher in duloxetine-treated patients.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Skljarevski et al.[194] (2010) Duloxetine 60 to 120 mg QD vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with chronic low back pain	N=236 13 weeks	Primary: Reduction of pain severity (BPI 24-hour average pain rating) Secondary: PGI-I, RMDQ-24, BPI-S, BPI-I, CGI-S, Athens Insomnia Scale response rates, health outcomes (EQ-5D and SF-36), WPAI	Primary: There was a significantly greater reduction in the BPI 24-hour average pain in patients treated with duloxetine compared to patients treated with placebo at all time points (-1.42 vs -0.78, respectively; P=0.016 at week four; -2.06 vs -1.17, respectively; P=0.001 at week seven; and -2.32 vs -1.50, respectively; P=0.004 at week 13). Secondary: Duloxetine-treated patients reported significantly greater improvements in PGI-I scores compared to placebo-treated patients at all time points (3.12 vs 3.51, respectively; P=0.007 at week four; 2.82 vs 3.32, respectively; P=0.001 at week seven; 2.59 vs 3.16, respectively; P=0.001 at week 13). There was a significant difference in RMDQ-24 scores at endpoint with duloxetine compared to placebo (-3.60 vs -1.93, respectively; P=0.009). The mean changes in pain scores, including BPI-S (worst pain, least pain, and pain right now) items; BPI-I average pain; and weekly mean of the 24-hour average pain, night pain, and worst pain scores from patient diaries were significantly improved with duloxetine compared to placebo. There was no significant difference in the CGI-S and Athens Insomnia Scale scores among the treatment groups. There was no significant difference in response rates with duloxetine compared to placebo (30% response: 53.2 vs 40.0%, respectively; P=0.060 and 50% response: 38.5 vs 27.0%, respectively; P=0.087). The depression and anxiety scores were not significantly changed from baseline to endpoint. The improvement in BPI average pain was because of the direct analgesic effect (80.4%; P=0.012) of duloxetine treatment and not dependent on the improvement in mood (BDI-II total score, 19.2%) or anxiety (HADS-A, 0.3%) symptoms. The United Kingdome and United States indexes of EQ-5D did not change significantly in patients treated with duloxetine compared to patients treated with placebo. Among the eight subscales of SF-36 only bodily pain

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(P=0.038), general health (P=0.041), and vitality (P=0.040) were significantly improved with duloxetine compared to placebo. In the WPAI, work activity impairment was the only item that significantly (P=0.002) improved with duloxetine compared to placebo. Significantly more patients in the duloxetine group (13.9%) compared to the placebo group (5.8%) discontinued because of adverse events (P=0.047). The most common treatment-emergent adverse events in the duloxetine group included nausea, dry mouth, fatigue, diarrhea, hyperhidrosis, dizziness, and constipation.
Skljarevski et al.[195] (2010) Duloxetine 60 to 120 mg QD	ES Patients ≥18 years of age with chronic low back pain	N=181 41 weeks	Primary: Reduction of pain severity (BPI 24-hour average pain rating) Secondary: Response rates, PGI-I, RMDQ-24, BPI-S, BPI-I, CGI-S, Athens Insomnia Scale response rates, health outcomes (EQ-5D and SF-36)	Primary: For patients who received duloxetine during the initial 13-week trial, pain reduction continued during the extension phase. The mean change in BPI average pain in the extension phase was -0.97 (P<0.001). Secondary: The 30%, 50%, and sustained response rates were ~10% higher for patients who received duloxetine during the initial 13-week trial compared to those who received placebo. A total of 94.8% of PC phase duloxetine responders still met response criteria at the end of the 41-week extension phase. The BPI average pain, worst pain, least pain, pain right now, and average interference all showed significant within-group improvement for both treatment groups. Both treatment groups showed significant improvement on the RMDQ-24 measures, CGI-S measures, and most of the health outcome assessments. No significant change was observed in the BDI total score and HADS depression score. Duloxetine was well tolerated with no new safety findings reported.
Skljarevski et al.[196] (2009)	DB, MC, PC, RCT Adult patients with	N=404 13 weeks	Primary: Weekly mean 24 hour average pain	Primary: Improvement in average weekly pain was significantly greater for duloxetine 60 and 120 mg/day doses beginning at week three, but the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Duloxetine 20, 60, or 120 mg/day vs placebo	non-radicular chronic low back pain		(duloxetine 60 mg/day vs placebo) Secondary: RMDQ-24, PGI-I, BPI, safety	significance was lost at weeks 12 and 13, respectively. The mean change from baseline to endpoint in average weekly pain did not differ significantly from placebo for 60 mg/day (P=0.104) or any other duloxetine doses. Analysis of average weekly pain response rates (30% reduction from baseline to end-point) showed a significantly greater percentage of responders with duloxetine 120 mg/day (57.8%) compared to placebo (43.4%; P=0.033), but neither 20 (41.1%) or 60 mg/day (53.6%) differed significantly from placebo (P values not reported). There were no significant differences between any doses in 50% response rates. Secondary: Patients overall improvement (PGI-I) was greater for patients receiving duloxetine 60 mg/day, and improvement in physical functioning (RMDQ-24) was greater for patients receiving duloxetine 60 and/or 120 mg/day compared to patients receiving placebo. Patients receiving duloxetine 60 mg/day also demonstrated significant improvement over patients receiving placebo on several measures of pain severity, interference of pain with activities, and sleep. Eight (1.98%) patients experienced at least one serious adverse event (three placebo-treated patients and one duloxetine 20- and 60 mg/day-treated patients, and three duloxetine 120 mg/day-treated patients). Duloxetine 120 mg/day was associated with a significantly higher proportion of treatment-emergent adverse events compare to placebo (P=0.038).
Chappell et al.[197] (2009) Duloxetine 60 to 120 mg QD vs placebo	DB, MC, PC, RCT Patients ≥40 years of age with osteoarthritis of the knee and pain for ≥14 days/month	N=231 13 weeks	Primary: Mean changes in the weekly mean 24-hour average pain score Secondary: Patients' perceived improvement as measured by PGI-I	Primary: Duloxetine was more effective than placebo on the primary efficacy measure (weekly mean 24-hour pain scores) beginning at week one and continuing through the treatment period (P<0.05). There was a significant reduction in the average pain score in the duloxetine group compared to the placebo group at each week. The mean change from baseline to endpoint in the 24-hour average pain score also showed a significant benefit for duloxetine over placebo (P=0.006). Analysis of the weekly 24-hour average pain score response rates (30%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			and on the change in patients' functioning as measured by the WOMAC physical functioning subscale, weekly mean of the 24-hour worst pain score, CGI-S, WOMAC pain and stiffness subscales, BPI-S and BPI-I, response to treatments, health outcomes, safety	reduction in score from baseline to endpoint) showed a significant difference between duloxetine (59.3%) and placebo (44.5%; P=0.033). The 50% response rates revealed a similar pattern (duloxetine, 47.2%; placebo, 29.4%; P=0.006). Secondary: There was a significant improvement with duloxetine in most secondary endpoints compared to placebo. Mean changes in BDI-II and HADS-A did not differ significantly between treatment groups. For patients randomly re-assigned to duloxetine at week seven, there was a significant improvement in mean change in the weekly 24-hour average pain score in the duloxetine 120 mg/day group compared to the duloxetine 60 mg/day group (P=0.039). No significant differences were observed between the two duloxetine groups in the Mixed Model Repeated Measures analysis of the weekly 24-hour average pain score or the 30% and 50% response rates at endpoint. Adverse event rates did not differ significantly between treatment groups (49.5% for duloxetine and 40.8% for placebo). A total of 45.0% of patients reported ≥1 treatment-emergent adverse events.
Chappell et al.[198] (2010) Duloxetine 60 to 120 mg QD vs placebo	DB, MC, PC, RCT Patients ≥40 years of age with osteoarthritis of the knee and pain for ≥14 days/month	N=256 13 weeks	Primary: BPI 24-hour average pain rating Secondary: Weekly mean 24-hour average pain and worst pain rating, patients' perceived improvement as measured by PGI-I and on the change in patients' functioning as	Primary: There was a significant reduction in the BPI average pain rating with duloxetine compared to placebo at all time points (P≤0.001). The BPI average pain response rates (≥30% pain reduction from baseline to endpoint) were significantly higher with duloxetine (65.3%) compared to placebo (44.1%; P≤0.001). The 50% response rates of BPI average pain did not significantly differ between the treatment groups (duloxetine, 43.8%; placebo, 32.3%; P=0.068). Secondary: The least squares mean changes in the weekly mean 24-hour average pain rating was significantly reduced with duloxetine compared to placebo as early as at week two and remained significant at all time points. The weekly mean 24-hour worst pain ratings were significantly improved

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			measured by the WOMAC physical functioning subscale, CGI-S, WOMAC pain and stiffness subscales, BPI-S and BPI-I, response to treatments, health outcomes, safety	with duloxetine compared to placebo. Patients receiving duloxetine experienced greater improvements in many secondary endpoints compared to placebo, including CGI-S, BPI-S items, and BPI-I items (general activity and normal work). The other BPI-I items (mood, walking ability, relations with other people, sleep, enjoyment of life, and average interference) were not significantly different between the two treatment groups. No significant improvement in PGI-I was observed in the duloxetine group compared to the placebo group (P=0.164). The mean changes from baseline to endpoint were improved significantly for WOMAC total score (P=0.004) and physical functioning subscale (P=0.016) in patients treated with duloxetine compared to placebo. The other two WOMAC subscales (pain and stiffness) did not show significant improvement with duloxetine treatment. Both the United Kingdome and the United States indexes of EQ-5D did not change significantly with either treatment. Physical component summary and three of the subscales of SF-36 were significantly improved with duloxetine compared to placebo. The other SF-36 items (mental component summary, general health, mental health, role-emotional, social functioning, and vitality) were not significantly improved with duloxetine compared to placebo. The frequency of nausea, constipation, and hyperhidrosis were significantly higher in the duloxetine group (P≤0.05). Significantly more duloxetine-treated patients discontinued therapy because of adverse events (P=0.002).
Frakes et al.[199] (2011) Duloxetine 60 to 120 mg QD vs placebo	DB, MC, PC, RCT Patients ≥40 years of age with osteoarthritis of the knee and pain for ≥14 days/month and who were using NSAIDs on most	N=524 10 weeks	Primary: Weekly mean of the daily average pain rating at week eight Secondary: Endpoint PGI-I, change in	Primary: Patients receiving duloxetine experienced significantly greater pain reduction at week eight than those receiving placebo. The estimated mean change was -2.46 for duloxetine compared to -1.55 for placebo (P<0.001). Duloxetine demonstrated greater improvement as early as week one (P<0.01), and at each subsequent week (P<0.001). Secondary: There was no significant difference in the use of acetaminophen as rescue

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Patients were also required to take an NSAID and PPI.	days of the week		WOMAC physical function	medication for knee pain due to osteoarthritis (P=0.08). The mean PGI-I and the change in the WOMAC physical function scale were significantly different between the duloxetine and placebo groups (P<0.001 for each). Estimated mean improvement in diary-based night pain and worst pain ratings were significantly greater for duloxetine compared to placebo (P<0.001 for each). Duloxetine-treated patients showed greater reductions for each item on the pain and interference ratings on the BPI compared to placebo-treated patients (P<0.001 for each). Mean reductions for the total score and remaining subscale scores (pain and stiffness) of the WOMAC were significantly different (P<0.001 for each). Treatment with duloxetine was associated with significantly more nausea, dry mouth, constipation, fatigue and decreased appetite than treatment with placebo (P<0.05). Discontinuation due to adverse events occurred more commonly in the duloxetine group than the placebo group (P=0.03).
Mazza et al.[200] (2010) Escitalopram 20 mg QD vs duloxetine 60 mg QD	RCT Adult patients with non-radicular chronic low back pain	N=85 13 weeks	Primary: Weekly mean of the 24-hour average pain ratings Secondary: CGI-S and the 36-item SF-36	Primary: The mean change in average weekly pain did not differ significantly between the escitalopram group and duloxetine group (P=0.15). The average weekly pain response rates (30% reduction from baseline to end point) showed no significant difference between the two groups (P=0.12). There were no significant differences between groups in 50% response rates. Secondary: Both escitalopram and duloxetine demonstrated significant improvement on CGI-S and SF-36. No patient experienced serious adverse events and the incidence of side effects did not differ significantly between treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Obsessive-compulsive Disorder (OCD)				
Alaghband-Rad et al.[201] (2009) Fluoxetine 20 mg/day vs citalopram 20 mg/day	DB, RCT Children 8 to 17 years of age with OCD	N=29 6 weeks	Primary: CY-BOCS total score, CGI-OCD, adverse events Secondary; Not reported	Primary: After three weeks of treatment, obsessive-compulsive symptom severity for both groups decreased to a similar extent using the CY-BOCS total scores. Scores decreased for both obsessions and compulsions. CGI scores did not change significantly from baseline in either group. After six weeks of treatment, obsessive-compulsive symptom severity for both groups decreased to a similar extent using the CY-BOCS total scores. Scores decreased for both obsessions and compulsions (P<0.01). CGI scores did not change significantly from baseline in either group (P=NS). The most frequently reported adverse events were headache (3.4%), tremor (6.8%), insomnia (3.4%), hypomanic episode (3.4%) for fluoxetine. Headache (3.4%), hypomanic episode (3.4%) for citalopram. Secondary; Not reported
Koran et al.[202] (1996) Fluvoxamine 100 to 300 mg/day vs clomipramine 100 to 250 mg/day	DB, RCT Patients with OCD	N=79 10 weeks	Primary: Y-BOCS, CGI, HAM-D Secondary; Not reported	Primary: The mean reduction in Y-BOCS for the fluvoxamine group was 30.2% and for the clomipramine group 30.0% (P=NS). At the end of treatment, 56% of fluvoxamine patients were classified as responders (≥25% decrease in Y-BOCS score), compared to 54% of clomipramine patients. Both groups showed steady improvement throughout the study; no statistically significant differences were observed between the groups for any efficacy variable at any time. A similar percentage of patients in both groups withdrew because of adverse events. No serious adverse events related to drug occurred with either drug. Insomnia, nervousness, and dyspepsia were more statistically frequent with fluvoxamine; dry mouth and postural hypotension were more frequent with clomipramine. Secondary; Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Mundo et al.[203] (1997) Fluvoxamine 100 to 300 mg daily vs paroxetine 20 to 60 mg daily vs citalopram 20 to 60 mg daily	RCT Patients with OCD	N=30 10 weeks	Primary: NIMH-OC, Y-BOCS, HAM-D, CGI Secondary; Not reported	Primary: No significant differences were noted between the treatment groups. Results performed on NIMH-OC and Y-BOCS obsessions, compulsions, and total scores did not show any significant effect of the variable group (treatment) but only a significant effect of time (NIMH-OC: P=0.000; Y-BOCS obsessions: P=0.000; Y-BOCS compulsions: P=0.000; Y-BOCS total: P=0.000) and no significant effect of their interaction. Similar results were derived from the ANOVA with repeated measures performed on HAM-D total scores (time effect: P=0.000). Secondary; Not reported
Denys et al.[204] (2003) Paroxetine 15 to 60 mg daily vs venlafaxine 75 to 300 mg daily	DB, PG, RCT Patients with OCD	N=150 12 weeks	Primary: Y-BOCS Secondary; Not reported	Primary: Both paroxetine and venlafaxine were efficacious with a mean decrease of 7.8 and 7.2 points, respectively, at the end of the study, as measured by the reduction in total Y-BOCS scores. Analyses of covariance, adjusted for the mean baseline Y-BOCS scores, revealed a highly significant treatment effect over the 12-week trial period for both treatment groups (P=0.001). A significant decrease in total Y-BOCS scores from baseline was found in the venlafaxine group at week three (P=0.008), whereas in the paroxetine group, a significant decrease in total Y-BOCS scores from baseline was evident as of the fifth week of treatment (P=0.018). Significant decreases in total Y-BOCS scores for both medications were observed until week 10, whereas from week 10 till week 12, no further decrease was detected. Secondary; Not reported
Panic Disorder				
Stahl et al.[205] (2003) Citalopram	DB, PC, RCT Patients 18 to 80 years of age	N=366 10 weeks	Primary: Frequency of panic attacks at week 10 assessed by the	Primary: A significant decrease in the frequency of panic attacks was observed in both the escitalopram and citalopram groups compared to placebo (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs escitalopram vs placebo	diagnosed with panic disorder		Modified Sheehan Panic and Anticipatory Anxiety Scale Secondary; Not reported	Secondary; Not reported
Dannon et al.[206] (2007) Citalopram 10 to 40 mg/day vs fluoxetine 10 to 40 mg/day vs fluvoxamine 50 to 200 mg/day vs paroxetine 10 to 40 mg/day	OL Adult patients with panic disorder or panic disorder with agoraphobia	N=200 12 months	Primary: Panic Self-Questionnaire, CGI-I Secondary; Not reported	Primary: Following 52 weeks of therapy, the clinical improvements observed were similar between the groups and there were no significant differences in treatment response as measured using the Panic Self-Questionnaire (P=0.13), VAS (P=0.43), or CGI-I (P=NS). There were no significant differences between the panic disorder and the panic disorder with agoraphobia groups in treatment response as measured at the 12 monthly follow-up visits. Secondary; Not reported
Rampello et al.[207] (2006) Escitalopram vs citalopram	OL Elderly patients diagnosed with panic attacks	N=40 8 weeks	Primary: Weekly rate of panic attacks Secondary: Change from base-line in HAMA, HAMD and Cooper Disability	Primary: No significant difference was observed at eight weeks in the weekly rate of panic attacks. Secondary: No significant differences were observed at eight weeks in the HAMA or HAMD, or in the Cooper Disability Scale scores. A significant improvement from baseline in outcome measures was

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Scale scores	observed in the escitalopram at two weeks and in the citalopram group at four weeks (P<0.001 and P<0.01 respectively).
Van Ameringen et al.[208] (2007) Nefazodone 300 to 600 mg daily vs placebo	DB, MC, PC, RCT Patients 18 to 65 years of age with GSP diagnosis confirmed by DSM-IV for more than 1 year	N=105 14 weeks	Primary: Percent of responders at endpoint Secondary: Not reported	Primary: At endpoint, 31.4% of nefazodone-treated patients and 23.5% of placebo-treated patients were considered responders (P=0.38). Secondary: Not reported
Sheehan et al.[209] (2005) Paroxetine CR 25 to 75 mg daily vs placebo	DB, MC, PC, RCT Patients with DSM-IV panic disorder with or without agoraphobia	N=889 10weeks	Primary: Patients free of panic attacks in the two weeks prior to endpoint Secondary: CGI-I, HAMA	Primary: Paroxetine CR was statistically more effective compared to placebo on the primary outcome measure: 63 vs 53%; P<0.005. Secondary: Paroxetine CR was statistically more effective compared to placebo in the proportion of patients with improved CGI-I (79 vs 55%; P<0.001). Paroxetine CR was statistically more effective compared to placebo in alleviating general anxiety symptoms as measured by HAMA; P<0.001. Adverse events leading to study withdrawal occurred in 11% of patients in the paroxetine CR group and 6% of patients in the placebo group.
Ballenger et al.[210] (1998) Paroxetine 10 mg daily vs paroxetine 20 mg daily vs	DB, PG, PC, RCT Patients with panic disorder 18 years of age or older	N=278 10 weeks	Primary: Change in panic attacks from baseline, CGI-S Secondary: Marks-Sheehan Phobia Scale, HARS, MASDR	Primary: The percent of patients free of panic attacks were 86% (40 mg), 65.2% (20 mg), and 67.4% (10 mg) (P<0.019 at weeks four and 10). No significant differences were noted between groups in mean change from baseline in number of full panic attacks. No significant differences were reported between groups in percentage of patients with a 50% reduction from baseline in number of full panic attacks. The mean CGI global and severity ratings were 81.2% (40 mg), 75.4% (20

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
paroxetine 40 mg daily				mg), 57.8% (10 mg), 51.5% (placebo) (significantly higher with 40 and 20 mg, P<0.019). Secondary: The mean score for public avoidance on the Marks-Sheehan Phobia Scale declined in all groups (P=NS). Significant improvement in the score on the HARS (total) was observed for the 40 mg paroxetine group (in the end-point but not in the completer analysis). Improvement in depressive symptoms (MADRS) was significantly greater for the 40 mg paroxetine group than for the placebo group at week 10.
Bandelow et al.[211] (2004) Sertraline 50 to 150 mg daily vs paroxetine 40 to 60 mg daily	DB, MC, PG, RCT Patients with panic disorder between 18 and 65 years of age	N=225 12 weeks	Primary: Clinician-rated PAS Secondary: CGI-I score	Primary: Treatment with sertraline and paroxetine resulted in equivalent levels of improvement on the primary outcome measure from baseline, the PAS total score (P=0.749). The efficacy of sertraline and paroxetine was equivalent (P=0.487) with regard to the PAS across the agoraphobia and non-agoraphobia subtypes. Secondary: Global response (CGI-I score ≤2) was achieved by 82% of the efficacy-evaluable population treated with sertraline compared to 78% of patients treated with paroxetine (P=0.320).
Pollack et al.[212] (2007) Venlafaxine ER 75 mg/day vs venlafaxine ER 225 mg/day vs	DB, MC, PC, RCT Outpatients ≥18 years of age with panic disorder (with or without agoraphobia)	N=653 12 weeks	Primary: Percentage of patients free from full-symptom panic attacks at endpoint (LOCF) Secondary: Changes from baseline in the Panic Disorder Severity Scale total	Primary: Each of the active treatment groups had a significantly higher proportion of patients who were free of full-symptom panic attacks than in the placebo group (venlafaxine ER 75 mg, 64.7% [P≤0.001 vs placebo]; venlafaxine ER 225 mg, 70.0% [P≤0.001 vs placebo; P≤0.05 vs paroxetine]; paroxetine, 58.3% [P≤0.05 vs placebo]; placebo, 47.8%). Secondary: All three treatment groups had significantly greater mean reductions in Panic Disorder Severity Scale total score compared to the placebo group at study endpoint. The venlafaxine ER 225 mg group had a significantly lower Panic Disorder Severity Scale total score (4.78 vs 6.26; P<0.05) at

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
paroxetine 40 mg/day vs placebo			score and panic attack frequency	endpoint than the paroxetine group. Each of the active treatment groups had significantly more CGI-I responders than the placebo group (venlafaxine ER 75 mg, 81.4%; venlafaxine ER 225 mg, 85.0%; paroxetine, 83.3%; placebo, 59.9%; P<0.001 vs placebo for all comparisons). The percentage of patients who experienced remission was higher in the active treatment groups (venlafaxine ER 225 mg, 50.0%; venlafaxine ER 75 mg, 41.0%; paroxetine 40 mg, 39.3%) than in the placebo group (26.8%).
Posttraumatic Stress Disorder (PTSD)				
Davidson et al.[213] (2005) Fluoxetine 10 to 60 mg daily vs placebo	OL, RCT Patients 18 to 70 years of age with PTSD	N=123 6 months	Primary: Rate of relapse defined by a change in CGI-I score that reverted back to no improvement relative to baseline or worse, CGI-I score which increased by at least two points Secondary: CGI-S	Primary: On the CGI-I, there was a significantly higher number of relapses in the group who received placebo (50%) compared to the group that received fluoxetine (22.2%; P=0.029). Secondary: Differences between the fluoxetine and the placebo group failed to meet significance for CGI-S (P=0.08).
Friedman et al.[214] (2007) Sertraline 250 to 200 mg daily vs placebo	DB, PC, RCT Patients with combat-related PTSD	N=169 12 weeks	Primary: Mean change in CAPS-2 total severity score from baseline to endpoint Secondary: IES, CGI-S	Primary: The adjusted mean changes on the CAPS-2 total severity score for the sertraline and placebo groups were –13.1 and –15.4, respectively; the difference was not statically different (P=0.26). Secondary: The adjusted mean changes for the IES total score were –8.7 and –8.1 for the sertraline and placebo groups, respectively. The difference was not statistically significant (P=0.28).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				For the CGI-S scale, there was no statically significant difference between treatment groups in changes from baseline to endpoint. The mean changes from baseline to endpoint were –0.5 and –0.6, respectively (P=0.41).
Premenstrual Dysphoric Disorder				
Pearlstein et al.[215] (2005) Paroxetine CR 12.5 mg daily or 25 mg daily vs placebo	DB, MC, PC, RCT Patients 18 to 45 years of age who had regular menstrual cycles with PMDD	N=47 3 menstrual cycles	Primary: VAS-Mood Secondary: VAS-Total	Primary: A statistically significant difference was observed in favor of paroxetine CR 25 mg vs placebo on the VAS-Mood (P<0.001) and for paroxetine CR 12.5 mg vs placebo (P=0.013). Secondary: Paroxetine CR demonstrated greater mean reduction in VAS-Total scores compared to placebo at each time point. At the treatment cycle three last-observation-carried-forward endpoint, statistically significant differences in mean changes were observed in favor of paroxetine CR 25 mg vs placebo (P<0.001) as well as for paroxetine CR 12.5 mg vs placebo (P=0.011).
Steiner et al.[216] (2005) Paroxetine CR 12.5 mg daily vs paroxetine CR 25 mg daily vs placebo	DB, MC, PC, RCT Patients 18 to 45 years of age who had regular menstrual cycles with PMDD	N=373 3 menstrual cycles	Primary: VAS-Mood Secondary: Change form baseline to treatment cycle three in the sum of the 11VAS symptoms; change from baseline in the SDS total score	Primary: A statistically significant difference was demonstrated in favor of paroxetine CR 25 and 12.5 mg compared to placebo (paroxetine CR 25 mg vs placebo: adjusted mean difference, –10.79 mm; 95% CI, –16.46 to –5.12; P<0.001; paroxetine CR 12.5 mg vs placebo: adjusted mean difference, –7.66 mm; 95% CI, –13.25 to –2.08; P=0.007) for change from baseline in mean luteal phase VAS-Mood score at the treatment cycle three last-observation-carried-forward endpoint. Secondary: The mean change from baseline in the VAS-Total score, (paroxetine CR 25 mg vs placebo, -77.82 mm; P=0.006, paroxetine CR 12.5 mg vs placebo, –73.13 mm; P=0.009) The mean change from baseline in the SDS total score (paroxetine CR 25 mg vs placebo, –2.74 mm; P=0.016, paroxetine CR 12.5 mg vs placebo, –2.33 mm; P=0.028) was greater compared to placebo.
Multiple Diseases				
Wernicke et al.[217] (2007)	MA (42 RCTs) Patients diagnosed	N=8,504 4 to 12 weeks	Primary: Vital signs, ECG findings,	Primary: Patients receiving duloxetine were noted to have statistically significant changes from baseline in ECG findings compared to patients receiving

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Duloxetine vs placebo	with either an MDD, diabetic peripheral neuropathy, fibromyalgia, GAD, or lower urinary tract infection		cardiovascular side effects of the study drug Secondary: Not reported	placebo (P<0.001). However, the differences in ECG findings of patients taking duloxetine were not judged to be of clinical significance. Demographic subgroup analysis suggests that there is no difference in risk of ECG abnormality or vital sign changes between patients ≥65 years of age and a younger population (P value not reported). Although patients receiving duloxetine experienced statistically significant pulse and blood pressure elevations compared to patients receiving placebo (P<0.001), those changes were transient returning to baseline values with sustained therapy. There was no statistically significant difference between placebo and duloxetine groups in sustained blood pressure (P=0.631), SBP (P=0.740), or DBP (P=1.00) measured during three consecutive visits. Patients randomized to duloxetine therapy experienced higher incidences of palpitations (P=0.004), tachycardia (P=0.007), orthostatic hypotension (P=0.004), increased blood pressure (P<0.001), blood total cholesterol (P=0.031), and peripheral coldness (P=0.044) compared to patients randomized to placebo. Secondary: Not reported
Mullins et al.[218] (2005) Sertraline vs paroxetine vs citalopram	RETRO Patients with depression, PTSD, or social anxiety disorder	N=14,933 Data gathered from 1/1/99 to 6/30/02	Primary: Persistence, switching, discontinuation Secondary: Not reported	Primary: Compared to patients receiving sertraline and citalopram, those receiving paroxetine had lower rates of persistence (23.79% for paroxetine vs 25.96% for sertraline [P=0.0093] and 26.56% for citalopram [P=0.0022]) and higher rates of switching (3.55% for paroxetine vs 3.32% for sertraline [P=0.5076] and 2.78% for citalopram [P=0.0359]) and discontinuation (72.66% for paroxetine vs 70.72% for sertraline [P=0.0258] and 70.66% for citalopram [P=0.0334]). Survival curves showed that persistence rates with sertraline and citalopram were significantly greater than with paroxetine (P<0.05). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Stein et al.[219] (2000) SSRIs, MAOIs, benzodiazepines, beta blockers, buspirone, gabapentin, olanzapine	MA Patients with social anxiety disorders	N=5,264 (36 trials) Variable duration	Primary: CGI-I scale Secondary: LSAS	Primary: Summary statistics for responder status (assessed using the CGI from 25 short-term comparisons demonstrated a higher degree of efficacy of various medications over placebo (RR of non-response, 0.63; 95% CI, 0.55 to 0.72). Response to treatment by SSRIs (N=11; RR, 0.67; 95% CI, 0.59 to 0.76), MAOIs (N=3; RR, 0.43; 95% CI, 0.24 to 0.76) supported the value of these agents. However, the SSRIs were significantly more effective than the other agents (P<0.00001). Secondary: LSAS showed a statistically significant difference between medication and placebo (weighed mean difference, –15.56; 95% CI, –17.95 to -13.16), with this effect once again most evident for the SSRIs. Medication was also significantly more effective compared to placebo in reducing symptom clusters, comorbid depressive symptoms, and associated disability. The value of long-term medication treatment in treatment responders was supported by three comparisons from maintenance studies (RR, 0.58; 95% CI, 0.39 to 0.85) and five comparisons from relapse prevention studies (RR, 0.33; 95% CI, 0.22 to 0.49).

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

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

Additional Evidence

Dose Simplification
Claxton et al. evaluated compliance rates with fluoxetine 90 mg once weekly compared to fluoxetine 20 mg once daily in patients who had previously received four weeks of fluoxetine 20 mg once daily.[220] At the end of 12 weeks, compliance significantly declined from 87 to 79% with the once daily fluoxetine; however, the effect on clinical outcomes was not measured. More patients in the once-weekly group discontinued therapy due to lack of efficacy than in the once-daily group, but this difference was not statistically significant.

Stable Therapy
Brent et al. evaluated the efficacy of 4 treatment strategies in adolescents who continued to have depression despite initial treatment with an selective serotonin-reuptake inhibitors (SSRIs).[65] The interventions included switching to a different SSRI, switching to a different SSRI plus cognitive behavioral therapy, switching to venlafaxine, or switching to venlafaxine plus cognitive behavioral therapy. The authors found that switching to a different treatment plus cognitive behavioral therapy was more effective than medication switch alone. A switch to another SSRI was as effective as switching to venlafaxine.

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

IX. Cost

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

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

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

Rx=prescription

Table 12. Relative Cost of the Antidepressants

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

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

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

X. Conclusions

The antidepressants are approved to treat a variety of mental disorders, including anxiety disorders, eating disorders (bulimia nervosa), mood disorders, premenstrual dysphoric disorder and moderate to severe vasomotor symptoms associated with menopause.[1-35] Some of the agents are also approved for the treatment of nonpsychiatric conditions, such as chronic musculoskeletal pain, diabetic peripheral neuropathy, fibromyalgia, insomnia, nocturnal enuresis and tobacco abuse.[1-32] The antidepressants are categorized into six different American Hospital Formulary Service (AHFS) subclasses, including monoamine oxidase inhibitors (MAOIs), selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs), selective serotonin-reuptake inhibitors (SSRIs), serotonin modulators, tricyclic antidepressants (TCAs) and miscellaneous agents. The agents which make up these subclasses differ with respect to their Food and Drug Administration (FDA)-approved indications,

mechanism of action, pharmacokinetics, adverse events and drug interactions. The majority of the products are available in a generic formulation, and there is at least one generic product available in each antidepressant subclass.

Numerous clinical trials have been conducted with the antidepressants and comparative studies have demonstrated similar efficacy in patients with major depressive disorder.[56,60,63,66-67,82-84,88,94,96-103,107-108,111,113,141,144-146,156] Guidelines do not give preference to one agent over another.[35-36,38] Rather, the selection of an antidepressant should be based on adverse events, tolerability and patient preference.[35-36]

Several antidepressants are approved for the treatment of anxiety disorders. The American Psychiatric Association recommends the initial use of either an SNRI or SSRI for the treatment of panic disorder due to their favorable safety and tolerability profiles.[47] The National Institute for Health and Clinical Excellence recommends the use of SSRIs as first-line therapy for the long-term treatment of generalized anxiety disorder.[39] SSRIs are also recommended for the initial treatment of obsessive-compulsive disorder.[40-41] The SNRIs, SSRIs and TCAs have all been shown to be more effective than placebo for the treatment of anxiety disorders, and comparative studies have demonstrated similar efficacy among the antidepressants.[52,55,59,61,64,68,122-123,125,127-129,131-134] Guidelines do not give preference to one agent over another.[39-43,47] The choice of treatment should be based on safety, adverse events, drug interactions, prior response to treatment and comorbid conditions.[40,47]

Duloxetine has been approved by the FDA for the treatment of chronic musculoskeletal pain, in addition to depression, generalized anxiety disorder, diabetic peripheral neuropathic pain and fibromyalgia.[9] It has been shown to be more effective than placebo in patients with chronic low back pain and osteoarthritis of the knee; however, the effects were modest.[140,147-148,150,155]

According to the boxed warning, antidepressants increased the risk of suicidal thinking and behavior in children, adolescents and young adults compared to placebo in short-term studies of major depressive disorder and other psychiatric disorders.[1-32] Short-term studies did not show an increase in the risk of suicidality in adults older than 24 years of age, and there was a reduction in risk in adults 65 years of age and older. Although the MAOIs are an effective treatment option for patients with major depressive disorder, drug interactions, dietary restrictions and serious adverse events limit their use. It is recommended that MAOIs be reserved for patients who are not responding to other treatment options.[35]

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

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

XI. Recommendations

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

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

XII. References

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Cerebral Stimulants/Agents Used for ADHD
Central Alpha-Agonists, AHFS Class 240816
Amphetamines, AHFS Class 282004
Respiratory and CNS Stimulants AHFS Class 282032
Central Nervous System Agents, Miscellaneous, AHFS Class 289200
May 14, 2014

I. Overview

Attention-Deficit/Hyperactivity Disorder (ADHD) is a common psychiatric disorder that is often diagnosed during childhood; however, children with ADHD may continue to manifest symptoms into adulthood.[1-3] The key diagnostic feature is a persistent pattern of inattention and/or hyperactivity-impulsivity that is more frequent/severe than seen in individuals at a comparable level of development.[1] There are three subtypes of ADHD, including a predominantly inattentive subtype, a predominantly hyperactive-impulsive subtype, and a combined subtype in which both symptoms are displayed.[1] Untreated (or undertreated) ADHD is associated with adverse sequelae, including delinquent behavior, antisocial personality traits, substance abuse and other comorbidities.[3]

There are several central nervous system agents that are approved for the treatment of ADHD. This includes cerebral stimulants (amphetamines and methylphenidate derivatives), as well as atomoxetine, extended-release clonidine and extended-release guanfacine.[4-20] The stimulants are thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space.[5-18] Due to their potential for abuse, the stimulants are classified as Schedule II controlled substances. Atomoxetine, extended-release clonidine and extended-release guanfacine are not considered controlled substances and have no known potential for abuse or dependence. Their mechanism of action in the treatment of ADHD is unknown. Atomoxetine is a selective norepinephrine reuptake inhibitor, while clonidine and guanfacine are alpha$_2$-adrenergic agonists.[4,19,20]

Since the last review, new generics have become available for Kapvay® (clonidine extended-release) and Metadate CD® (methylphenidate). In addition, two new agents have become available, including Zenzedi® (dextroamphetamine), which offers two unique dosage strengths of dextroamephatmine, and Quillivant XR® (methylphenidate extended-release), which offers an extended-release oral suspension formulation.

The cerebral stimulants/agents used for ADHD that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Table 2 classifies the agents based on their duration of action. Many of the products are available in a generic formulation. This class was last reviewed in August 2012.

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

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Central Alpha-Agonists			
Clonidine	sustained-release tablet	Kapvay®*	none
Amphetamines			
Amphetamine aspartate, amphetamine sulfate, and dextroamphetamine	extended-release capsule, tablet	Adderall®*, Adderall XR®*‡	Adderall XR®*‡
Dextroamphetamine	sustained-release capsule, solution, tablet	Dexedrine®*, ProCentra®, Zenzedi®*	dextroamphetamine
Lisdexamfetamine	capsule	Vyvanse®	Vyvanse®
Methamphetamine	tablet	Desoxyn®*	methamphetamine
Anorexigenic Agents and Respiratory and Cerebral Stimulants, Miscellaneous			
Dexmethylphenidate	extended-release capsule, tablet	Focalin®*, Focalin XR®	dexmethylphenidate, Focalin XR®*
Methylphenidate	chewable tablet,	Concerta®*, Daytrana®,	methylphenidate,

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
	extended-release capsule, solution and tablet, sustained-release tablet, solution, tablet, transdermal patch	Metadate CD®*, Metadate ER®*, Methylin®*, Ritalin®*, Ritalin LA®*, Ritalin-SR®*, Quillivant XR®	Ritalin®*, Ritalin-SR®*
Central Nervous System Agents, Miscellaneous			
Atomoxetine	capsule	Strattera®	none
Guanfacine	extended-release tablet	Intuniv®	Intuniv®

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

Table 2. Cerebral Stimulants/Agents Used for ADHD Classified by Duration of Action[4-23]

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

II. Evidence-Based Medicine and Current Treatment Guidelines

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

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

Clinical Guideline	Recommendation(s)
American Academy of Pediatrics: **Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit Hyperactivity Disorder in Children and Adolescents**	<u>Preschool-aged children (four to five years of age)</u> • The primary care clinician should prescribe evidence-based parent- and/or teacher-administered behavior therapy as the first-line of treatment. • Methylphenidate may be prescribed if the behavior interventions do not provide significant improvement and there is moderate-to-severe continuing disturbance in the child's function. <u>Elementary school-aged children (six to 11 years of age)</u> • The primary care clinician should prescribe Food and Drug Administration (FDA)-approved medications for attention deficit-hyperactivity disorder

Clinical Guideline	Recommendation(s)
(2011)[24]	(ADHD) and/or evidence-based parent and/or teacher-administered behavior therapy as treatment for ADHD, preferably both. • The evidence is particularly strong for stimulant medications and sufficient but less strong for atomoxetine, extended-release guanfacine, and extended-release clonidine (in that order). <u>Adolescents (12 to 18 years of age)</u> • The primary care clinician should prescribe FDA-approved medications for ADHD with the assent of the adolescent and may prescribe behavior therapy as treatment for ADHD, preferably both. <u>General considerations</u> • Stimulant medications are highly effective for most children in reduction of core symptoms of ADHD. • Atomoxetine, extended-release guanfacine and extended-release clonidine reduce core symptoms; however, they have a smaller evidence base than stimulants. • Extended-release guanfacine and extended-release clonidine have evidence to support their use as adjunctive therapy with stimulant medications. • Before beginning medication treatment for adolescents with newly diagnosed ADHD, clinicians should assess these patients for symptoms of substance abuse. • Clinicians should monitor symptoms and prescription-refill requests for signs of misuse or diversion of ADHD medications and consider prescribing medications with no abuse potential, such as atomoxetine, extended-release guanfacine, or extended-release clonidine (which are not stimulants) or stimulant medications with less abuse potential, such as lisdexamfetamine, dermal methylphenidate, or osmotic-release oral system methylphenidate). • Primary care clinicians should titrate doses of medication for ADHD to achieve maximum benefit with minimum adverse effects.
Institute for Clinical Systems Improvement: **Diagnosis and Management of Attention Deficit Hyperactivity Disorder in Primary Care for School-Age Children and Adolescents (2012)**[25]	<u>Medication trials</u> • Prescribe FDA-approved treatments for ADHD in children, including psychostimulants and/or non-stimulants. • The decision to use medications should be made in conjunction with parents following a thorough discussion of expected benefits and potential risks. Factors such as the child's age, severity of symptoms and presence of comorbidity should also be considered and may involve decision-making regarding choice of medication. • Obtain cardiology consultation for patients with known structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems that could place patients at an increased risk to the sympathomimetic effects of central nervous system stimulants and/or atomoxetine. • Review the personal and family cardiovascular history, and complete a physical examination of each patient prior to starting stimulant therapy and/or atomoxetine. Medication history or physical exam changes consistent with possible cardiac disease during treatment with stimulant medication and/or atomoxetine may require additional evaluation by a cardiologist. • Optimal medication management alone is superior to other modalities for the core symptoms of ADHD. • Response to one stimulant does not predict response to the others. If a child is a non-responder to one stimulant, it is advisable to attempt a second or third trial with other stimulants. • Treatment with psychostimulants is often safe and effective in managing many children with ADHD with mild to moderate tics. Nevertheless, frequency and severity of tics should be carefully monitored in these patients. No routine blood work is necessary before or during psychostimulant therapy.

Clinical Guideline	Recommendation(s)
	• Current evidence does not support a higher risk of sudden cardiac death with stimulant medication compared to the general population; however, certain conditions may place a patient at higher risk for such an outcome. • Atomoxetine is a good option for patients with comorbid anxiety, sleep initiation disorder, substance abuse, or tics, or if initially preferred by parents and/or physician. Atomoxetine is a non-controlled substance that may make it preferable in certain clinical situations. • Extended-release guanfacine and extended-release clonidine are the first ADHD medications to achieve FDA approval as adjunctive therapy with stimulant medications. • Extended-release guanfacine is the first ADHD medication to look for improvement of oppositional symptoms in addition to ADHD core symptoms. Alternative medications • When adequate stimulant, atomoxetine or alpha adrenergic trials are unsuccessful due to either poor response or adverse effects, or if associated comorbidity is present, alternative medication trials should be considered. Second-line medications for ADHD therapy include tricyclic antidepressants (imipramine, desipramine), alpha adrenergic agonist (clonidine) a non- tricyclic antidepressant (bupropion), or immediate-release guanfacine.

National Institute for Health and Clinical Excellence: **Attention Deficit Hyperactivity Disorder: Diagnosis and Management of Attention Deficit Hyperactivity Disorder in Children, Young People, and Adults (2008)**[26]	Treatment for children and adolescents with ADHD
	• Methylphenidate, atomoxetine and dexamphetamine are recommended as options for the management of ADHD in children and adolescents.
	• The decision regarding which product to use should be based on the following:
	  o The presence of comorbid conditions.
	  o The different adverse effects of the drugs.
	  o Specific issues regarding compliance identified for the individual child or adolescent.
	  o The potential for drug diversion.
	  o The preferences of the child/adolescent and/or his or her parent or guardian.
	• Healthcare professionals should consider the following treatment recommendations:
	  o Methylphenidate for patients with ADHD without significant comorbidities.
	  o Methylphenidate for patients with ADHD with comorbid conduct disorder.
	  o Methylphenidate or atomoxetine when tics, Tourette's syndrome, anxiety disorder, stimulant misuse or risk of stimulant diversion are present.
	  o Atomoxetine if methylphenidate has been tried and has been ineffective at the maximum tolerated dose, or the child or young person is intolerant to low or moderate doses of methylphenidate.
	• Modified-release preparations should be considered for the following reasons:
	  o Convenience.
	  o Improving adherence.
	  o Reducing stigma (because the child or young person does not need to take medication at school).
	  o Reducing problems schools have in storing and administering controlled drugs.
	  o Their pharmacokinetic profiles.
	• Immediate-release preparations may be considered if more flexible dosing regimens are required, or during initial titration to determine correct dosing levels.

Clinical Guideline	Recommendation(s)
	Treatment of adults with ADHD • Drug treatment is the first-line treatment for adults with ADHD with either moderate or severe levels of impairment. • Methylphenidate is recommended as the first-line drug. • If methylphenidate is ineffective or unacceptable, atomoxetine or dexamphetamine can be tried. • Caution should be exercised when prescribing dexamphetamine to those likely to be at risk of stimulant misuse or diversion.
American Academy of Child and Adolescent Psychiatry: **Practice Parameter for the Assessment and Treatment of Children and Adolescents With Attention-Deficit/ Hyperactivity Disorder (2007)**[3]	• Initial pharmacologic therapy should be with an agent approved by the FDA for the treatment of ADHD. This includes dextroamphetamine, methylphenidate, mixed salts of amphetamine, and atomoxetine. • Stimulants have been shown to be highly effective for the treatment of ADHD in many clinical trials. • Available evidence suggests that both methylphenidate and amphetamines are equally efficacious in the treatment of ADHD. • Immediate-release stimulant medications have the disadvantage that they must be taken two to three times per day to control ADHD symptoms throughout the day. • The long-acting formulations are equally efficacious as immediate-release formulations. • Long-acting formulations may be used as initial therapy. There is no need to titrate to the appropriate dose on short-acting forms and then transfer children to a long-acting form. Short-acting stimulants are often used as initial treatment in small children (<16 kg in weight), for whom there are no long-acting forms in a sufficiently low dose. • Once a medication is initiated, the dose should be titrated every one to three weeks until the maximum dose is reached, the symptoms of ADHD remit, or side effects prevent further titration. • It is recommended that the patient be in contact with the physician during the titration period and visit the physician after one month of therapy to assess effectiveness and determine long-term therapy plans. • Some patients may respond similarly to different stimulant classes; whereas, other patients may preferentially respond to only one class of stimulants. There is no method to predict which stimulant will produce the best response in a given patient. • For the treatment of preschoolers, the available evidence suggests that the titration of stimulants be done slowly and that lower doses may be effective. This may be due to slower metabolism of methylphenidate in preschoolers. • In studies published comparing atomoxetine to stimulants, greater efficacy was seen in those patients treated with stimulants. • Atomoxetine may have less pronounced effects on appetite and sleep than stimulants, although they may produce relatively more nausea or sedation. • Atomoxetine may be considered as a first-line agent in patients with an active substance abuse problem, comorbid anxiety, tics, or in those who experience severe side effects while taking stimulants. • It is the choice of the family and the clinician as to which agent should be used for the patient's treatment and each patient's treatment must be individualized.
British Association of Psychopharmacology: **Evidence-Based Guidelines for the Management of Attention Deficit Hyperactivity Disorder in Adolescents in**	Treatment recommendations for children • Proven first-line treatments in children include psychostimulants and atomoxetine. • Second-line treatment options include imipramine and bupropion. • Clonidine and guanfacine may be used as adjunctive treatments. • Qualitative assessments suggest that all agents are more effective than placebo and have similar efficacy; however, there have been few head-to-head comparisons. • The agents are not equivalent in terms of adverse effects.

Clinical Guideline	Recommendation(s)
Transition to Adult Services and in Adults (2006)[27]	• The response to different agents varies between individuals and with different doses. <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 better efficacy than other treatments for core symptoms. However, amphetamines, methylphenidate and atomoxetine are all effective but not equivalent, since they have different actions and hazards. <u>Abuse potential</u> • Abuse potential is related to drug action and formulation. Abuse is generally low among patients but it can occur with stimulants. Slow-release preparations of these agents or atomoxetine are preferred for patients with a history of substance abuse, or who are at risk for substance abuse.
American Academy of Sleep Medicine: **Practice Parameters for the Treatment of Narcolepsy and Other Hypersomnias of Central Origin (2007)**[28]	• Most of the agents used to treat excessive sleepiness have little effect on cataplexy or other rapid eye movement sleep associated symptoms. Most antidepressants and anticataplectics have little effect on alertness. However, some compounds act on both symptoms. Compounds should be selected depending on the diagnosis and the targeted symptoms. Coadministration of two or more classes of compounds may be needed in some patients to adequately address their symptoms. • Modafinil is effective for treatment of daytime sleepiness due to narcolepsy. • Sodium oxybate is effective for treatment of cataplexy, daytime sleepiness, and disrupted sleep due to narcolepsy. Sodium oxybate may be effective for treatment of hypnagogic hallucinations and sleep paralysis. • Amphetamine, methamphetamine, dextroamphetamine, and methylphenidate are effective for treatment of daytime sleepiness due to narcolepsy. • Selegiline may be an effective treatment for cataplexy and daytime sleepiness. • Tricyclic antidepressants, selective serotonin reuptake inhibitors, and venlafaxine may be effective treatment for cataplexy. • Scheduled naps can be beneficial to combat sleepiness, but seldom suffice as primary therapy for narcolepsy.
European Federation of Neurological Sciences: **Guidelines on Management of Narcolepsy in Adults (2011)**[29]	<u>Excessive daytime sleepiness and irresistible episodes of sleep</u> • Modafinil should be prescribed when excessive daytime sleepiness is present. Modafinil should be dosed as 100 to 400 mg/day, given once in the morning or twice daily. • Sodium oxybate may be used when excessive daytime somnolence coexists with cataplexy and poor sleep. Depressed patients should not receive sodium oxybate. • Sodium oxybate should be initiated with 4.5 g/night, increasing by increments of 1.5 g at four-week intervals and should not be used with other sedatives, respiratory depressants or muscle relaxants. Monitor patients for possible development of sleep-disordered breathing. Adverse effects may limit the dose, and require slower titration. • The optimal response on excessive daytime sleepiness may take up to 12 weeks. • Supplementation with modafinil is generally more successful than sodium oxybate alone. • Methylphenidate may be considered if modafinil is insufficient and sodium oxybate is not recommended. • The short-acting effect of methylphenidate is of interest when modafinil needs to be supplemented at a specific time of the day, or in situations where maximum alertness is required.

Clinical Guideline	Recommendation(s)
	Cataplexy • First-line pharmacological treatment of cataplexy is sodium oxybate at a starting dose of 4.5 g/night divided into two equal doses of 2.25 g/night. The dose may be increased to a maximum of 9 g/night, divided into two equal doses of 4.5 g/night, by increments of 1.5 g at two-week intervals. • Adverse effects may limit the dose, and require slower titration and the optimal response on excessive daytime sleepiness may take up to 12 weeks. • Antidepressants are recommended as second-line pharmacological treatment. Tricyclic antidepressants, particularly clomipramine (10 to 75 mg), are potent anticataplectic drugs; however, anticholinergic adverse effects are common. • Selective serotonin reuptake inhibitors are slightly less active but have fewer adverse effects. • Venlafaxine is widely used but clinical evidence supporting its use is limited. • Reboxetine and atomoxetine, also lack published clinical evidence. • Given the efficacy of sodium oxybate and antidepressants, the place for other compounds is fairly limited. • There is no accepted behavioral treatment of cataplexy. Poor sleep • Sodium oxybate appears to be the most appropriate to treat poor sleep. • Benzodiazepine or non-benzodiazepine hypnotics may be effective in consolidating nocturnal sleep, but objective evidence is lacking over intermediate- or long-term follow-up. • The improvement in poor sleep reported by some patients once established on modafinil is noteworthy. Obstructive sleep apnea/hypopnea syndrome, periodic limb movements in sleep, neuropsychiatric symptoms • Obstructive sleep apnea/hypopnea syndrome should be similarly in narcoleptic patients and general population, although continuous positive airway pressure does not improve excessive daytime sleepiness in most narcolepsy subjects. • There is usually no need to treat periodic limb movements in narcoleptic patients. Antidepressants and psychotherapy should be used in depressed narcoleptic patients as in non-narcoleptic depressed patients.
American Academy of Sleep Medicine: **Clinical Guideline for the Evaluation, Management and Long-term Care of Obstructive Sleep Apnea in Adults (2009)**[30]	Weight reduction • Successful dietary weight loss may improve the apnea-hypopnea index in obese obstructive sleep apnea patients. • Dietary weight loss should be combined with a primary treatment for obstructive sleep apnea. • Bariatric surgery may be adjunctive in the treatment of obstructive sleep apnea in obese patients. Pharmacologic agents • Modafinil is recommended for the treatment of residual excessive daytime sleepiness in obstructive sleep apnea patients who have sleepiness despite effective positive airway pressure treatment and who are lacking any other identifiable cause for their sleepiness. • Selective serotonin reuptake inhibitors, protriptyline, methylxanthine derivatives (aminophylline and theophylline), and estrogen therapy are not recommended for treatment of obstructive sleep apnea. Supplemental oxygen • Oxygen supplementation is not recommended as a primary treatment for obstructive sleep apnea.

Clinical Guideline	Recommendation(s)
	Medical therapies intended to improve nasal patency • Short-acting nasal decongestants are not recommended for treatment of obstructive sleep apnea. • Topical nasal corticosteroids may improve the apnea-hypopnea index in patients with obstructive sleep apnea and concurrent rhinitis, and thus may be a useful adjunct to primary therapies for obstructive sleep apnea. Positional therapies • Positional therapy is an effective secondary therapy or can be a supplement to primary therapies for obstructive sleep apnea in patients who have a low apnea-hypopnea index in the non-supine vs that in the supine position. vs
American Academy of Sleep Medicine: **Practice Parameters for the Clinical Evaluation and Treatment of Circadian Rhythm Sleep Disorders (2007)**[31]	Shift work disorder • Planned napping before or during the night shift is indicated to improve alertness and performance among night shift workers. • Timed light exposure in the work environment and light restriction in the morning, when feasible, is indicated to decrease sleepiness and improve alertness during night shift work. • Administration of melatonin prior to daytime sleep is indicated to promote daytime sleep among night shift workers. • Hypnotic medications may be used to promote daytime sleep among night shift workers. Carryover of sedation to the nighttime shift with potential adverse consequences for nighttime performance and safety must be considered. • Modafinil is indicated to enhance alertness during the night shift for shift work disorder. • Caffeine is indicated to enhance alertness during the night shift for shift work disorder.

III. Indications

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

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

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

Generic Name(s)	Attention Deficit-Hyperactivity Disorder	Narcolepsy	Exogenous Obesity
Guanfacine	✔ *		

*As monotherapy and as adjunctive therapy to stimulant medications.
†Immediate-release formulations.
‡Sustained-release formulations.
§As a short-term adjunct in a regimen of weight reduction based on caloric restriction, for patients in whom obesity is refractory to alternative therapy (e.g., repeated diets, group programs, and other drugs).

IV. Pharmacokinetics

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

Table 5. Pharmacokinetic Parameters of the Cerebral Stimulants/Agents Used for ADHD[4-23]

Generic Name(s)	Onset (hours)	Duration (hours)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Central Alpha-Agonists							
Clonidine	0.5 to 1.0	6 to10	89	20 to 40	Liver (50)	Renal (40 to 60)	12 to 16
Amphetamines							
Amphetamine aspartate, amphetamine sulfate, and dextroamphetamine†	1 to 3	IR: 4 to 6 XR: 10 to 12	Well absorbed	Not reported	Liver (not reported)	Renal (67 to 73)	9 to 14
Dextroamphetamine	2 to 3	IR: 4 to 6 SR: 6 to 8	Well absorbed	Not reported	Liver (not reported)	Renal (17 to 73)	10 to 12
Lisdexamfetamine	Not reported	10	Rapid	Not reported	Blood (not reported)	Renal (96.0) Feces (0.3)	<1
Methamphetamine	Not reported	Not reported	Rapid	Not reported	Liver (not reported)	Renal (62)	4 to 5
Anorexigenic Agents and Respiratory and Cerebral Stimulants, Miscellaneous							
Dexmethylphenidate	1	IR: 5 to 6 XR: 12	22 to 25	12 to 15	Liver (not reported)	Renal (90)	2.0 to 4.5
Methylphenidate	IR: 2 SR: 4 to 7 ER: 1 to 2 XR: 0.5 to 1.0 TD: 2	IR: 3 to 6 SR: 8 ER: 10 to 12 XR: 8 to 12 TD: 10 to 12	10 to 52	10 to 33	Liver (not reported)	Renal (90) Fecal (1 to 3)	3 to 4
Central Nervous System Agents, Miscellaneous							
Atomoxetine	1 week	Not reported	63 to 94	98	Liver (not reported)	Renal (>80) Feces (<17)	5 to 22
Guanfacine	Not reported	Not reported	80	70	Liver (50)	Renal (50)	16

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

V. Drug Interactions

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

Table 6. Significant Drug Interactions with the Cerebral Stimulants/Agents Used for ADHD[21]

Generic Name(s)	Significance Level	Interaction	Mechanism
Central Alpha-Agonists			
Clonidine	1	Beta-adrenergic blockers	Withdrawal hypertension may be more severe in patients receiving clonidine and beta-adrenergic blockers. This combination may, on occasion, cause paradoxical hypertension.
Clonidine	1	Tricyclic antidepressants	The antihypertensive effects of clonidine may be decreased by tricyclic antidepressants. Tricyclic antidepressants may worsen rebound reactions from abrupt clonidine withdrawal.
Clonidine	2	Tizanidine	The potential for symptomatic additive hypotension exists when tizanidine is coadministered with clonidine.
Amphetamines			
Amphetamines	1	MAOIs	Toxicity of amphetamines may be increased by MAOIs. Headache, hyperpyrexia, elevated blood pressure and bradycardia may occur. Amphetamines can liberate large quantities of intraneuronal norepinephrine that have accumulated during treatment with MAOIs.
Amphetamines	1	Furazolidone	Toxicity of amphetamines may be increased by furazolidone. Headache, hyperpyrexia, and elevated blood pressure may occur. Amphetamines can liberate large quantities of intraneuronal catecholamines that have accumulated during treatment with furazolidone, due to monoamine oxidase inhibition.
Amphetamines	2	Urinary alkalinizers	Interaction may lead to pH-dependent diminished urinary elimination of amphetamines and increases risk of amphetamine toxicity.
Amphetamines	2	Guanethidine	Interaction may lead to a decrease in guanethidine effectiveness, probably due to antagonistic pharmacologic activity.
Anorexigenic Agents and Respiratory and Cerebral Stimulants, Miscellaneous			
Methylphenidates	1	MAOIs	Pharmacologic effects of methylphenidates may be increased. Headache, gastrointestinal symptoms and hypertension may occur. The mechanism of this interaction is not clear. Liberation of intraneuronal catecholamine stores may play a role.
Methylphenidates	2	Halogenated anesthetics	Coadministration of methylphenidates and halogenated anesthetics may cause a sudden increase in blood pressure during surgery. The mechanism of this interaction is unknown.

Generic Name(s)	Significance Level	Interaction	Mechanism
Central Nervous System Agents, Miscellaneous			
Atomoxetine	1	MAOIs	Toxic effects may be increased with concurrent administration of atomoxetine and MAOIs. Serious and sometimes fatal reactions have occurred. Pharmacologic effects of atomoxetine and MAOIs may be additive.
Atomoxetine	2	Serotonin-reuptake inhibitors	Certain serotonin-reuptake inhibitors may inhibit the metabolism (CYP2D6) of atomoxetine and increase plasma concentrations.
Atomoxetine	2	Quinidine	Plasma concentrations and pharmacologic effects of atomoxetine may be increased by quinidine. Quinidine may decrease the metabolism of atomoxetine and increase atomoxetine plasma concentrations.
Atomoxetine	2	Yohimbine	Coadministration of atomoxetine and yohimbine may increase the risk of new or worsened preexisting supine hypertension in patients with autonomic failure.
Guanfacine	2	Tricyclic antidepressants	Tricyclic antidepressants may antagonize the pharmacodynamic action of guanfacine at the central nervous system alpha-$_2$ adrenergic receptor. The antihypertensive effect of guanfacine may be decreased by tricyclic antidepressants.
Guanfacine	2	Tizanidine	An additive effect on alpha$_2$-adrenergic receptors by tizanidine and guanfacine may occur. The potential for symptomatic additive hypotension exists when tizanidine is coadministered with guanfacine.

MAOIs=monoamine oxidase inhibitors
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 attention deficit-hyperactivity disorder (ADHD) are listed in Tables 7 to 10. The boxed warnings for the cerebral stimulants/agents used for ADHD are listed in Tables 11 to 16. Methylphenidate and amphetamines increase dopamine levels in the brain similar to cocaine and methamphetamine. They are classified as Schedule II controlled substances by federal regulation. Long-term abusive use can lead to tolerance and psychological dependence. There is no evidence to suggest that drug abuse results from prescribed stimulants if they are properly monitored.[1,32-34] Methylphenidate is a less potent sympathomimetic amine than mixed amphetamine salts, which may be associated with a lower potential for abuse.[33] The osmotic-release formulation of methylphenidate cannot be crushed and may decrease the potential for abuse. It has also been proposed that transdermal methylphenidate may possess less potential for abuse compared to orally-administered cerebral stimulants. Atomoxetine, clonidine and guanfacine are not controlled substances.

Table 7. Adverse Drug Events (%) Reported with the Central Alpha-Agonists[4]

Adverse Events	Clonidine
Cardiovascular	
Atrioventricular block	✔
Bradycardia	≤4
Cardiac arrhythmia	✔

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

Adverse Events	Clonidine
Libido decreased	✔
Nocturia	1
Pollakiuria	3
Sexual disturbances	3
Hepatic	
Hepatitis	✔
Liver function test abnormalities	≤1
Musculoskeletal	
Arthralgia	1
Leg cramps	≤1
Myalgia	1
Pain in extremities	✔
Weakness	10
Respiratory	
Asthma	4
Epistaxis	3
Lower respiratory tract infection	2
Nasal congestion	2 to 4
Nasal dryness	✔
Nasopharyngitis	2
Upper respiratory tract infection	2 to 7
Special Senses	
Accommodation difficulties	✔
Blurred vision	✔
Dry eyes	✔
Eye pain	✔
Other	
Body temperature increase	≤2
Ear infection	✔
Ear pain	4
Flu-like syndrome	≤3
Throat pain	3 to 5
Thrombocytopenic purpura	✔
Viral infection	≤3

✔ Percent not specified.

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

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

Adverse Events	Amphetamine Aspartate/ Amphetamine Sulfate/ Dextroamphetamine	Dextro-amphetamine	Lisdex-amfetamine	Meth-amphetamine
Agitation	8*	-	3	-
Anxiety	8*	-	6	-
Depression	✔ †*	-	✔	-
Dizziness	2 to 7*	✔	5	✔
Dyskinesia	✔ †*	✔	✔	-
Dysphoria	✔ †*	✔	✔	✔
Euphoria	✔ †*	✔	✔	✔
Fever	5*	-	2	-
Headache	✔ †, 26*	✔	12	✔
Insomnia	12 to 27*	✔	13 to 27	✔
Irritability	✔ †*	-	10	-
Labile affect	-	-	3	-
Mania	-	✔	✔	✔
Nervousness	6 to 13*	-	-	-
Overstimulation	✔ †	✔	✔	✔
Psychotic episodes	✔ †	✔	✔	✔
Restlessness	✔ †*	✔	3	✔
Seizures	✔ *	-	✔	✔
Somnolence	2 to 4*	-	2	-
Speech disorder	2 to 4*	-	-	-
Stroke	✔ *	✔	✔	✔
Tic exacerbation	✔ †*	✔	2	✔
Tourette's exacerbation	✔ †*	✔	✔	✔
Tremor	✔ †*	✔	2	✔
Twitching	2 to 4*	-	-	-
Dermatological				
Diaphoresis	2 to 4*	-	-	-
Hyperhidrosis	-	-	3	-
Photosensitivity	2 to 4*	-	-	-
Rash	✔ †*	✔	3	✔
Stevens-Johnson syndrome	✔ †*	-	✔	-
Toxic epidermal necrolysis	✔ †*	-	✔	-
Urticaria	✔ †*	✔	✔	✔
Gastrointestinal				
Abdominal pain	11 to 14*	-	12	-
Anorexia	-	✔	5	✔
Appetite decreased	22 to 36*	-	27 to 39	-
Constipation	✔ †, 2 to 4*	✔	✔	✔
Diarrhea	2 to 6*	✔	7	✔
Dry mouth	2 to 35*	✔	4 to 26	✔
Dyspepsia	2 to 4*	-	-	-
Nausea	2 to 8*	-	6 to 7	✔
Other gastrointestinal disturbances	-	✔	-	✔
Unpleasant taste	✔ †*	✔	✔	✔
Vomiting	2 to 7*	-	9	✔
Weight loss	4 to 11*	✔	9	✔
Genitourinary				
Changes in libido	2 to 4*	✔	≤2	✔
Impotence	2 to 4*	✔	✔	✔
Urinary tract infection	5*	-	-	-

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

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

Table 9. Adverse Drug Events (%) Reported with the Anorexigenic Agents and Respiratory and Cerebral Stimulants, Miscellaneous[11-18]

Adverse Events	Dexmethylphenidate	Methylphenidate
Cardiovascular		
Angina	✔	✔
Cardiac arrhythmia	✔	✔
Chest pain	-	✔
Hypertension	✔	✔
Hypotension	✔	✔
Myocardial infarction	-	✔
Palpitations	✔	✔
Pulse increase/decrease	✔	✔
Raynaud's phenomenon	-	✔
Sudden death	✔	-
Systolic blood pressure increased	-	-
Tachycardia	3	✔
Vasodilation	-	-
Central Nervous System		
Aggressive behavior	✔	✔
Agitation	-	-
Anxiety	5 to 11	-
Attention disturbance	-	-
Cerebral arteritis	✔	✔
Cerebral occlusion	✔	✔
Depression	✔	✔
Dizziness	6	✔
Drowsiness	✔	✔
Dyskinesia	✔	✔
Emotional instability	-	6†
Fatigue/lethargy	-	-
Fever	5	✔
Hallucinations	-	✔ †
Headache	25 to 39	✔ , 28†
Hyperkinesia	-	-
Hypertonia	-	-
Insomnia	✔	✔ , 13 to 30†

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

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

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

Table 10. Adverse Drug Events (%) Reported with the Central Nervous System Agents, Miscellaneous[19,20]

Adverse Events	Atomoxetine	Guanfacine
Cardiovascular		
Atrioventricular block	-	✔
Chest pain	-	-
Diastolic blood pressure increased	4 to 22	-
Flushing	≥2	-
Hypertension	1 to 9	✔
Hypotension	<2	4
Palpitations	3	-
QT prolongation	<1	-
Reynaud's phenomenon	✔	-
Sinus arrhythmia	-	✔
Stroke	✔	-
Systolic blood pressure increased	4 to 13	-
Tachycardia	2 to 24	-
Central Nervous System		
Abnormal dreams	4	-
Aggressive behavior	✔	-
Agitation	✔	✔
Akathisia	✔	-
Anxiety	✔	✔
Ataxia	-	-
Attention disturbance	-	-
Chills	3	-
Confusion	-	-
Crying	2	-
Depression	-	✔
Disorientation	-	-
Dizziness	5 to 6	6 to 8
Early morning awakening	<2	-
Fatigue/lethargy	6 to 9	14
Fever	3	-
Hallucinations	-	✔
Headache	2 to 19	21 to 24
Hostility	✔	-
Insomnia	2 to 15	12
Irritability	≤ 6	2
Jittery feeling	2	-
Mania	✔	-
Mood swings	1 to 2	-
Nervousness	-	-
Nightmare	-	✔
Panic disorder	✔	-
Paresthesia	4	-
Rigors	3	-
Seizure	-	✔
Sleep disorder	-	-
Sleep disturbance	3	-
Sleep paralysis	-	-
Sleep walking	-	-
Somnolence	4 to 11	18 to 38
Suicidal ideation	✔	-
Syncope	✔	✔
Tremor	2	-

Adverse Events	Atomoxetine	Guanfacine
Dermatological		
Dermatitis	2 to 4	-
Diaphoresis	2	-
Flushing	2	-
Hyperhidrosis	4	-
Rash	2	-
Urticaria	✔	-
Endocrine and Metabolic		
Dysmenorrhea	6	-
Hot flushes	8	-
Menstrual disturbances	2 to 3	-
Gastrointestinal		
Abdominal pain	7 to 18	10 to 11
Anorexia	<3	-
Appetite decreased	11 to 16	2
Constipation	1 to 9	3
Diarrhea	4	-
Dry mouth	4 to 21	3
Dyspepsia	4 to 6	✔
Fecal incontinence	-	-
Flatulence	2	-
Nausea	7 to 26	4
Stomach discomfort	-	✔
Vomiting	3 to 11	✔
Weight increase	-	✔
Weight loss	2 to 30	-
Genitourinary		
Dysuria	3	-
Ejaculatory disturbance	3	-
Enuresis	-	✔
Erectile disturbance	9	-
Impotence	3	-
Libido decreased	4	-
Orgasm abnormal	2	-
Prostatitis	2	-
Urinary incontinence	-	-
Urinary retention	7	-
Hepatic		
Hepatotoxicity	✔	-
Jaundice	✔	-
Hypoesthesia	-	-
Myalgia	-	-
Myasthenia	-	-
Weakness	-	-
Respiratory		
Asthma	-	✔
Bronchitis	-	-
Cough	11	-
Dyspnea	-	-
Nasopharyngitis	-	-
Rhinitis	-	-
Rhinorrhea	4	-
Sinus headache	3	-
Sinusitis	6	-

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

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

Table 11. Boxed Warning for the Amphetamines[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 reactions.

Table 12. Boxed Warning for Atomoxetine[21]

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

Table 13. Boxed Warning for Dexmethylphenidate[21]

WARNING
Drug dependence: Give dexmethylphenidate cautiously to patients with a history of drug dependence or alcoholism. Chronic, abusive use can lead to marked tolerance and psychological dependence with varying

WARNING
degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during drug withdrawal from abusive use because severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow-up.

Table 14. Boxed Warning for Lisdexamfetamine[21]

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

Table 15. Boxed Warning for Methamphetamine[21]

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

Table 16. Boxed Warning for Methylphenidate[21]

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

VII. Dosing and Administration

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

Table 17. Usual Dosing Regimens for the Cerebral Stimulants/Agents Used for ADHD[4-20]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Central Alpha-Agonists			
Clonidine	Safety and efficacy has not been established in adults.	ADHD in patients ≥6 years of age: Tablet (SR): initial, 0.1 mg at bedtime; increase by 0.1 mg/day every seven days until desired response; doses should be administered twice daily; maximum, 0.4 mg/day	Tablet (SR): 0.1 mg 0.2 mg
Amphetamines			
Amphetamine aspartate, amphetamine sulfate,	ADHD: Capsule (ER) (adults): 20 mg once daily in the morning	ADHD: Capsule (ER): 10 mg once daily in the morning;	Capsule (ER): 5 mg 10 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
and dextroamphetamine	Tablet: 2.5 to 5 mg once or twice daily; maintenance, up to 40 mg/day Narcolepsy: Capsule (ER), tablet (adults): 5 to 60 mg daily in divided doses	maximum, 30 mg/day Tablet: 2.5 to 5 mg once or twice daily; maintenance, up to 40 mg/day Narcolepsy in children six to 12 years of age: Capsule (ER), tablet: 5 mg once daily; may increase by 5 mg weekly until optimal response Narcolepsy in children 12 years of age and older: Capsule (ER), tablet: 10 mg once daily; may increase by 10 mg weekly until optimal response	15 mg 20 mg 25 mg 30 mg Tablet: 5 mg 7.5 mg 10 mg 12.5 mg 15 mg 20 mg 30 mg
Dextroamphetamine	ADHD: Solution, tablet: initial, 2.5 to 5 mg once or twice daily; maintenance, up to 40 mg/day Capsule (SR): initial, 5 mg once or twice daily; maintenance, up to 40 mg/day Narcolepsy: Capsule (SR), solution, tablet: 5 to 60 mg/day administered in divided doses	ADHD in children six years of age and older: Solution, tablet: initial, 2.5 to 5 mg once or twice daily; maintenance, up to 40 mg/day Capsule (SR): initial, 5 mg once or twice daily; maintenance, up to 40 mg/day Narcolepsy in adolescents 12 years of age and older: Capsule (SR), solution, tablet: 5 to 60 mg/day administered in divided doses	Capsule (SR): (Dexedrine® Spansule) 5 mg 10 mg 15 mg Solution: (Procentra®) 5 mg/5 mL Tablet: (Dexedrine®, Zenzedi®) 2.5 mg 5 mg 7.5 mg 10 mg
Lisdexamfetamine	ADHD: Capsule: initial, 30 mg once daily in the morning; maximum, 70 mg/day	ADHD in children six years of age and older: Capsule: initial, 30 mg once daily in the morning; maximum, 70 mg/day	Capsule: 20 mg 30 mg 40 mg 50 mg 60 mg 70 mg
Methamphetamine	Exogenous obesity: Tablet: 5 mg taken one half hour before each meal ADHD: Tablet: initial, 5 mg once or twice daily; maintenance, 20 to 25 mg/day	Exogenous obesity in children 12 years of age and older: Tablet: 5 mg taken one half hour before each meal ADHD in children six years of age and older: Tablet: initial, 5 mg once or twice daily; maintenance, 20 to 25 mg/day	Tablet: 5 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Anorexigenic Agents and Respiratory and Cerebral Stimulants, Miscellaneous			
Dexmethylphenidate	ADHD: Capsule (ER) (new starts): initial, 5 to 10 mg once daily in the morning; maximum, 40 mg/day Capsule (ER) (patients currently receiving methylphenidate): initial, half the dose of racemic methylphenidate Tablet (new starts): initial, 2.5 mg twice daily; maximum, 10 mg twice daily Tablet (patients currently receiving methylphenidate): initial, half the dose of racemic methylphenidate; maximum, 10 mg twice daily	ADHD in children six years of age and older: Capsule (ER) (new starts): initial, 5 to 10 mg once daily in the morning; maximum, 30 mg/day Capsule (ER) (patients currently receiving methylphenidate): initial, half the dose of racemic methylphenidate Tablet (new starts): initial, 2.5 mg twice daily; maximum, 10 mg twice daily Tablet (patients currently receiving methylphenidate): initial, half the dose of racemic methylphenidate; maximum, 10 mg twice daily	Capsule (ER): 5 mg 10 mg 15 mg 20 mg 25 mg 30 mg 35 mg 40 mg Tablet: 2.5 mg 5 mg 10 mg
Methylphenidate	Treatment of ADHD: Chewable tablet, solution, tablet: 20 to 30 mg/day administered in two or three divided doses Capsule (ER) (new starts): initial, 20 mg once daily in the morning; maximum, 60 mg/day Capsule (ER) (patients currently receiving methylphenidate): administer equivalent total daily doses Suspension (ER): initial, 20 mg once daily in the morning; maximum, 60 mg/day Tablet (ER) (new starts): initial, 18 to 36 mg/day; maximum, 72 mg/day Tablet (ER) (patients currently receiving methylphenidate): dosing is based on current dose regimen and clinical judgment Tablet (ER): may be used in place of tablets when the eight hour dosage of the tablet (ER)	ADHD in children six years of age and older: Chewable tablet, solution, tablet: initial, 5 mg twice daily; maintenance, increase dose gradually Tablet (ER) (new starts): initial, 18 mg once daily in the morning; maximum, 54 (children) and 72 mg/day (adolescents) Tablet (ER) (patients currently receiving methylphenidate): dosing is based on current dose regimen and clinical judgment Tablet (ER): may be used in place of tablets when the eight hour dosage of the tablet (ER) corresponds to the titrated eight hour dosage with the tablets Tablet (SR): may be used in place of tablets when the eight hour dosage of the tablet (SR) corresponds to the titrated eight hour dosage with the tablets	Capsule (ER): (Metadate CD®, Ritalin LA®) 10 mg 20 mg 30 mg 40 mg 50 mg 60 mg Suspension (ER): (Quillivant XR®) 25 mg/ 5 mL Chewable tablet: (Methylin®) 2.5 mg 5 mg 10 mg Solution: (Methylin®) 5 mg/5 mL 10 mg/5 mL Tablet (ER): (Concerta®, Metadate ER®) 18 mg 27 mg 36 mg 54 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	corresponds to the titrated eight hour dosage with the tablets Tablet (SR): may be used in place of tablets when the eight hour dosage of the tablet (SR) corresponds to the titrated eight hour dosage with the tablets Transdermal patch: initial, 10 mg; maintenance, titrate to effect Narcolepsy: Chewable tablet, solution, tablet (adults): 20 to 30 mg/day administered in two or three divided doses Tablet (ER): may be used in place of tablets when the eight hour dosage of the tablet (ER) corresponds to the titrated eight hour dosage with the tablets Tablet (SR): may be used in place of tablets when the eight hour dosage of the tablet (SR) corresponds to the titrated eight hour dosage with the tablets	Transdermal patch: initial, 10 mg; maintenance, titrate to effect Narcolepsy in children six years of age and older: Chewable tablet, solution, tablet: initial, 5 mg twice daily; maintenance, increase dose gradually Tablet (ER): may be used in place of tablets when the eight hour dosage of the tablet (ER) corresponds to the titrated eight hour dosage with the tablets Tablet (SR): may be used in place of tablets when the eight hour dosage of the tablet (SR) corresponds to the titrated eight hour dosage with the tablets	Tablet: (Methylin®, Ritalin®) 5 mg 10 mg 20 mg Tablet (SR): (Ritalin SR®) 20 mg Transdermal patch: 10 mg/9 hours 15 mg/9 hours 20 mg/9 hours 30 mg/9 hours
Central Nervous System Agents, Miscellaneous			
Atomoxetine	ADHD: Capsule (>70 kg and adults): initial, 40 mg/day; maintenance, 80 mg/day; maximum, 100 mg/day	ADHD in children six years of age and older: Capsule (≤70 kg): initial, 0.5 mg/kg/day; maintenance, 1.2 mg/kg/day; maximum, 1.4 mg/kg/day Capsule (>70 kg and adults): initial, 40 mg/day; maintenance, 80 mg/day; maximum, 100 mg/day.	Capsule: 10 mg 18 mg 25 mg 40 mg 60 mg 80 mg 100 mg
Guanfacine	ADHD as monotherapy and as adjunctive therapy to stimulant medications: Tablet (ER): initial, 1 mg once daily; maintenance, 1 to 4 mg/day	ADHD as monotherapy and as adjunctive therapy to stimulant medications in children six years of age and older: Tablet (ER): initial, 1 mg once daily; maintenance, 1 to 4 mg/day	Tablet (ER): 1 mg 2 mg 3 mg 4 mg

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

VIII. Effectiveness

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

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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Attention Deficit Hyperactivity Disorder				
McCracken et al.[35] (2003) AMP-IR (Adderall®) 10 mg daily vs AMP-XR (Adderall XR®) 10 to 30 mg daily vs placebo	DB, PC, RCT, XO Children six to 12 years of age diagnosed with ADHD (combined or hyperactive-impulsive subtype)	N=51 5 weeks	Primary: SKAMP scales Secondary: Examination of the time course of AMP-XR	Primary: AMP-IR and AMP-XR were judged to have similar efficacy, and both exceeded placebo on attention and deportment SKAMP scales (P<0.0001). Secondary: The AMP-XR group displayed continued efficacy (in SKAMP score improvements) at time points beyond that of the AMP-IR group (i.e., 12 hours post dose).
Pliszka et al.[36] (2000) AMP-IR (Adderall®) 12.5 mg daily vs MPH-IR 25 mg daily vs	DB, PC, PG, RCT Children in grades one through five diagnosed with ADHD	N=58 3 weeks	Primary: CGI-S (parent and teacher) Secondary: Not reported	Primary: More responders were reported with AMP-IR than MPH-IR or placebo on both CGI-S scores (P<0.05). Behavioral effects of AMP-IR appeared to persist longer than with MPH-IR. Fourteen (70%) patients in the AMP-IR group required only a single morning dose, and 17 (85%) patients in the MPH-IR group received two or more doses per day (P=0.003). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				
Pelham et al.[37] (1999) AMP-IR (Adderall®) 7.5 or 12.5 mg twice daily vs MPH-IR (Ritalin®) 10 or 17.5 mg twice daily vs placebo	DB, PC, RCT, XO Children five to 12 years of age diagnosed with ADHD	N=25 6 weeks	Primary: Time course and dose-dependent response information Secondary: Not reported	Primary: Both doses of AMP-IR were generally more efficacious in reducing negative behaviors and improving academic productivity than low-dose MPH-IR (10 mg BID) throughout the course of the entire day. The differences were more pronounced when the effects of MPH-IR were wearing off at midday and late afternoon/early evening (P<0.025). Conversely, AMP-IR 7.5 mg BID and MPH-IR 17.5 mg BID produced equivalent behavioral changes throughout the entire day. The doses of AMP-IR that were assessed produced greater improvement than did the assessed doses of MPH-IR, particularly the lower dose of MPH-IR (P<0.01). Both drugs produced low and comparable levels of clinically significant side effects. Secondary: Not reported
Faraone et al.[38] (2002) AMP-IR (Adderall®) vs MPH-IR	MA (4 trials) Patients diagnosed with ADHD	N=216 3 to 8 weeks	Primary: CGI-S (parent, teacher and investigator) Secondary: Not reported	Primary: Combined results showed slightly greater efficacy with AMP-IR vs MPH-IR in clinician and parent ratings (P<0.05). No statistically significant difference was found in CGI-S scores with teacher ratings (P≥0.26). Secondary: Not reportedvs
Biederman et al.[39] (2002) AMP-XR (Adderall XR®) 10 to 30 mg daily	DB, MC, PC, RCT Children six to 12 years of age diagnosed with ADHD (hyperactive-	N=584 3 weeks	Primary: CGI-S (teachers and parents) Secondary: Variation in responses based on	Primary: Each AMP-XR treatment group had a statistically significant improvement in both CGI-S teacher and parent scales (P<0.001). Secondary: The CGI-S teacher scores calculated for the morning and afternoon assessments showed all doses of AMP-XR to be more effective than

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	impulsive or combined subtypes)		morning and afternoon assessments	placebo (P<0.001) at each assessment. The CGI-S teacher scores in the AMP-XR group were statistically significantly improved at all time points compared to those in the placebo group (P<0.001).
Goodman et al.[40] (2005) AMP-XR (Adderall XR®) 10 to 60 mg daily	MC, OL, PRO Adults ≥18 years of age diagnosed with ADHD (any subtype)	N=725 10 weeks	Primary: ADHD-RS, CGI-I Secondary: SF-36	Primary: At the end of the study, the mean ADHD-RS scores significantly decreased in the AMP-XR group regardless of dose compared to baseline (P<0.0001). Statistical analysis comparing the individual AMP-XR doses was not performed. At the end of the study, most patients obtained CGI-I ratings of much/very much improved (522/702; 74.4%). Secondary: At the end of the study, the AMP-XR groups reported significant improvements in all quality of life measurements (P<0.0001 for all) measured by the SF-36, including physical functioning and mental health parameters.
Biederman et al.[41] (2002) Atomoxetine 1.2 to 1.8 mg/kg/day vs placebo	2 DB, MC, PC, RCT Females seven to 13 years of age diagnosed with ADHD	N=51 9 weeks	Primary: ADHD-RS Secondary: CPRS-R, CGI-S (parents)	Primary: Atomoxetine significantly decreased ADHD-RS scores compared to placebo (P<0.05) for the entire duration of the study. Secondary: Atomoxetine statistically significantly decreased the parent-rated CPRS-R index scores compared to placebo (10.3 vs 1.0; P<0.001). Atomoxetine also statistically significantly decreased the parent-rated CGI-S scores compared to placebo (1.5 vs 0.6; P<0.001).
Durell et al.[42] (2013) Atomoxetine vs placebo	DB, PC, RCT Young adults 18 to 30 years of age with ADHD	N=445 12 weeks	Primary: CAARS-Inv: SV total ADHD symptoms score with adult prompts Secondary: AAQoL-29, CGI-	Primary: Compared to placebo, treatment with atomoxetine resulted in a greater improvement in CAARS: Inv: SV (-13.6±0.8 vs -9.3±0.8; 95% CI, -6.35 to -2.37; P<0.001). Secondary: Compared to placebo, treatment with atomoxetine resulted in a greater improvement in CGI-S (-1.1±0.1 vs -0.7±0.1; 95% CI, -0.63 to -0.24;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			S, Patient Global Impression-Improvement, CAARS self report, BRIEF-Adult Version Self Report and assessments of depression, anxiety, sleepiness, driving behaviors, social adaptation and substance abuse	P<0.001) and CAARS Self-Report (-11.9±0.8 vs -7.8±0.7; 95% CI, -5.94 to -2.15; P<0.001) but not on the Patient Global Impression-Improvement score. Treatment with atomoxetine was superior to placebo on the AAQoL-29 and BRIEF-Adult Version Self-Report.
Michelson et al.[43] (2001) Atomoxetine 1.2 to 1.8 mg/kg/day vs placebo	MC, OL, PC, RCT Children eight to 18 years of age diagnosed with ADHD	N=297 8 weeks	Primary: ADHD-RS Secondary: CPRS-R, CHQ	Primary: Significant reduction in ADHD-RS was seen in both active groups (P<0.001). No difference was seen between the 1.2 and the 1.8 mg/kg/day treatment arms. Secondary: Atomoxetine 1.2 mg/kg showed significant decreases in all scales of CPRS-R (P<0.05). Atomoxetine 1.8 mg/kg showed significant increase in all scales of CHQ (P<0.05).
Kratochvil et al.[44] (2011) Atomoxetine 0.5 to 1.8 mg/kg/day vs placebo	DB, MC, PC, RCT Children five to six years of age diagnosed with ADHD	N=101 8 weeks	Primary: ADHD-RS Secondary: CGI-S, CGI-I	Primary: Atomoxetine significantly reduced mean parent (P<0.009) and teacher (P=0.02) ADHD-RS total score compared to placebo. Secondary: A total of 40% of children treated with atomoxetine and 22% of children who received placebo had CGI-I scores much too very much improved (P=0.1) with no significant differences between groups. A total of 62% of children treated with atomoxetine had CGI-S scores

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				of moderately or severely ill at the end of the study compared to 77% of children who received placebo. Common adverse events included decreased appetite, gastrointestinal upset, and sedation. Most adverse events were considered mild or moderate by the study investigator.
Spencer et al.[45] (2002) Atomoxetine up to 90 mg daily vs placebo	DB, MC, PC, RCT (pooled data) Children seven to 13 years of age diagnosed with ADHD	N=291 9 weeks	Primary: ADHD-RS Secondary: CPRS-R:S, CGI-S	Primary: Significant mean reductions in both active groups in all scales were reported (both studies) for ADHD-RS (P<0.001) and CPRS-R:S (P=0.023 for study one and P<0.001 for study two). Secondary: Atomoxetine displayed a significant mean reduction in CPRS-R:S index over placebo in both studies (study 1: -5.7 vs -2.6; P=0.023 and study 2: -8.8 vs -2.1; P<0.001). Atomoxetine displayed a statistically significant mean change in CGI-S scores over placebo in both studies (study 1: -1.2 vs -0.5; P=0.023 and study 2: -1.5 vs -0.7; P=0.001).
Dittmann et al.[46] (2011) Atomoxetine 0.5 mg/kg/day for seven days, then 1.2 mg/kg/day (fast titration) vs atomoxetine 0.5 mg/kg/day for seven days, then 0.8 mg/kg/day for seven days, then 1.2 mg/kg/day (slow titration)	DB, PC, RCT Patients six to 17 years of age ADHD with comorbid ODD or conduct disorder	N=181 9 week	Primary: SNAP-ODD, SNAP-ADHD Secondary: CGI-S	Primary: Treatment with atomoxetine once daily at week nine, using either fast or slow titration to a target dose of 1.2 mg/kg/day, was significantly better compared to placebo in reducing ODD symptoms measured by SNAP-ODD scores (P<0.001). Comparing fast and slow titration separately, the decrease in ODD symptoms severity was significant for both individual titration groups (atomoxetine-fast: 8.6; 95% CI, 7.2 to 9.9; atomoxetine-slow: 9.0; 95% CI, 7.7 to 10.3; and placebo: 12.0; 95% CI, 10.6 to 13.5). Atomoxetine was significantly more effective than placebo in reducing the severity of ADHD symptoms measured by SNAP-ADHD scores. Scores reflecting severity of conduct disorder symptoms, attention-deficit and disruptive behavior, were significantly reduced after nine weeks of atomoxetine treatment.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				Secondary: CGI-S and individual treatment behaviors showed were significantly reduced after treatment with atomoxetine. The most common adverse events included fatigue, sleep disorders, nausea, and gastrointestinal complaints and were reported the first three weeks of treatment in 60.0% of atomoxetine-fast, 44.3% of atomoxetine-slow, and 18.6% of placebo group study patients.
Hammerness et al.[47] (2009) Atomoxetine 0.5 to 1.4 mg/kg/day	OL, PRO Children six to 17 years of age diagnosed with ADHD who had a prior trial of stimulant treatment	N=34 6 weeks	Primary: ADHD-RS, CGI Secondary: Not reported	Primary: There was a significant reduction in ADHD RS symptoms compared to baseline. There was a significant reduction in ADHD-RS symptoms score from baseline to the second week of atomoxetine treatment. There was a significant reduction in ADHD symptoms of inattention (-8.1; P<0.001) and hyperactivity (-5.7; P<0.001) at the end of atomoxetine treatment. A total of 56% of patients met criteria for the a priori definition of response; much or very much improved on the CGI plus >30% reduction in ADHD-RS symptoms. Commonly reported adverse events (>10%) included gastrointestinal problems, headache and sedation. Secondary: Not reported
Adler et al.[48] (2008) Atomoxetine 60 to 120 mg/day	MC, OL Adults diagnosed with ADHD	N=384 4 years	Primary: CAARS-Inv:SV total ADHD symptom score Secondary: CAARS-Self:SV, CGI-ADHD-S, HAM-D-17,	Primary: The mean CAARS-Inv:SV total ADHD symptom scores decreased 30.2% from baseline to endpoint (-8.8; P<0.001). Secondary: Significant decreases were found on the CAARS-Inv:SV subscales, and the CAARS-Self:SV total and subscales (P<0.001). CGI-ADHD-S and WRAADDS scores improved significantly from

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			HAMA, WRAADDS, SDS	baseline (-1.1 and -5.0, respectively; P<0.001 for both). SDS total and subscale scores improved 25.3% (-3.8; P<0.001). A slight increase was noted in HAM-D-17 scores (0.8; P=0.004), but this small change is not likely clinically relevant. There was no significant change in HAMA scores (0.4; P=0.216). HR, DBP, SBP increased. Weight loss over the course of the study was statistically significant (-0.94 kg; P<0.001).
Wietecha et al.[49] (2012) Atomoxetine 40 mg daily titrated to 100 mg daily after two weeks vs placebo	DB, PC, RCT Adults with ADHD having both a spouse/partner and child	N=502 24 weeks	Primary: CAARS-Inv: SV and CGI-S Secondary: Not reported	Primary: Treatment with atomoxetine resulted in a greater improvement in CAARS-Inv: SV (-16.43 vs -8.65; P<0.001) and CGI-S compared to placebo at week 24 (P<0.001). Secondary: Not reported
Biederman et al.[50] (2006) Atomoxetine 0.5 mg to 1.2 mg/kg daily vs AMP-XR (Adderall XR®) 10 to 30 mg daily	DB, FD, MC, RCT Females six to 12 years of age diagnosed with ADHD	N=57 18 days	Primary: SKAMP-A SKAMP-D Academic testing Secondary: Adverse events	Primary: The AMP-XR group experienced significantly greater mean changes in SKAMP-D scores from baseline compared to the atomoxetine group (-0.48 vs -0.04; P<0.001). The AMP-XR group experienced significantly greater mean changes in SKAMP-A scores from baseline compared to the atomoxetine group (-0.45 vs -0.05; P<0.001). Both AMP-XR and atomoxetine groups experienced a significant increase in the mean number of math problems attempted and answered correctly from baseline (P<0.001), but patients in the AMP-XR group attempted a significantly greater number of math problems than those in the atomoxetine group (P=0.04). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Both AMP-XR and atomoxetine were well tolerated. The number of adverse events was similar in both groups. Most adverse events reported were of mild or moderate severity.
Kemner et al.[51] (2005) Atomoxetine 0.5 mg/kg once daily vs MPH-ER (Concerta®) 18 mg once daily	MC, OL, PRO, RCT Children six to 12 years of age diagnosed with ADHD	N=1,323 3 weeks	Primary: Investigator-related ADHD-RS and CGI-I, performed at weeks one, two, and three; PSQ Secondary: Not reported	Primary: The ADHD-RS change from baseline measured at each time point showed that both treatments were effective. MPH ER produced significantly greater improvements in ADHD-RS scores at weeks, one, two, and three (P<0.001). At week three, rates of treatment response (i.e., ≥25% reduction in ADHD-RS score) were significantly greater with MPH ER than were seen with atomoxetine (P<0.001). Significantly more children treated with MPH ER than with atomoxetine achieved a CGI-I score ≤2 after week three (P<0.001). Parent-rated PSQ scores revealed statistically significantly greater improvements with MPH ER than with atomoxetine. Secondary: Not reported
Newcorn al.[52] (2008) <u>Acute Comparison Trial</u> Atomoxetine 0.8 mg to 1.8 mg/kg/day administered twice daily vs MPH-ER (Concerta®)	DB, PC, RCT, XO Children six to 16 years of age diagnosed with ADHD (any subtype)	Acute Comparison Trial: N=516 6 weeks XO Trial: N=178 6 weeks	Primary: ADHD-RS Secondary: CGI-S, CPRS, CHQ, and Daily Parent Ratings of Evening and Morning Behavior-Revised	Acute Comparison Trial Primary: The proportion of patients responding to atomoxetine (45%) was significantly higher than the rate for placebo (24%; P=0.003). MPH-ER (56%) was also more effective than placebo (24%; P≤0.001). MPH-ER was found to be more effective than atomoxetine (P=0.02). Secondary: Atomoxetine and MPH-ER produced greater improvements in CGI-S, CPRS and CHQ compared to placebo. MPH-ER also produced greater improvements compared to atomoxetine on CGI-S, CPRS and CHQ (P=0.004, P=0.003, P=0.02, respectively). XO Trial The responses to the two treatments in these patients were as follows:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
18 mg to 54 mg once daily vs placebo <u>XO Trial</u> Atomoxetine 0.8 mg to 1.8 mg/kg/day administered twice daily Patients on MPH-ER were switched to atomoxetine during the XO trial.				34% responded to either atomoxetine or MPH-ER, but not both; 44% responded to both treatments; 22% did not respond to either treatment. Of the 70 patients who did not respond to MPH-ER in the initial trial, 43% subsequently responded to atomoxetine in the XO trial. Of the 69 patients who did not respond to atomoxetine in the second trial, 42% had previously responded to MPH-ER. Of the patients classified as MPH-ER, 36% showed significantly worse response on atomoxetine, 18% showed significantly better response on atomoxetine, and 46% showed roughly the same response to treatment with atomoxetine. Of the 70 patients classified as MPH-ER nonresponders, 10% showed significantly worse response, 51% showed significantly better response, and 39% showed roughly the same response to treatment with atomoxetine.
Starr et al.[53] (2005) Atomoxetine 0.5 mg/kg once daily vs MPH-ER (Concerta®) 18 mg once daily	OL, RCT African-American children six to 12 years of age diagnosed with ADHD	N=183 3 weeks	Primary: Investigator-related ADHD-RS and CGI-I, performed at weeks one, two, and three; PSQ Secondary: Not reported	Primary: For the ADHD-RS scores, both treatment groups achieved significant improvements from baseline at all time points (P<0.001). Improvements from baseline, defined as ADHD-RS score reductions of ≥30% or ≥50%, were significantly greater in the MPH ER group starting at week three (P<0.03 for ≥30% reduction, P<0.006 for ≥50% reduction). Significantly more children treated with MPH ER than atomoxetine achieved a CGI-I score ≤2 after week three (P<0.01). Parent-rated PSQ scores revealed statistically significantly greater improvements with MPH ER than with atomoxetine. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Wang et al.[54] (2007) Atomoxetine 0.8 mg to 1.8 mg/kg/day vs MPH-IR 0.2 mg to 0.6 mg/kg/day in two divided doses	DB, MC, RCT Children six to 16 years of age diagnosed with ADHD	N=330 8 weeks	Primary: ADHD-RS Secondary: CPRS-R:S, CGI-S, treatment-emergent adverse events, weight	Primary: Atomoxetine was not significantly different than MPH in improving ADHD symptoms based on ADHD-RS scores (atomoxetine, 77.4%; MPH, 81.5%; P=0.404). Secondary: Both atomoxetine and MPH-IR treatment groups significantly improved CPRS-R:S and CGI-S scores from baseline (P<0.001 for all), the groups were not statistically significant from each other in both measures (P>0.05). Treatment-emergent adverse events that occurred significantly more frequently in the atomoxetine group, compared to the MPH group, included anorexia (37.2 vs 25.3%; P=0.024), nausea (20.1 vs 10.2%; P=0.014), somnolence (26.2 vs 3.6%; P<0.001), dizziness (15.2 vs 7.2%; P=0.024) and vomiting (11.6 vs 3.6%; P=0.007), most of which were of mild or moderate severity. Patients in the atomoxetine group experienced a small but significantly greater mean weight loss at the end of eight weeks compared to those in the MPH group (-1.2 vs -0.4 kg; P<0.001).compared to
Kratochvil et al.[55] (2002) Atomoxetine titrated up to 2 mg/kg/day vs MPH-IR titrated up to 60 mg daily	MC, OL Males seven to 15 years of age and females seven to nine year of age diagnosed with ADHD	N=228 10 weeks	Primary: ADHD-RS Secondary: CPRS-R, CGI-S, safety	Primary: Both atomoxetine and MPH-IR were associated with marked improvement in inattentive and hyperactive-impulsive symptom clusters but were not statistically different (P=0.66). Secondary: There were no statistically significant differences between treatment groups on all of the CPRS-R and CGI-S outcome measures (P<0.001). Tolerability was also similar between the two drugs with no statistical differences in discontinuations (P=0.18). Statistically significant increases in pulse and BFI were seen with both atomoxetine and MPH-IR (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Sutherland et al.[56] (2012) Atomoxetine 40 mg to 100 mg/day vs atomoxetine 40 mg to 100 mg/day and buspirone 15 mg to 45 mg/day vs placebo	DB, MC, PC, RCT Men and women 18 to 60 years of age diagnosed with ADHD	N=241 8 weeks	Primary: AISRS Secondary: Not reported	Primary: There was a significantly greater decrease in the AISRS total score for atomoxetine plus buspirone than placebo at weeks one to seven, with an estimated mean difference of -4.80 (P=0.001). There was a greater decrease in the AISRS total score for atomoxetine plus buspirone than for atomoxetine at weeks one to seven, but only statistically significant at week four (P<0.09). The most commonly reported adverse events from both treatment groups included insomnia, dry mouth, headache, and asthenia. Dizziness was most commonly reported for the atomoxetine plus buspirone treatment group. Discontinuations due to treatment-related adverse events were 15.5% for atomoxetine plus buspirone, 11.3% for atomoxetine and 14.9% for placebo. Secondary: Not reported.
Ni et al.[57] (2013) Atomoxetine titrated up to 1.2 mg/kg/day vs MPH-IR titrated up to 60 mg/day	OL, RCT Patients 18 to 50 years of age diagnosed with ADHD	N=63 8 to 10 weeks	Primary: ASRS, CGI-ADHD-S, AAQoL, WFIS-S and safety Secondary: Not reported	Primary: At visit one (weeks four and five), both the MPH-IR and atomoxetine treatment groups experienced statistically significant reductions from baseline in ASRS scores for inattention (-5.77 and -8.93, respectively; P<0.001 for both) and hyperactivity-impulsivity (-3.69 and -8.11, respectively; P<0.001). The differences between the treatment groups was significant, favoring treatment with atomoxetine (P<0.05). Significant reductions from baseline in ASRS scores were apparent at visit two (eight to 10 weeks) for both the inattention (-9.25 and -10.20, respectively; P<0.001) and hyperactivity-impulsivity subtypes (-6.21 and -7.80, respectively; P<0.001); however, differences between treatment groups were not statistically significant. Both treatment groups experienced improved CGI-ADHD-S scores at all time points compared to baseline values (P<0.001 for all); however, differences between groups were not statistically significant.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The mean AAQoL scores significantly increased from baseline to visit one (weeks four and five) and visit two (weeks eight to 10) for both treatment groups. The effect sizes as assessed by Cohen's d ranged from 0.59 to 1.63 (P<0.01). Both treatment groups experienced significant improvements in the severity of functional impairment (WFIS-S) from baseline to visit one (weeks four to five) or (weeks eight to 10). Cohen's d ranged from 0.49 to 1.70 for the MPH-IR group and 0.42 to 1.11 for the atomoxetine group. Differences between the treatment groups were not statistically significant. Decreased appetite, vomiting and palpitation were frequently reported in both treatment groups. There was no significant difference in the occurrence of adverse events between treatment groups. Moreover, there was no significant change in body weight, BP, or HR during the study period (P>0.05 for all). Secondary: Not reported
Sutherland et al.[58] (2012) Atomoxetine 40 to 100 mg daily vs atomoxetine 40 to 100 mg daily plus buspirone 15 to 45 mg daily vs placebo	DB, MC, PC, RCT Patients 18 to 60 years of age diagnosed with ADHD	N=241 8 weeks	Primary: AISRS Secondary: Not reported	Primary: There was a significantly greater decrease in the AISRS total score for atomoxetine plus buspirone than placebo at weeks one to seven, with an estimated mean difference -4.80 (P=0.001). There was a greater decrease in the AISRS total score for atomoxetine plus buspirone than for atomoxetine at weeks one to seven, but only statistically significant at week four (P<0.09). The most commonly reported adverse events from both treatment groups included insomnia, dry mouth, headache, and asthenia. Dizziness was most commonly reported for the atomoxetine plus buspirone treatment group. Discontinuations due to treatment-related adverse events were 15.5% for atomoxetine plus buspirone, 11.3% for atomoxetine, and 14.9% for

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				placebo. Secondary: Not reported
Prasad et al.[59] (2007) Atomoxetine 0.5 mg to 1.8 mg/kg/day vs standard current therapy	MC, OL, RCT Children seven to 15 years of age diagnosed with ADHD	N=201 10 weeks	Primary: CHIP-CE Secondary: ADHD-RS, CGI-S, CGI-I, HSPP, FBIM	Primary: Quality of life greatly improved over the 10 weeks in the atomoxetine group vs the standard current therapy group as demonstrated by the significant increase in CHIP-CE (P<0.001). Secondary: ADHD-RS, CGI-S, and CGI-I scores were significantly improved in the atomoxetine group over the standard current therapy group (P<0.001 for all). The atomoxetine group was significantly better in improving the HSPP Social Acceptance domain over the standard current therapy group (P=0.03), but the groups were not significantly different in the other five HSPP domains (P>0.05). There was not a statistically significant difference between groups in reduction in FBIM scores (P>0.05).
Cheng et al.[60] (2007) Atomoxetine vs placebo	MA (9 trials) Patients diagnosed with ADHD	N=1,828 Variable duration	Primary: ADHD-RS Secondary: CTRS-RS, CPRS-R:S, CGI-S, CHQ	Primary: Atomoxetine significantly improved ADHD-RS scores compared to placebo (P<0.01 for all). Secondary: Atomoxetine significantly improved CTRS-RS, CPRS-R:S, and CGI-S scores compared to placebo (P<0.01 for all). Atomoxetine significantly improved quality of life as measured by the CHQ compared to placebo (P<0.01).
Hazell et al.[61] (2003) Clonidine 0.1 to 0.2 mg/day	PC, RCT, TB Children six to 14 years of age with ADHD and co-morbid ODD or	N=67 6 weeks	Primary: CBC (subscales conduct and hyperactive index) Secondary:	Primary: Significantly more children treated with clonidine than placebo improved on the CBC-Conduct scale (21 of 37 vs 6 of 29; P<0.01) but not the Hyperactive Index (13 of 37 vs 5 of 29; P=0.16). Compared to placebo, clonidine was associated with a greater

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	conduct disorder		Not reported	reduction in standing SBP measured and with transient sedation and dizziness. Study patients treated with clonidine have a greater reduction in a number of unwanted effects associated with psychostimulant treatment compared to placebo. Secondary: Not reported
Jain et al.[62] (2011) Clonidine XR 0.2 mg/day vs Clonidine 0.4 mg/day vs placebo	DB, PC, RCT Patients six to 17 years of age diagnosed with ADHD	N=236 8 weeks	Primary: ADHD-RS (total score) Secondary: ADHD-RS (inattention and hyperactivity), CPRS-R:S, CGI-S, CGI-I, PGA, treatment-emergent adverse events	Primary: Improvement from baseline to week five in ADHD-RS total score was significantly greater in both clonidine ER groups vs placebo (P<0.001). A significant improvement in ADHD-RS total score occurred beginning week one for the clonidine ER 0.2 mg/day group (P=0.02) and week two for the clonidine ER 0.4 mg/day group (P<0.0001) as compared to the placebo group and continued throughout the treatment period. Secondary: A significant improvement in mean change in ADHD-RS inattention score at week five vs baseline was -7.7 for both clonidine ER groups vs -3.4 for the placebo group (P<0.001 for clonidine ER 0.2 mg/day; P<0.006 for clonidine ER 0.4 mg/day). Improvements from baseline to week five in ADHD-RS hyperactivity score were -4.1 in the placebo group, -7.9 in the clonidine ER 0.2-mg/day group, and -8.8 in the clonidine ER 0.4-mg/day group (P<0.0012). Mean improvement in CPRS-R total score was significantly greater than placebo in both clonidine ER groups (P<0.01) at weeks three and five. Improvement in CGI-S and CGI-I from baseline to week five was significantly greater in both treatment groups vs placebo (P<0.0001 for

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				CGI-S and P<0.003 for CGI-I). Significant improvement in PGA score from baseline in both treatment groups vs placebo was observed at week two (P<0.001) and was maintained through week seven (P<0.02) in the clonidine ER 0.2 mg/day group and through week five in the clonidine ER 0.4 mg/day group (P<0.009). The most common treatment-emergent adverse event was mild-to-moderate somnolence. Changes on ECG were minor and due to the pharmacology of clonidine.
Kollins et al.[63] (2011) Clonidine-XR 0.1 mg to 0.4 mg/day and psychostimulant vs placebo and psychostimulant	DB, MC, PC, RCT Children and adolescents diagnosed with hyperactive or combined subtype ADHD who had inadequate response to their psychostimulant therapy	N=198 8 weeks	Primary: ADHD-RS (total score) Secondary: ADHD-RS (hyperactivity and inattention), CPRS, CGI-S, CGI-I, PGA	Primary: At week five, study patients in the clonidine ER plus psychostimulant group experienced a greater improvement in ADHD-RS total score compared to patients in the placebo plus psychostimulant group (P=0.009). Secondary: Scores from baseline ADHD-RS hyperactivity and inattention subscale (P=0.014 and P=0.017, respectively), CPRS (P<0.062), CGI-S (P=0.021), CGI-I (P=0.006), and PGA (P=0.001) were significantly improved in the clonidine ER plus psychostimulant group compared to the placebo plus psychostimulant group. The most commonly treatment-emergent adverse event reported were mild to moderate in severity and included somnolence, headache, fatigue, upper abdominal pain, and nasal congestion.
Wigal et al.[64] (2004) DXM (Focalin®) 2.5 to 10 mg twice daily vs MPH-IR 5 to 20	DB, MC, PC, RCT Children six to 17 years of age diagnosed with ADHD (any subtype)	N=132 4 weeks	Primary: SNAP-T Secondary: SNAP-P, CGI-I Math test performance (clinic and home)	Primary: Both DXM and MPH-IR significantly improved SNAP-T scores compared to placebo (P=0.004 and P=0.0042, respectively) Secondary: The DXM group decreased SNAP-P scores at both 3 and 6 PM assessments compared to placebo (P<0.0001 and P=0.0003 respectively). The MPH-IR group significantly decreased 3 PM SNAP-P assessments compared to the placebo group (P=0.0073) but did not reach statistical significance at the 6 PM assessment (P=0.064).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg twice daily vs placebo				Both DXM and MPH-IR improved CGI-I scores in significantly more patients than the placebo group (67% [P=0.0010] and 49% [P=0.0130] compared to 22%, respectively). Both DXM and MPH-IR significantly improved clinic-based math test scores compared to placebo (P=0.001 and P=0.0041 respectively). DXM significantly improved home-based math test scores compared to placebo (P=0.0236). MPH-IR did not reach statistical significance compared to placebo.
Greenhill et al.[65] (2006) DXM-XR (Focalin XR®) 5 to 30 mg daily vs placebo	DB, MC, PC, RCT Children six to 17 years of age diagnosed with ADHD (any subtype)	N=97 7 weeks	Primary: CADS-T Secondary: CADS-P, CGI-I, CGI-S, CHQ (physical and psychosocial)	Primary: DXM-XR significantly increased CADS-T scores from baseline compared to placebo (16.3 vs 5.7; P<0.001). Secondary: DXM-XR significantly increased CADS-P scores from baseline compared to placebo (17.6 vs 6.5; P<0.001). DXM-XR improved overall CGI-I scores in a greater percent of patients compared to placebo (67.3 vs 13.3%; P<0.001). DXM-XR significantly improved CGI-S scores in a greater percent of patients than placebo (64.0 vs 11.9%; P<0.001). There was not a statistical difference between DXM-XR and placebo on the mean change in CHQ physical scores. DXM-XR did significantly improve mean CHQ psychosocial scores compared to placebo (11.9 vs 4.3; P<0.001).
Spencer et al.[66] (2007) DXM-XR (Focalin XR®) 20 to 40 mg daily vs	DB, MC, PC, RCT Adults 18 to 60 years of age diagnosed with ADHD (any subtype), childhood onset of symptoms,	N=184 5 weeks	Primary: ADHD-RS Secondary: ADHD-RS, CGI-I, CGI-S, CAARS, Q-LES-Q	Primary: All doses of DXM-XR significantly improved ADHD-RS scores from baseline compared to placebo (P<0.05). Secondary: The 20 and 40 mg doses of DXM-XR achieved improved ADHD-RS scores ≥30% and were significant compared to placebo, the 30 mg group did not reach statistical significance. The percent of patients

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo	and a baseline ADHD-RS score ≥24			who achieved ≥30% were as follows: DXM-XR 20 mg, 57.9% (P=0.017); DXM-XR 30 mg, 53.7% (P=0.054); DXM-XR 40 mg, 61.1% (P=0.007); and placebo, 34.0%. All doses DXM-XR significantly improved CGI-I scores over placebo (P<0.05 for all). The 20 and 40 mg doses of DXM-XR improved CGI-S scores in a greater percent of patients compared to placebo, but the 30 mg group did not reach statistical significance. The percents of patients were as follows: 20 mg, 68.4% (P=0.09); 30 mg, 61.1% (P value not significant); 40 mg, 64.8% (P=0.031); and placebo, 41.5%. All doses of DXM-XR significantly improved CAARS scores compared to placebo (P<0.05 for all). None of the groups improved Q-LES-Q scores from baseline nor were there significant differences between groups.
Adler et al.[67] (2009) DXM-XR (Focalin XR®) 20 to 40 mg/day vs placebo After completion of DB phase, patients could enter an OL extension phase with flexible dosing 20 to 40 mg/day for six	DB, MC, RCT Patients 18 to 60 years of age diagnosed with ADHD	N=103 6 months	Primary: Long-term safety and tolerability Secondary: ADHD-RS, CGI-I	Primary: DXM-XR was well tolerated; the most common adverse events were headache (27.6%), insomnia (20.0%), and decreased appetite (17.6%). Most adverse events were considered mild or moderate by the study investigator. Secondary: Mean improvements in ADHD-RS scores were -10.2 for study patients switched from placebo to DXM-XR and -8.4 for those maintained on DXM-XR. Improvements in CGI-I scores were reported in 95.1% of study patients switched from placebo to DXM-XR and 95.0% of study patients maintained on DXM-XR.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
months.				
Brams et al[68] (2012) DXM-XR 20 mg daily vs DXM-XR 30 mg daily vs placebo	DB, RCT, XO Children 6 to 12 years of age with ADHD previously stabilized on MPH (40 mg to 60 mg/day) or DXM (20 mg to 30 mg/day)	N=165 3 weeks	Primary: Change in average SKAMP-combined score from pre-dose to 10, 11 and 12 hours post-dose Secondary: Not reported	Primary: The mean change from pre-dose in SKAMP-combined score was significantly greater in the DXM-XR 30 mg group compared to the DXM-XR 20 mg group (-4.47 vs -2.02; P=0.002). Significantly greater improvement in ADHD symptoms was observed in the DXM-XR 30 mg group compared to the DXM-XR 20 mg group at hours 10 through 12. Secondary: Not reported
Stein et al.[69] (2011) DXM-XR (Focalin XR®) 10 to 30 mg/day vs AMP-XR (Adderall XR®) 10 to 30 mg/day	DB, PC, RCT Patients nine to 17 years of age with ADHD	N=56 8 weeks	Primary: ADHD-RS, CGI-I, CGI-S, WFIS, SSERS Secondary: Not reported	Primary: There were significant dose-related decreases in total and hyperactive-impulsive symptom scores (P<0.001 and P<0.001, respectively) that did not differ by type of stimulant. There were significant dose-related decreases for Inattention symptoms (P<0.001) that were more modest and did not differ by type of stimulant. There were significant dose-related decreases in CGI-S scores (P<0.001) that did not differ by type of stimulant. There were significant effects of dose on the WFIS total score (P=0.008), on the Family (P=0.010), Learning (P=0.002), Social Activities (P=0.018), and Risk Taking (P=0.050) subscales, but not on the Living Skills or Self-Esteem subscales. The most common adverse events were mild to moderate in severity and included decreased appetite and insomnia. Adverse events were more common at higher dose levels for both stimulants. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Muniz et al.[70] (2008) DXM-XR (Focalin XR®) 20 mg/day vs DXM-XR (Focalin XR®) 30 mg/day vs MPH-ER (Concerta®) 36 mg/day vs MPH-ER (Concerta®) 54 mg/day vs placebo	DB, MC, RCT Children six to 12 years of age diagnosed with ADHD and stabilized on MPH ≥2 weeks	N=84 10 weeks	Primary: SKAMP Secondary: Not reported	Primary: Mean change in combined SKAMP score at two hours post-dose was significantly larger for MPH-ER 20 vs 36 mg/day (P<0.001). MPH-ER 20 and 30 mg doses have a more rapid onset and a greater effect in the morning relative to MPH-ER 36 and 54 mg doses while MPH-ER 36 and 54 mg had a greater effect at the end of the 12 hour day. All active treatments provided a significant benefit over placebo at most time points to 12 hours post-dosing. Secondary: Not reported
Scahill et al.[71] (2001) Guanfacine 0.5 mg at bedtime, day four added 0.5 mg in the morning, day eight added	DB, PC, PG, RCT Children seven to 15 years of age diagnosed with ADHD and tic disorder	N=34 8 weeks	Primary: ADHD-RS, CGI-I, CPRS-R (hyperactivity index), YGTSS, CPT Secondary:	Primary: Guanfacine was associated with a mean improvement of 37% in the teacher-rated ADHD-RS total score compared to 8% improvement for placebo (P<0.01). Nine of 17 patients who received guanfacine were rated on the CGI-I as either much improved or very much improved, compared to 0 of 17 patients who received placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
0.5 mg afternoon dose vs placebo			Not reported	The mean CPRS-R on the parent-rated hyperactivity index improved by 27% in the guanfacine group and 21% in the placebo group, not a significant difference. Tic severity decreased by 31% in the guanfacine group, compared to 0% in the placebo group (P=0.05). For CPT, commission errors decreased by 22% and omission errors by 17% in the guanfacine group, compared to increases of 29% in commission errors and of 31% in omission errors in the placebo group. No significant adverse events were observed; one study patient taking guanfacine withdrew with sedation. Guanfacine was associated with an insignificant decrease in BP and pulse. Secondary: Not reported
Kollins et al.[72] (2011) Guanfacine ER 1 to 3 mg once daily vs placebo	DB, MC, PC, RCT Patients six to 17 years of age diagnosed with ADHD	N=182 6 weeks	Primary: CANTAB-CRT Secondary: CANTAB-SWM, DSST, PERMP	Primary: There were no significant differences between guanfacine ER and placebo groups on measures of psychomotor functioning or alertness on the CANTAB-CRT (mean difference, 2.5; P=0.8 for CRT, 2.5; P=0.84 for correct responses, 15.5; P=0.30 for movement time, and -8.2; P=0.72 for total time). Secondary: Guanfacine ER treatment was associated with significant improvement in ADHD symptoms (P=0.001) Most sedative adverse events were mild to moderate and occurred during dose titration, decreased with dose maintenance, and resolved during the study period.
Sallee et al.[73] (2009) Guanfacine ER 1 to 4 mg once daily	DB, MC, PC, RCT Patients six to 17 years of age with ADHD and a	N=324 9 weeks	Primary: ADHD-RS-IV total score Secondary:	Primary: The mean reduction in ADHD-RS-IV total scores from baseline to endpoint across all guanfacine ER dose groups was -19.6 compared to -12.2 for the placebo group. The placebo-adjusted mean endpoint changes from baseline were -6.75 (P=0.0041), -5.41 (P=0.0176), -7.34

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	baseline score of 24 on the ADHD-RS-IV		CPRS-R, CGI-I, PGA	(P=0.0016), and -7.88 (P=0.0006) in the guanfacine ER 1, 2, 3, and 4 mg groups, respectively. Placebo-adjusted mean baseline-to-endpoint changes for symptoms of inattentiveness were: -4.2 (P=0.002), -3.0 P=0.02), -3.5 (P=0.007), and -4.0 (P=0.002) for guanfacine ER 1, 2, 3, and 4 mg, respectively. Placebo-adjusted mean baseline-to-endpoint changes for symptoms of hyperactivity/impulsivity were: -2.7 (P=0.028), -2.5 (P=0.03), -3.9 (P=0.001), and -4.0 (P=0.0008) for guanfacine ER 1, 2, 3, and 4 mg, respectively. Secondary: Using placebo-adjusted LSMD in change from baseline at endpoint in CPRS-R total scores, the 4 mg guanfacine ER dose demonstrated significant efficacy at eight hours (-10.2; P=0.004) and 12 hours (-7.5; P=0.04). The 3 mg guanfacine ER dosage group demonstrated significant improvements in CPRS-R results at eight (-11.8; P=0.002), 12 (-9.6; P=0.01), and 14 hours (-9.8; P=0.0156) postdose. The 2 mg guanfacine ER dosage group demonstrated significant improvements in CPRS-R scores at eight hours (-9.0; P=0.01) postdose. For the 1 mg guanfacine ER dosage group, the placebo-adjusted LSMD in CPRS-R at eight, 12, 14, and 24 hours were -12.8 (P=0.0004), -11.4 (P=0.002), -10.4 (P=0.0077), and -8.9 (P=0.02), respectively. Based on CGI-I scores, the percentages of the patients showing clinical improvement were 30% (placebo), 54% (guanfacine ER 1 mg; P=0.007 vs placebo), 43% (guanfacine ER mg; P=0.1404 vs placebo), 55% (guanfacine ER mg; P=0.006 vs placebo), and 56% (guanfacine ER mg; P=0.004 vs placebo). Improvements in PGA scores were 30% (placebo), 51% (guanfacine ER 1 mg; P=0.030 vs placebo), 36% (guanfacine ER 2 mg; P=0.4982 vs placebo), 62% (guanfacine ER mg; P=0.002 vs placebo), and 57% (guanfacine ER 4 mg; P=0.0063 vs placebo). Mild to moderate treatment-emergent adverse events in patients taking guanfacine ER were somnolence, headache, fatigue, sedation,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				dizziness, irritability, upper abdominal pain, and nausea. There were no significant differences in sleepiness between the patients taking placebo and guanfacine ER. Guanfacine ER was not associated with abnormal changes in height or weight. SBP, DBP, and pulse rate decreased as the guanfacine ER dose increased and then increased during dose maintenance and tapering. The range of mean changes from baseline for seated SBP for the placebo group was -1.30 to -0.48 mm Hg and -7.38 to 0.54 mm Hg for the guanfacine ER randomized dose groups.
Sallee et al.[74] (2009) Guanfacine ER 1 to 4 mg once daily	ES, OL Patients six to 17 years of age with ADHD and a baseline score of 24 on the ADHD-RS-IV	N=257 24 months	Primary: ADHD-RS-IV, CPRS-R, CGI-I, CHQ-PF50, CTRS-R, PGA Secondary: Not reported	Primary: Somnolence (30.5%), headache (24.3%), upper respiratory tract infection (17.8%), nasopharyngitis (14.3%), fatigue (13.9%), upper abdominal pain (12.7%) and sedation (11.2%) were the most frequently reported adverse events. The majority of somnolence, sedation, or fatigue events was moderate or mild in severity and resolved by end of treatment. Hypotension was reported in 5.0% of patients. Decreased DBP was found in 3.5% of patients, decreased BP in 2.7% of patients, and decreased SBP in 2.3% of patients. Decreased appetite (13.2%), irritability (13.2%), and pharyngitis (11.3%) were among the most common treatment-emergent adverse events that differed in the subgroup coadministered psychostimulants relative to monotherapy or the overall safety population. Mean changes in ADHD-RS-IV total score from baseline to end point showed significant improvement: overall, -20.1 (P<0.001), and for all guanfacine ER dose groups, -23.8, -22.5, -20.0, and -18.4 for the 1, 2, 3, and 4 mg dose groups, respectively (P<0.001 for each). CPRS-R mean changes from baseline to end point were statistically significant in the overall treatment group (-18.2; P<0.001). The overall mean change from baseline demonstrated significant improvement in CPRS-R scores at each postdose assessment (P<0.001). Investigator-rated CGI-I scores at end point showed that investigators

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				rated the majority of patients very much improved (29.3%) or much improved (28.8%). For the PGA, 59.7% of patients were rated as very much or much improved at end point. Mean changes in CHQ-PF50 Physical Summary Scores from baseline to end point were not statistically significant. CHQ-PF50 Psychosocial Summary Scores demonstrated significant improvement from baseline to end point for the overall full analysis set (P<0.001). Secondary: Not reported
Sallee et al.[75] (2012) Guanfacine ER 1 to 4 mg daily vs placebo	DB, PC, RCT (Post-hoc analysis) Patients 6 to 17 years of age with ADHD	N=631 Variable duration	Primary: Change in ADHD-RS total scores Secondary: Not reported	Primary: For patients with the predominantly inattentive subtype of ADHD, patients treated with guanfacine ER achieved significantly greater mean reductions from baseline in ADHD-RS total scores compared to placebo (P≤0.020). For patients with combined-type ADHD, patients treated with guanfacine ER achieved significantly greater reductions in ADHD-RS total score from baseline compared to placebo at treatment weeks one through five and at study end (P≤0.011). Secondary: Not reported
Connor et al.[76] (2010) Guanfacine ER 1 to 4 mg once daily vs placebo	DB, MC, PC, RCT Patients six to 12 years of age with a diagnosis of ADHD and the presence of oppositional symptoms	N=217 9 weeks	Primary: Change from baseline to endpoint in the oppositional subscale of the CPRS-R:L Secondary: Change in ADHD-RS-IV total score and safety	Primary: The mean change from baseline in the oppositional subscale of the CPRS-R:L was -10.9 for those receiving guanfacine ER and -6.8 for those receiving placebo (P<0.001). The mean percentage reductions from baseline were 56.3% with guanfacine ER and 33.4% with placebo (P<0.001). Secondary: The mean decrease from baseline to endpoint in ADHD-RS-IV total score was 23.8 points for guanfacine ER compared to 11.5 for placebo (P<0.001). The mean percentage reductions from baseline were 56.7% with guanfacine ER and 26.5% with placebo (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Adverse events were reported in 84.6% of those receiving guanfacine ER group and 60.3% of those receiving placebo. Treatment-emergent adverse events occurred more frequently with guanfacine ER than with placebo (83.8 vs 57.7%, respectively). The most common treatment-emergent adverse events in the guanfacine ER group were somnolence (50.7%), headache (22.1%), sedation (13.2%), upper abdominal pain (11.8%) and fatigue (11.0%).
Biederman et al.[77] (2008) Guanfacine ER 2 to 4 mg once daily vs placebo	DB, MC, PC, RCT Patients six to 17 years of age with ADHD combined subtype, predominantly inattentive subtype, or predominantly hyperactive-impulsive subtype	N=345 8 weeks	Primary: ADHD-RS-IV total score observed during the last treatment week of the dosage escalation period (weeks one to five) Secondary: CGI-S, CGI-I, PGA, CPRS-R, and CTRS-R observed during the last treatment week of the dosage escalation period (weeks one to five)	Primary: The mean reduction in ADHD-RS-IV score at end point across all guanfacine ER groups was -16.7 compared to -8.9 for placebo. Placebo-adjusted LS mean end point changes from baseline in the guanfacine ER 2, 3, and 4 mg groups were -7.70 (P=0.0002), -7.95 (P=0.0001), and -10.39 (P<0.0001), respectively. Mean changes from baseline in hyperactivity/impulsivity in the placebo and guanfacine ER 2, 3, and 4 mg groups were -3.51, -7.33 (P=0.0002 vs placebo), -7.32 (P=0.0002 vs placebo), and -9.31, (P<0.0001 vs placebo) respectively. Mean changes from baseline in inattentiveness were -4.92, -8.7 (P=0.0011 vs placebo), -9.11 (P=0.0006 vs placebo), and -9.44 (P=0.0002 vs placebo), respectively. Secondary: Significant improvement in CGI-I scores at end point was shown in 25.64, 55.95, 50.00, and 55.56% of patients in the placebo and guanfacine ER 2, 3, and 4 mg groups, respectively. Improvement in CGI-I scores was significant in the guanfacine ER 2 mg group compared to the placebo group by week two (P=0.0194) and in all guanfacine ER groups by week three continuing through week five (P<0.05). Significant improvement in PGA scores at end point was shown in 23.08, 62.12, 50.82, and 66.10% of patients in the placebo and guanfacine ER 2, 3, and 4 mg groups, respectively. On the CPRS-R, placebo-adjusted LS mean day total end point changes from baseline were -6.55 in the 2 mg group (P=0.0448), -7.36 in the 3 mg group (P=0.0242), and -12.70 in the 4 mg group

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(P<0.0001). On the CTRS-R, placebo-adjusted LS mean day total end point changes from baseline were -11.57 (P<0.0001), -13.48 (P<0.0001), and -12.53 (P<0.0001), for the 2, 3, and 4 mg doses, respectively. The most commonly reported treatment-emergent adverse events were somnolence, fatigue, upper abdominal pain and sedation. The incidence of somnolence in patients who were receiving guanfacine ER 1, 2, 3, and 4 mg doses was 12.7, 11.4, 20.9, and 17.5%, respectively. SBP, DBP, and pulse rate decreased as guanfacine ER dosages increased, then increased as dosages stabilized and tapered down. The greatest mean changes from baseline in SBP and DBP for patients who were receiving guanfacine ER 2, 3, and 4 mg doses were -7.0 mm Hg (week 3) and -3.8 mm Hg (week 2), -7.0 mm Hg (week 3) and -4.7 mm Hg (weeks three and five), and -10.1 mm Hg (week four) and -7.1 mm Hg (week four), respectively. The greatest mean changes from baseline in pulse rate for patients who were receiving guanfacine ER 2, 3, and 4 mg doses were -5.7 beats per minute (week three), -8.1 beats per minute (week three), and -8.0 beats per minute (week four), respectively. Mean changes in height and weight from baseline to end point were not significant across the treatment groups.
Biederman et al.[78] (2008) Guanfacine ER 2 to 4 mg once daily	ES, OL Patients six to 17 years of age with ADHD combined subtype, predominantly inattentive subtype, or predominantly hyperactive-impulsive subtype	N=240 24 months	Primary: Safety Secondary: ADHD-RS-IV, PGA, CHQ-PF50	Primary: Somnolence (30.4%), headache (26.3%), fatigue (14.2%), and sedation (13.3%) were the most frequently reported adverse events. Changes from baseline to endpoint in SBP, DBP, and pulse rate were -0.8 mm Hg, -0.4 mm Hg, and -1.9 beats per minute, respectively. Mean changes in pulse rate and QRS intervals were generally unchanged across study visits. Hypotension was reported in 2.9% of patients and bradycardia was reported in 2.1% of patients. There were no unexpected changes in mean height or weight. Approximately 7.0% of patients reported weight increase possibly or probably related to study drug. Weight decrease was not reported.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Appetite increase was reported by 2.1% of patients, appetite decrease by 3.3% of patients, and anorexia by 0.8% of patients. Secondary: The mean ADHD-RS-IV total score was significantly reduced from baseline to endpoint (-18.1; P<0.001 vs baseline). Mean reductions in ADHD-RS-IV scores were significant for both the inattention (-9.5; P<0.001 vs baseline) and the hyperactivity/impulsivity (-8.5; P<0.001 vs baseline) subscales. For PGA scores, 58.6% of patients were 'improved' at endpoint compared to baseline of the preceding study. For the CHQ-PF50, physical summary scores did not change significantly from baseline to endpoint overall or in any dose or age group.
Spencer et al.[79] (2009) Guanfacine ER 1 mg to 4 mg once daily added to existing stimulant therapy	MC, OL Patients six to 17 years of age with ADHD (combined, predominantly inattentive, or predominantly hyperactive-impulsive subtype) and who were on a stable regimen of either MPH or AMP ≥1 month with suboptimal control of ADHD symptoms	N=75 9 weeks	Primary: ADHD-RS-IV, CPRS-R, CGI-I, CGI-S, CHQ-PF50, and PGA Secondary: Not reported	Primary: The most common treatment-related adverse events were fatigue (34.7%), headache (33.3%), upper abdominal pain (32.0%), irritability (32.0%), somnolence (18.7%), and insomnia (16.0%). Most adverse events were mild to moderate in severity. The incidences of the treatment-emergent adverse events were comparable between both psychostimulant subgroups except for fatigue (28.6% in the guanfacine ER plus MPH subgroup vs 18.2% in the guanfacine ER plus AMP subgroup) and irritability (14.3% in the guanfacine ER plus MPH subgroup vs 33.3% in the guanfacine ER plus AMP subgroup). Twenty patients have a decrease in BP judged to be of clinical interest. Twelve patients exhibited orthostatic BP decreases. None of the patients with BP decreases reported syncope or lightheadedness. At baseline, the mean PDSS score was 15.0. Decreases were observed at visit six (-4.8) and end point (-3.1).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				During treatment, there was an increase from screening in the number of patients reporting clinically significant dullness, tiredness, and listlessness on the PSERS. There was a decrease in the number of patients with clinically significant loss of appetite and trouble sleeping. The psychostimulant subgroups were generally comparable. Significant decreases from baseline (psychostimulant only) to end point in ADHD-RS-IV total score were observed overall and in both psychostimulant combination subgroups, indicating improvement in ADHD symptoms (overall, -16.1; guanfacine ER plus MPH group, -17.8; guanfacine ER plus AMP group, -13.8; *P*<0.0001 for all). The mean percentage reduction from baseline to end point in ADHD-RS-IV score overall was 56.0%. Improvement was significant for the mean day CPRS-R total score (-19.8; *P*<0.0001), as well as for all three time points (-23.2 at 12 hours postdose, -18.5 at 14 hours postdose, and -17.8 at 24 hours postdose; *P*<0.0001 for all). The percentage of patients showing improvement at end point on the CGI was 73.0%. On the PGA, 84.1% of patients showed improvement. No significant improvement occurred at end point in the CHQ-PF50 physical summary score. Mean improvement for the CHQ-PF50 psychosocial score was 10.2 (*P*<0.0001). Secondary: Not reported
Wilens et al.[80] (2012) Guanfacine ER 1 to 4 mg/day in the morning and placebo at bedtime vs	DB, MC, PC, RCT Children and adolescents six to 17 years of age diagnosed with ADHD	N=461 9 weeks	Primary: ADHD-RS Secondary: CGI-S, CGI-I	Primary: At the end of the study, guanfacine ER treatment groups showed significantly greater improvement from baseline ADHD-RS total scores compared to placebo plus psychostimulant (guanfacine ER in the morning; P=0.002; guanfacine ER in the evening; P<0.001). Secondary: Significant benefits of guanfacine ER treatment compared to placebo plus psychostimulant were observed on the CGI-S (guanfacine ER in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo in the morning and guanfacine ER 1 mg to 4 mg/day in the afternoon vs placebo Patients continued stable dose of psychostimulant given in the morning.				the morning; P=0.013, guanfacine ER in the evening; P<0.001) and CGI-I (guanfacine ER in the morning; P=0.024, guanfacine ER in the evening; P=0.003). At study endpoint, small mean decreases in pulse, SBD, and DBP were observed in guanfacine ER treatment groups compared to placebo plus psychostimulant group. The most common treatment-emergent adverse events were mild to moderate in severity and included headache, somnolence and upper respiratory infections.
Faraone et al.[81] (2010) Guanfacine ER 1 to 4 mg once daily	MA Patients six to 17 years of age with ADHD (combined subtype, predominantly inattentive subtype, or predominantly hyperactive-impulsive subtype)	N=813 6 to 9 weeks	Primary: Predictors of efficacy and sedation using various models Secondary: Not reported	Primary: Actual Dose Model The presence or absence of ADHD symptoms was influenced by the actual doses of medication received by the participants (P=0.006). In participants with residual ADHD symptoms, greater total ADHD-RS symptom scores were significantly related to shorter treatment duration (P<0.001) and higher baseline total ADHD-RS symptom scores (P<0.001). The only significant influence on the frequency of sedation-related adverse events was treatment duration (P=0.034). mg/kg Dose Model: The presence or absence of ADHD symptoms was significantly influenced by the dose of medication received by the participant as expressed in mg/kg (P=0.001). Treatment duration (P<0.001) and baseline total ADHD-RS symptom scores (P<0.001) were predictors of weekly total ADHD-RS symptom scores. The only significant influence on the frequency of sedation-related adverse events was treatment duration (P=0.034).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Titration Rate Dose Model: The presence or absence of ADHD symptoms was significantly influenced by the titrated dose of medication received by the participant (P=0.005). The number of symptoms was significantly influenced by treatment duration (P<0.001) and baseline total ADHD-RS scores (P<0.001). The only significant influence on the frequency of sedation-related adverse events was treatment duration (P=0.034). Secondary: Not reported
Adler et al.[82] (2013) LDX 30 to 70 mg daily vs placebo	DB, PC, RCT Adults 18 to 55 years of age with a primary diagnosis of ADHD and executive function deficits (assessed by baseline BRIEF-A GEC T-scores ≥65)	N=161 10 weeks	Primary: BRIEF-A scales (GEC, index and clinical subscales) Secondary: Not reported	Primary: At week 10 or early termination, treatment with LDX was associated with significantly greater reductions from baseline in mean BRIEF-A GEC T-scores compared to placebo (P<0.0001) and significantly greater reductions from baseline in mean T-scores for both BRIEF-A index scales (metacognition scale) and all nine clinical subscales (P≤0.0056 for all). At week 10 or early termination, patients treated with LDX had mean T-scores for BRIEF-A indices and clinical subscales that were below levels of clinically significant deficits in executive function. The mean GEC T-scores were 57.2 and 68.3 for the LDX and placebo groups, respectively. Secondary: Not reported
Babcock et al.[83] (2012) LDX 30 to 70 mg daily vs placebo	DB, MC, RCT (Post-hoc analysis) Adults with ADHD who remained symptomatic on AMP therapy prior to enrollment in a four-week trial	N=36 4 weeks	Primary: Mean change in ADHD-RS score from baseline Secondary: Change in CGI-S, CGI-I	Primary: At study end, the change from baseline in mean ADHD-RS scores for LDX -treated patients was similar in the AMP group and the overall study group. The prior AMP non-responders in the placebo group had a change from baseline in ADHD-RS total score of -13.5. In the overall efficacy population, the placebo group experienced a change from baseline of -7.8. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Mean CGI scores were similar between the prior AMP subgroup and overall efficacy population in the LDX groups. In addition, the percentage of clinical responders and symptomatic remitters was comparable at all time points assessed in both LDX groups.
Biederman et al.[84] (2007) LDX 30 to 70 mg daily vs placebo	DB, MC, PC, RCT Children six to 12 years of age diagnosed with ADHD and with an ADHD-RS score ≥28	N=209 4 weeks	Primary: ADHD-RS Secondary: CPRS-R, CGI-S, CGI-I	Primary: ADHD-RS scores were significantly greater with each of the three LDX doses compared to placebo (P<0.001). The greatest efficacy was seen in the 70 mg group with a mean ADHD-RS change of -4.91 from baseline between the 30 and 70 mg groups (P<0.05). Secondary: Each LDX group significantly improved CPRS-R scores throughout the day compared to the placebo group (P<0.01 for all). Mean CGI-S scale scores significantly improved from baseline to treatment end point for all LDX groups compared to the placebo group (P<0.001 for all). CGI-I ratings were either "very much improved" or "much improved" in ≥70% of patients in the LDX groups compared to 18% of patients in the placebo group (P<0.001 for all).
Biederman et al.[85] (2007) LDX 30 to 70 mg daily vs placebo (AMP-XR 10 to 30 mg was used as a control arm)	DB, MC, PC, RCT, XO Children six to 12 years of age diagnosed with ADHD	N=52 12 weeks	Primary: SKAMP scale Secondary: PERMP, CGI-I	Primary: SKAMP scores significantly improved in both the LDX and AMP-XR groups compared to the placebo group (P<0.0001 for both). Secondary: PERMP scores for both the LDX and AMP-XR groups significantly decreased compared to the placebo group (P<0.0001 for both). The CGI-I scores significantly improved in the both LDX and AMP-XR groups compared to the placebo group (P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Brams et al.[86] (2012) LDX 30 to 70 mg daily vs placebo	DB, RCT Withdrawal study Adults 18 to 55 years of age with baseline ADHD-RS with adult prompt total scores <22 and CGI-S ratings of 1, 2 or 3	N=116 6 weeks	Primary: Proportion of patients with symptom relapse (≥50% increase in ADHD-RS score and ≥2 rating-point increase in CGI-S score) Secondary: Not reported	Primary: At study end, 8.9% of patients in the LDX group and 75.0% of patients in the placebo group experienced symptom relapse (P<0.0001), with most patients showing relapse after one and two weeks of the randomized withdrawal period. Secondary: Not reported
Coghill et al.[87] (2013) LDX 30 to 70 mg daily vs MPH-ER (Concerta®) 18 to 54 mg daily vs placebo	DB, MC, PC, PG, RCT Children and adolescents six to 17 years of age diagnosed with ADHD	N=336 7 weeks	Primary: ADHD-RS Secondary: CGI-I	Primary: The LS mean change from baseline in ADHD-RS total score was significantly greater for patients treated with LDX (-24.3±1.2) and MPH-ER (-18.7±1.1) compared to placebo (-5.7±1.1; P<0.001 for both). The LS mean change from baseline in ADHD-RS total score was significantly greater with LDX or MPH-ER compared to placebo at every time point evaluated (P<0.001 for all visits). Effect sizes based on the difference in LS mean change in ADHD-RS total score from baseline to endpoint were 1.80 and 1.26 for LDX and MPH-ER, respectively. The decreases in both the ADHD-RS hyperactivity/impulsivity and inattention subscale scores from baseline were also significantly greater for patients treated with LDX or MPH-ER compared to placebo. The LS mean change from baseline to endpoint in hyperactivity/impulsivity was significantly greater with LDX compared to placebo (-8.7; 95% CI -10.3 to -7.2; P<0.001) as was the change in inattention score (-9.9; 95% CI, -11.5 to -8.3; P<0.001). The LS mean change from baseline to endpoint significantly favored MPH-ER compared to placebo for hyperactivity/impulsivity (-6.0; 95% CI, -7.5 to -4.5; P<0.001) and inattention (-7.0; 95% CI, -8.6 to -5.4; P<0.001) scores.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: The proportions of patients with a CGI-I rating of 'very much improved' or 'much improved' after seven weeks of treatment were 78 and 61% for patients treated with LDX or MPH-ER, respectively, compared to 14% of patients treated with placebo (P<0.001 for both).
Findling et al.[88] (2011) LDX 30 to 70 mg daily vs placebo	DB, PC, RCT Adolescents 13 to 17 years of age diagnosed with ADHD	N=314 4 weeks	Primary: ADHD-RS Secondary: CGI-I, YQOL-R, treatment-emergent adverse events	Primary: Differences in ADHD-RS total scores favored all LDX doses compared to placebo at all weeks (P<0.0076). Secondary: Patients were rated much or very much improved at the end of the study with all doses of LDX (69.1%) compared to placebo (39.5%; P<0.0001). YQOL-R scores at the end of the study indicated improvement with LDX treatment, but did not result in significant differences compared to placebo. The most common treatment-emergent adverse events for all combined LDX doses included decreased appetite, headache, insomnia, decreased weight, and irritability. The severity of treatment-emergent adverse events was generally mild or moderate Clinically insignificant mean increases in pulse, BP and ECG changes were noted with LDX.
Findling et al.[89] (2008) LDX 30 to 70 mg daily	MC, OL, SA Children six to 12 years of age diagnosed with ADHD	N=274 12 months	Primary: ADHD-RS Secondary: CGI-S	Primary: Mean ADHD-RS total score improved by 27.2 points (P<0.001). Mean ADHD-RS inattentive subscale score improved by 13.4 points (P<0.001). Mean ADHD-RS hyperactivity score improved by 13.8 points (P<0.001). After improvements during the first four weeks, improvements in ADHD-RS scores were maintained throughout eleven months of treatment.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Improvement in scale scores seen in >80% of study patients at endpoint and >95% of completers at 12 months were rated as improved. Adverse event included insomnia and vomiting and considered mild or moderate by the study investigator. There were no clinical meaningful changes in BP or electrocardiographic parameters.
Jain et al.[90] (2013) LDX 20 to 70 mg daily vs placebo	OL, PC, RCT, SA, XO (Post-hoc analysis) Children 6 to 12 years of age with ADHD and baseline ADHD-RS IV total score ≥28 who had received MPH within six months of study enrollment	N=150 Variable duration	Primary: Study 1 Change in ADHD-RS total score from baseline Study 2 Mean SKAMP-D subscore over the course of a laboratory school day Secondary: Study 1 CGI-S, EESC, BRIEF-Parent form Study 2 SKAMP-A, PERMP math scores, ADHD-RS and CGI scores	Study 1 Primary: Of patients treated with LDX, the mean change from baseline in ADHD-RS total score was similar for the overall study population and the prior MPH group, with a 64.9% improvement observed in the prior MPH group. Secondary: Of patients treated with LDX, the mean change in BRIEF scores from baseline were similar for the overall study population and the prior MPH group. The mean change in CGI-I scores, EESC total scores and the BRIEF index subscale scores from baseline were similar between the overall study population and the prior MPH group. In addition, the BRIEF index subscale scores were normalized at endpoint. The rates of symptomatic remission were similar between the overall study population and the prior MPH group; however, the prior MPH group had numerically lower remission rates compared to the overall group. A clinical response was achieved in 89.6% and 86.7% of the overall population and the prior MPH group, respectively. Study 2 Primary: Improvements in SKAMP-D subscores were similar for both the overall study population and the prior MPH group. For both groups, SKAMP-D scores were improved at all post-dose time points from 1.5 hours to 13 hours with LDX vs placebo ($P \leq 0.0046$ and $P \leq 0.0284$ for all time points in the overall study population and prior MPH group, respectively). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Improvements in SKAMP-A scores were similar in the overall study population and prior MPH group from 1.5 hours to 13 hours post-dose with LDX vs placebo (P<0.0001 and P≤0.0114 for all time points in the overall study population and prior MPH group, respectively). The PERMP-A and PERMP-C scores were improved to a similar degree in both the overall study population and the prior MPH group at all post-dose time points from 1.5 to 13.0 hours with LDX vs placebo (P<0.0001 for all time points in the overall study population and prior MPH group, respectively, for both PERMP-A and PERMP-C). The change from baseline in mean ADHD-RS total scores for the overall study population and the prior MPH groups were similar when taking LDX and placebo during the XO phase (57.1 and 18.1% for patients who had previously received MPH in the LDX group and the placebo group, respectively). At visit five during the XO period, mean CGI-I scores were 1.7 and 3.5 for patients taking LDX and placebo, respectively, for the overall study population and 1.7 and 3.7, respectively, for the prior MPH group who had received ≥1 mg/kg/day of MPH.
Mattingly et al.[91] (2013) LDX 30 to 70 mg daily vs placebo	Post-hoc analysis of Weisler et al[82] Adults aged 18 to 55 years of age diagnosed with ADHD who had completed ≥2 weeks of treatment with LDX	N=345 12 months	Primary: ADHD-RS-IV Secondary: Not reported	Primary: Baseline ADHD-RS-IV total scores were lower in the predominantly inattention and hyperactivity/impulsivity symptom cluster subgroups. LDX decreased ADHD-RS-IV total scores in all predominant symptom cluster subgroups. Mean percent reduction from baseline to endpoint was 55.9, 71.0, and 62.6% for the predominantly inattention, hyperactivity/impulsivity, and combined symptom cluster subgroups, respectively, and was 61.1% for the overall population. At trial end, 285/345 patients were classified as clinical responders (ADHD-RS-IV total score decrease of ≥30% from baseline and CGI-I score of one or two). Of the 93 patients with predominantly inattention symptom cluster at baseline, 74 were classified as clinical responders at trial end. All 13 patients who had predominantly hyperactivity/impulsivity symptom cluster at baseline were classified as clinical responders at endpoint. At endpoint, 236 of patients who had combined type ADHD at baseline, 196 were classified as clinical responders.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Weisler et al.[92] (2009) LDX 30 to 70 mg daily	DB, PC, RCT, SA Adults aged 18 to 55 years of age diagnosed with ADHD	N=349 12 months	Primary: ADHD-RS Secondary: CGI-S, CGI-I	Primary: Mean ADHD-RS total scores improved at week one of treatment and sustained throughout the eleven month treatment period (P<0.001). Mean ADHD-RS total scores improved by 24.8 points from baseline to study endpoint (P<0.001). Secondary: All study patients rated as moderately ill with a mean CGI-S of 4.8 with improvement in their mean score of 1.7 at endpoint. At weeks one, two, three, and four, the proportion of study patients rated as improved on the CGI-I was 43.9, 68.3, 83.4 and 89.1%, respectively. At month 12, 92.6% were improved on the CGI-I. Common adverse events included upper respiratory tract infection, insomnia, headache, dry mouth, decreased appetite and irritability. Most adverse events were considered mild or moderate by the study investigator. Small but statistically significant increases in pulse and BP noted at treatment endpoint.
Wigal et al.[93] (2011) MPH-ER (Concerta®) 18 to 54 mg daily vs placebo	DB, PC, RCT Children nine to 12 years of age diagnosed with ADHD	N=78 5 months	Primary: PERMP, SKAMP, TOVA, Finger Windows forward and backward subtest Secondary: Not reported	Primary: MPH-ER significantly improved performance on the number of problems attempted and number of problems correctly answered on the PERMP compared to placebo (P<0.001). MPH-ER significantly improved performance on inattention, deportment, and total ratings of the SKAMP measure (P<0.001) as compared to placebo. Children taking MPH-ER had statistically significantly better scores than children taking placebo on response time (P<0.000). MPH-ER significantly improved performance on memory as compared to placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Most common adverse effects included decreased appetite, upper abdominal pain, headache and irritability. Most adverse events were considered mild or moderate by the study investigator. Secondary: Not reported
Casas et al.[94] (2011) MPH-ER (Concerta®) 54 mg to 72 mg/day vs placebo	DB, MC, PC, RCT Men and women 18 to 65 years of age diagnosed with ADHD	N=279 13 weeks	Primary: CAARS-Inv: SV Secondary: CGI-S, CGI-C, CAARS-Self: SV, SDS, AIMA-A	Primary: Improvements in CAARS-Inv:SV were significantly greater with MPH-ER 72 mg compared to placebo (P=0.0024). There was no significant difference between MPH-ER 54 mg and placebo. Secondary: Mean improvement in CGI-S score was significantly greater with MPH-ER 72 mg than placebo (P<0.001); however, there was no significant difference with MPH-ER 54 mg compared to placebo. Median improvement in CGI-C score was significantly greater with MPH-ER 72 mg (2.0) compared to placebo (3.0; P=0.0018); however, there was no significant difference with MPH-ER 54 mg (2.5) compared to placebo. CAARS-Self:SV scores decreased significantly compared to placebo in both MPH-ER treatment groups (P<0.05). There was no significant change in SDS score from baseline in either treatment group. Significant benefit compared to placebo was observed on several AIM-A subscales, which included performance and daily functioning, communication and relationships, living with ADHD and general well-being. The most common adverse events with MPH-ER were mild to moderate in severity and included headache, decreased appetite, dry mouth and nausea.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Wigal et al.[95] (2013) MPH-ER suspension (Quillivant XR®) 20 to 60 mg daily vs placebo	DB, MC, PC, RCT, XO Children six to 12 years of age diagnosed with ADHD	N=45 2 weeks	Primary: SKAMP combined score Secondary: Onset of action and duration of clinical effect, subscale scores for SKAMP, PERMP, CGI-S and CGI-I	Primary: Children treated with MPH-ER suspension experienced a statistically significant improvement in SKAMP combined score at four hours post-dose compared to children treated with placebo. The LS mean SKAMP combined score was 7.12 in children receiving MPH-ER suspension compared to 19.58 in children receiving placebo (LS mean difference, -12.46; P<0.0001). Secondary: There were statistically significant improvements from baseline with MPH-ER suspension compared to placebo at each time point tested (45 minutes, two, four, eight, 10 and 12 hours), with the onset of action at 45 minutes post-dose and a duration of effect continuing to be significant compared to placebo at 12 hours post-dose. The results of the remaining secondary endpoints were not presented in this study.
Wilens et al.[96] (2004) MPH-ER (Concerta®) 18 to 54 mg daily	MC, OS, PRO Children six to 13 years of age diagnosed with ADHD	N=432 1 year	Primary: HR and BP after one year Secondary: Not reported	Primary: Compared to baseline, MPH-ER was associated with minor clinical, although statistically significant, DBP elevations (1.5 mm Hg; P<0.001), SBP elevations (3.3 mm Hg; P<0.001) and HR (3.9 beats per minute; P<0.0001) at the 12-month end point. Secondary: Not reported
Mattos et al.[97] (2012) MPH-ER (Concerta®) 18 mg to 72 mg/day	MC, OL Men and women 18 to 65 years of age diagnosed with ADHD	N=60 12 weeks	Primary: ASRS, AAQoL, STAI, HAMD, CGI-I Secondary: Not reported	Primary: ADHD symptom severity improved with the ASRS scores (total score, inattention and hyperactivity) significantly reduced from baseline to weeks four, eight, and 12 (P<0.001). AAQoL subscales (P<0.001), as well as AAQoL total score (P<0.001), significantly improved from baseline to week 12. A significant reduction in STAI, CGI-I, and HAMD, scores were observed (P<0.0001). The most common adverse events included appetite changes (25%),

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				dry mouth (16.7%), headache (11.7%), irritability (5%) and insomnia (5%). Adverse events were mild to moderate in severity as reported by the study investigators. Secondary: Not reported
Cox et al.[98] (2006) MPH-ER (Concerta®) 36 mg once daily on days one to five, then 72 mg once daily on days 6 to 17 vs AMP-XR (Adderall XR®) 15 mg once daily on days one to five, then 30 mg once daily on days 6 to 17 vs placebo	DB, PC, RCT, XO Adolescents 16 to 19 years of age diagnosed with ADHD and licensed to drive	N=35 21 to 38 days	Primary: IDS, assessed using an Atari Research Driving Simulator on days 10 and 17; subjective ratings of driving performance by participants and investigators Secondary: Not reported	Primary: Overall IDS values were significantly better than with placebo with MPH-ER (P<0.001), but not with AMP-ER (P=0.24). Simulator-rated driving performance as indicated by IDS was also significantly better in the MPH-ER group than in those receiving AMP-ER (P=0.03). MPH-ER was significantly better than placebo in the categories off-road excursions (P=0.02), speeding (P=0.01), SD speed (P=0.02), and time at a stop sign deciding where to turn (P=0.003). AMP-ER was significantly better than placebo in the category of inappropriate braking (P=0.04). Subjective ratings of driving performance by participants and investigators rated MPH-ER as better for driving performance (P=0.008). Secondary: Not reported
Yang et al.[99] (2011) MPH-ER 18 mg to 54 mg/day	RCT, SB Children and adolescents seven to 14 years of age diagnosed with ADHD	N=142 4 to 6 weeks	Primary: RCFT, Digit span, Stroop color word test Secondary: Not reported	Primary: Both MPH-ER and atomoxetine significantly improved visual memory, verbal memory, and word inference time. Visual and verbal memory was not significantly different from the control group at post-treatment assessment (P>0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs atomoxetine 0.5 mg to 1.4 mg/kg/day				Although word interference time was more improved than the control group, there was no statistically significant difference (P>0.05). Secondary: Not reported
Wolraich et al.[100] (2001) MPH-ER (Concerta®) 18 to 54 mg daily vs MPH-IR 5 to 15 mg three times daily vs placebo	DB, PC, PG, RCT Children six to 12 years of age diagnosed with ADHD (any subtype)	N=282 28 days	Primary: Iowa Conners I/O and O/D rating scale (parents and teachers) Secondary: SNAP-IV scores (teachers and parents), CGI-I scores (investigators), global assessment of efficacy (parents and teachers)	Primary: Both MPH-ER and MPH-IR demonstrated a statistically significant improvement in the Iowa Conners I/O and O/D rating scale scores compared to placebo at week one and at the end of the study (P<0.001). There was no significant difference in the mean Iowa Conners scale scores between the MPH-ER and MPH-IR groups at week one (P=0.838) or at the end of the study (P=0.539). Secondary: Teacher and parent SNAP-IV scores were significantly better for patients in the MPH-ER and MPH-IR groups than for those in the placebo group (P<0.001). There was not a significant difference in SNAP-IV scores between the MPH-ER and MPH-IR groups. CGI-I scores significantly improved in the MPH-ER and MPH-IR groups compared to the placebo group (P<0.001). Both the parent and teacher global assessment of efficacy scores were significantly higher with the MPH-ER and MPH-IR groups than the placebo group (P<0.001).compared to
Pelham et al.[101] (2001) MPH-ER (Concerta®) 18 to 54 mg daily vs	DB, PC, RCT, XO Children six to 12 years of age diagnosed with ADHD (any subtype) who were taking MPH prior to	N=68 1 week	Primary: Iowa Conners I/O and O/D rating scales (teacher and parents), SKAMP scale (teacher) Secondary:	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,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
MPH-IR 5 to 15 mg three times daily vs placebo	study entry		Not reported	but both were significantly better than placebo. Secondary: Not reported
Gau et al.[102] (2006) MPH-ER (Concerta®) 18 to 36 mg daily vs MPH-IR 5 to 10 mg three times daily	OL, RCT Children six to 15 years of age diagnosed with ADHD (any subtype) who were taking MPH (10 to 40 mg/day)	N=64 28 days	Primary: CTRS-RS, CPRS-RS, SKAMP-A, SKAMP-D Secondary: SAICA, CGI	Primary: Each of the four groups displayed a significant decrease in all measures of CTRS-RS, CPRS-RS, SKAMP-A, SKAMP-D at each of the follow-up visits (P<0.001 for all) compared to baseline, but there were no significant differences between the groups (P>0.05 for all). Secondary: Patients in both the MPH-XR and MPH-IR groups experienced significant improvements from baseline in academic performance and less severe problems at school (P<0.05). Patients in the MPH-XR group also significantly improved from baseline in attitude toward their teachers, school social interaction, and relationships with peers and siblings (P<0.05). The MPH-XR group had a significantly greater number of patients being very much or much improved (84.4%) than the MPH-IR group (56.3%) (P=0.014) based on the CGI score.
Lopez et al.[103] (2003) MPH-ER (Concerta®) 18 to 36 mg daily vs MPH-XR (Ritalin LA®)	DB, PC, RCT Children six to 12 years of age diagnosed with ADHD who were previously stabilize on MPH (equivalent dose of 10 mg BID)	N=36 28 days	Primary: SKAMP scales Secondary: Not reported	Primary: Both MPH-ER and MPH-XR statistically improved SKAMP scale scores compared to placebo (P<0.001). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
20 mg daily vs placebo				
Swanson et al.[104] (2004) MPH-ER (Concerta®) 18 to 54 mg daily vs MPH-XR (Metadate CD®) 20 to 60 mg daily vs placebo	DB, MC, PC, RCT, XO Children six to 12 years of age diagnosed with ADHD (inattentive type, hyperactive-impulsive type, or combined type) being treated with MPH in doses of 10 to 60 mg/day	N=184 7 weeks	Primary: SKAMP scales, PERMP Secondary: Not reported	Primary: MPH-ER and MPH-XR demonstrated similar efficacy, and both were better than placebo in SKAMP and PERMP scores (P<0.016). Secondary: Not reported
Silva et al.[105] (2005) MPH-ER (Concerta®) 18 mg vs MPH-ER (Concerta®) 36 mg vs MPH ER 20 mg	MC, RCT, SB, XO Children six to 12 years of age diagnosed with ADHD and stabilized on MPH (20 to 40 mg/day)	N=54 6 weeks	Primary: SKAMP-A rating subscale Secondary: SKAMP-D and SKAMP-C rating subscales and written math tests	Primary: All doses of the study medications significantly improved SKAMP-A scores from baseline at all time points, compared to placebo (P<0.038). ER-MPH 20 and 40 mg showed significantly greater differences from predose on the SKAMP-A than did MPH ER, 36 mg at two hours postdose, and also when scores were integrated over zero to four hours (P=0.022 for the 20 mg dose and P=0.001 for the 40 mg dose), but showed no significant improvement over eight to 12 hours. Secondary: Single morning doses of ER-MPH and MPH ER, were effective in improving SKAMP-D scores and academic productivity for the majority of the 12-hour classroom session.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs MPH ER 40 mg vs placebo All medications were dosed once per study day (six consecutive Saturdays). Patients continued their regular ADHD medications on Sunday through Thursday of the study weeks, with no medications allowed on Friday.				
Jahromi et al.[106] (2009) MPH-IR 0.125 mg/kg/dose twice daily for one week (low dose) vs MPH-IR 0.25 mg/kg/dose twice daily for one week	DB, RCT, XO Children five to 13 years of age with PDD and hyperactivity	N=33 4 weeks	Primary: JAMES, Caregiver-Child Interaction measure (competing demands and clean-up task) captured social communi-cation, self-regulation and affective behavior	Primary: Significant positive effect of MPH was seen on social communication (P<0.05); comparing each of the three MPH doses of MPH compared to placebo, the low dose showed significant improvement compared to placebo (P<0.05); no significant differences found between placebo and the medium or high doses. No significant improvement in self-regulation for the competing demands task when comparing best dose MPH to placebo (P=0.09); significant improvement in self-regulation behaviors comparing low dose MPH (P<0.05) and medium dose effect (P<0.01) compared to placebo; no improvement found in high dose MPH over placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(medium dose) vs MPH-IR 0.50 mg/kg/dose twice daily for one week (high dose) vs placebo for one week			Secondary: Not reported	No significant improvement in self-regulation behaviors for the clean-up task for any of the three dose levels of MPH compared to placebo, or between placebo and the best dose of MPH (P>0.05). Significant improvement in affective behavior for the competing demands task when comparing medium MPH dose (P <0.05) and high MPH dose compared to placebo (P<0.05); no improvement found in best dose of MPH compared to placebo (P=0.09); or low dose (P=0.07). No significant improvement on affective behavior for the clean-up task and any MPH dose (P>0.05). Secondary: Not reported
Spencer et al.[107] (2011) MPH-IR three times daily vs MPH-ER once daily (OROS-MPH)	PG, RCT, SB Patients 19 to 60 years of age diagnosed with ADHD who were on stable therapy with MPH-IR	N=61 6 weeks	Primary: AISRS Secondary: Not reported	Primary: MPH-IR responders randomized to MPH-IR or MPH-ER had no effect on AISRS score at the study endpoint (11.2 vs 10.7; P=0.80). Study patients stabilized on MPH-IR and switched to MPH-ER remained satisfied over 71% of the time. MPH-IR treatment group missed significantly more doses than the MPH-ER treatment group (7.3 vs 3.3; P=0.02). Secondary: Not reported
Efron et al.[108] (1997) MPH-IR 0.3 mg/kg/dose twice daily vs DEX-IR	DB, RCT, XO Children five to 15 years of age diagnosed with ADHD	N=125 4 weeks	Primary: SERS Secondary: Not reported	Primary: There was a statistically significant decrease in the mean number of side effects in the MPH-IR group vs the DEX-IR group (8.19 vs 7.19; P=0.03) based on the results of the SERS questionnaire which assess the 17 most common side effects of stimulants including trouble sleeping, decreased appetite and anxiousness. Mean severity of side effects statistically significantly improved in the MPH-IR group compared to the DEX-IR group (3.24 vs 3.73; P<0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
0.15 mg/kg/dose twice daily Patients received one drug for two weeks then crossed over to the other stimulant for two weeks.				A majority of parents rated their children as improved compared to their "usual selves" in both of the treatment groups (68.8% in the DEX-IR groups and 72% in the MPH-IR). Secondary: Not reported
Pelham et al.[109] (1990) MPH-IR 10 mg twice daily vs MPH-SR (Ritalin SR®) 20 mg daily vs DEX-SR (Dexedrine®) 10 mg daily vs pemoline 56.25 mg daily vs placebo	DB, PC, RCT, XO Males eight to 13 years of age diagnosed with ADHD	N=22 8 weeks	Primary: Evaluated social behavior during activities, classroom performance, and performance on a continuous performance task Secondary: Not reported	Primary: Each of the active treatment groups were more effective than placebo on most measures of social behavior from the medication assessment (P<0.05). DEX-SR and pemoline tended to produce the most consistent effects. The continuous performance task results showed that all four medications had an effect within two hours, and the effects lasted for nine hours vs placebo (P<0.025). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Palumbo et al.[110] (2008) MPH-IR 5 mg to 60 mg/day vs clonidine 0.05 mg to 0.6 mg/day vs MPH-IR and clonidine vs placebo	DB, MC, PC, RCT Children seven to 12 years of age diagnosed with ADHD	N=122 16 weeks	Primary: CASQ-T Secondary: CASQ-P, CGAS	Primary: For CASQ-T, clonidine did not improve ADHD symptoms. Study patients treated with MPH showed significant improvement compared to those not treated with MPH. Secondary: Study patients treated with clonidine had greater improvements on the CASQ-P and CGAS, but a higher rate of sedation compared to patients not treated with clonidine.
Greenhill et al.[111] (2002) MPH-XR (Metadate CD®) 20 to 60 mg daily vs placebo	DB, MC, PC, RCT Children six to 16 years of age diagnosed with ADHD	N=321 3 weeks	Primary: CGI-S (teacher) Secondary: CGI-S (parents), CGI-I scores, adverse events	Primary: CGI-S teacher scores significantly improved in the MPH-XR group (12.7±7.2 to 4.9±4.7) compared to the placebo group (11.5±7.3 to 10.3±6.9; P<0.001). Secondary: CGI-S parent scores significantly improved from 13.6±6.6 to 7.4±5.9 with MPH-XR vs 12.9±7.6 to 10.1±6.7 with placebo (P<0.001 for both scales). Eighty-one percent of the patients in the MPH-XR group compared to 50% of the patients in the placebo group were classified as responders based on their CGI-I scores (P<0.001). In the MPH-XR group, 52% of children reported at least one adverse event vs 38% from the placebo group (P=0.014). The rate of anorexia was more significant in the MPH-XR group vs the placebo group (9.7 vs 2.5%; P=0.007).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
McGough et al.[112] (2006) MTS 10 to 27 mg daily vs standard current therapy	OL, RCT (first five weeks) then DB, PC Children six to 12 years of age diagnosed with ADHD	N=80 7 weeks	Primary: Evaluate time course effects of MPH transdermal patch vs placebo transdermal patch via SKAMP-A, SKAMP-D, PERMP, ADHD-RS-IV, CPRS-R, CGI-I, and PGA rating scales Secondary: Acute efficacy and tolerability of MPH transdermal patch	Primary: Mean SKAMP-D scores were improved with MPH transdermal patch vs placebo (mean score, 3.2 vs 8.0) and at all time points assessed including 12 hours post-application (P<0.01). Mean (SKAMP-A) scores were improved with MPH transdermal patch vs placebo (6.2±0.50 vs 9.9±0.50, respectively; P<0.0001). PERMP scale results: Mean number of math problems attempted and math problems correct were significantly higher with MPH transdermal patch vs placebo (113.8 vs 86.2 and 109.4 vs 80.7, respectively; P<0.0001). Across the double-blind period, mean scores for the ADHD-RS-IV and CPRS-R scales were significantly improved with MPH transdermal patch vs placebo (P<0.0001). Those in the MPH transdermal patch group (79.8%) were more likely to be deemed improved on clinician rated CGI-I scores vs those in the placebo group (79.85 and 11.6%, respectively; P<0.0001). Statistically significant differences were observed with PGA ratings; 71.1% of MPH transdermal patch participants and 15.8% of placebo participants were rated as improved (P<0.0001). Secondary: More treatment-emergent adverse events were recorded with MPH transdermal patch therapy (39 events, 24 participants) vs placebo therapy (25 events, 18 participants). The most common treatment-related adverse events were decreased appetite, anorexia, headache, insomnia, and upper abdominal pain, all reported by less than 5% of study participants.
Pelham et al.[113] (2005) MPH transdermal	DB, DR, MC, RCT Children seven to 12 years of age	N=36 8 days	Primary: MPH transdermal patch efficacy and influence of	Primary: All doses of MPH transdermal patches were significantly improved vs placebo on measures of social behavior in recreational settings, classroom functioning, and parent ratings of evening behavior

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
patches: 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 MPH transdermal patches 6.25 cm^2, 12.5 cm^2 or 25 cm^2 patches or placebo in a random order on separate days and at two time points (6:00 AM or 7:00 AM).	diagnosed with ADHD		exposure time on morning effects Secondary: Not reported	(P<0.05). Beneficial effects of MPH transdermal patches were observed at all time points after application of the patch and were still seen for three hours after the patch had been removed (i.e., throughout the 12-hour assessment). Incidence of skin rash was reported as 40 to 50%. Secondary: Not reported
Pelham et al.[114] (2005) MPH transdermal patches: 12.5 cm^2, 25 cm^2 and 37.5 cm^2 plus behavior modification Each participant had two days on each treatment without concomitant plus behavior modification and four days on each	DR, RCT Children aged six to 12 years diagnosed with ADHD	N=27 6 weeks	Primary: Proportion that reached individual target goals in Daily Report Card scores Secondary: Not reported	Primary: The percentage of individualized target criteria met by children in their Daily Report Card assessment was significantly (P<0.05 for all) higher with MPH transdermal patch 12.5, 25, and 37.5 cm^2 vs placebo, both without behavior modification (41.9, 63.1, and 66.2 vs 20.8%) and with behavior modification (73.7, 87.5, and 86.2 vs 54.7%; all P<0.05). Response rates were higher in the MPH transdermal patches 25 cm^2 group than in the 12.5 cm^2 group, both with and without behavior modification (P<0.05 for both); increasing the size of the patch to 37.5 cm^2 added no further advantage. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
treatment with plus behavior modification.				
Faraone et al.[115] (2009) MPH transdermal patches 10 to 30 mg daily worn for nine hours per day or MPH-ER (Concerta®) 18 to 54 mg daily vs placebo	DB, MC, PC, RCT Children six to 12 years of age diagnosed with ADHD (predominantly hyperactive-impulsive, predominantly inattentive, or combined type)	N=268 5 weeks	Primary: CSHQ Secondary: Not reported	Primary: No significant difference in the severity of sleep problems was observed among the treatment and placebo groups (P≥0.233). No significant differences in the numbers of sleep problems were observed between MPH transdermal patch/MPH-ER and placebo (P≥0.554). There was no significant effect of MPH dosage on sleep problems (P=0.135). The effects of each MPH treatment and the various doses of these treatments on each CSHQ subscale were identical to the effects observed for the total CSHQ scale. Secondary: Not reported
Findling et al.[116] (2008) MTS 10 to 30 mg daily or OROS-MPH 18 to 54 mg daily vs placebo	DB, PC, RCT Children six to 12 years of age diagnosed with ADHD	N=282 7 weeks	Primary: ADHD-RS Secondary: CTRS-R, CPRS-R, CGI-S, CGI-I	Primary: Mean total ADHD-RS scores were similar between MPH transdermal patch, MPH-ER, and placebo at baseline (43.0, 43.8, and 41.9, respectively), but not at endpoint (18.8, 21.8, and 32.1, respectively). Mean change from baseline in ADHD-RS scores was greater in study patients receiving MPH transdermal patch and MPH-ER compared to patients receiving placebo (P<0.001). There was a two-fold improvement of ADHD symptoms in active treatments compared to placebo from baseline to study endpoint. Secondary: MPH transdermal patch and MPH-ER showed improvements over placebo in mean total parent and teacher scores from baseline to endpoint. More study patients receiving MPH transdermal patch and MPH-ER

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				compared to placebo were rated as improved by clinicians and parents (P<0.001). Adverse events included decreased appetite, nausea, vomiting and insomnia. Most adverse events were considered mild or moderate by the study investigator.
Chou et al.[117] (2012) MPH-ER (Concerta®) 18, 36, or 54 mg once daily	OS Children six to 19 years of age with ADHD who have received MPH-IR for ≥1 month	N=521 10 weeks (six weeks forced-titration phase to achieve remission, followed by a four week maintenance phase)	Primary: Symptomatic remission Secondary: Changes in efficacy and satisfaction, safety	Primary: Using the forced-titration of MPH-ER dosage to increase the dosage during the first six weeks, the remission rate significantly increased with time from 4.8% (at baseline), 25% (week two), 44.2% (week four), 58.8% (week six), up to 59.6% (week 10) among 507 ITT patients. Among 439 patients who completed the 10 week follow-up assessments, 290 (66.1%) patients achieved symptomatic remission (95% CI, 61.6 to 70.5). The non-remission group had higher mean daily doses compared to the remission group from visit two to trial end. Secondary: Among the 439 patients who completed the treatment, there was a significant decrease in the total score and three sub-scores of the Chinese SNAP-IV (P<0.001), CGI-ADHD-S (P<0.001), and CGI-ADHD-I (P<0.001) as intra-individual comparison from the baseline to each visit through the trial period. Among the items on the Barkley SERS, poor appetite was the only one exacerbated on visit three, but improved on later visits. The other side effects gradually decreased in intensity throughout the trial period, and the difference from baseline reached significance from visit three to trial end. At trial end, there was a decrease in both mean body weight (-0.85 kg) and mean respiratory rate (-0.44/minute), and an increase in mean pulse rate (5.09 beats per minute) in comparison with baseline with significance (P<0.001). Five percent of patients withdrew from the trial because of adverse events, and these patients mostly left due to poor appetite and insomnia.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Three patients experienced at least one serious adverse event that was not deemed to be treatment-related.
Faraone et al.[118] (2006) AMP-IR, AMP-XR, atomoxetine, bupropion, DEX-IR, DEX-ER, DEX-IR, modafinil, MPH-ER, MPH-IR, MPH-XR, MPH transdermal patches, pemoline	MA (29 trials) Patients diagnosed with ADHD	N=2,988 Variable duration	Primary: Effect sizes Secondary: Not reported	Primary: All of the drugs groups produced a significant measure of effect compared to the placebo group (P<0.0001). The effect sizes for non stimulant medications were significantly less than those for immediate-release stimulants (P<0.0001) or long-acting stimulants (P=0.0008). The two classes of stimulant medications (short acting and long acting) did not differ significantly from one another (P=0.14). Secondary: Not reported
Schelleman et al.[119] (2011) ADHD medications vs nonusers	RETRO Children three to 17 years of age who were dispensed a prescription for an AMP, atomoxetine, or MPH	N=241,417 Variable duration	Primary: Sudden cardiac death, or ventricular arrhythmia, stroke, MI Secondary: All-cause death	Primary and Secondary: No statistically significant difference between incident users and nonusers was observed in the rate of validated sudden death or ventricular arrhythmia (HR, 1.6; 95% CI, 0.19 to 13.60) or all-cause death (HR, 0.76; 95% CI, 0.52 to 1.12). None of the strokes identified during exposed time to ADHD medications were validated. No MIs were identified in study patients who used ADHD medication. No statistically significant difference between prevalent users and nonusers was observed for validated sudden death or ventricular arrhythmia (HR, 1.43; 95% CI, 0.31 to 6.61); stroke (HR, 0.89; 95% CI, 0.11 to 7.11); stroke/MI (HR, 0.72; 95% CI, 0.09 to 5.57); or all-cause death (HR, 0.77; 95% CI, 0.56 to 1.07).
Olfson et al.[120] (2012)	RETRO Patients six to 21	N=171,126 Variable	Primary: Cardiac events (inpatient diagnosis	Primary: There were 0.92 new cardiac events and 3.08 new cardiac symptoms per 1,000,000 days of current stimulant use.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
AMP and MPH vs nonusers	years of age diagnosed with ADHD who were prescribed AMP or MPH	duration	of chest pain, cardiac dysrhythmia or transient cerebral ischemia) and cardiac symptoms (tachycardia, palpitations, or syncope) Secondary: Not reported	Current stimulant use compared to no stimulant use was not associated with less severe cardiovascular event (adjusted OR, 0.69; 95% CI, 0.42 to 1.12). Past stimulant use compared to no stimulant use was not associated with less severe cardiovascular event (adjusted OR, 1.18; 95% CI, 0.83 to 1.66). The adjusted ORs for cardiac symptoms were 1.18 (95% CI, 0.89 to 1.59) for current and 0.93 (95% CI, 0.71 to 1.21) for past stimulant use when compared to no stimulant use. Current and past stimulant use was not associated with cardiac symptoms. No significant differences were observed in risks of cardiovascular events (adjusted OR, 2.14; 95% CI, 0.82 to 5.63) or symptoms (adjusted OR, 1.08; 95% CI, 0.66 to 1.79) for current MPH use compared to AMP use. Secondary: Not reported
Schelleman et al.[121] (2012) AMP, atomoxetine, MPH	RETRO Patients three to 17 years of age with a prescription for an AMP, atomoxetine, or MPH	N=219,954 Variable duration	Primary: Sudden death, ventricular arrhythmia, stroke, MI Secondary: Not reported	Primary: No significant difference between incident users and nonusers was observed in the rate of sudden death or ventricular arrhythmia (HR, 1.60; 95% CI, 0.19 to 3.60) or all-cause death (HR, 0.76; 95% CI, 0.52 to 1.12). None of the strokes identified during exposed time to ADHD medications were validated. No MIs were identified in ADHD medication users. No significant difference between prevalent users and nonusers was observed (HR for validated sudden death or ventricular arrhythmia, 1.43; 95% CI, 0.31 to 6.61; stroke, 0.89; 95% CI, 0.11 to 7.11; stroke/MI, 0.72; 95% CI, 0.09 to 5.57; and all-cause death, 0.77; 95% CI, 0.56 to 1.07).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Hanwella et al.[122] (2011) Atomoxetine vs MPH	MA (five trials) Children and adolescents six to 16 years of age diagnosed with ADHD	N=2,762 Variable duration	Primary: ADHD-RS Secondary: Not reported	Primary: The MA did not find a significant difference in efficacy between MPH and atomoxetine when comparing SMD in ADHD-RS scores (SMD, 0.09; 95% CI, -0.08 to 0.26). There was no significant difference in response rates between the two medications (RR, 0.93; 95% CI, 0.76 to 1.14). Treatment effects between the formulations of MPH showed a significant SMD in ADHD-RS favoring OROS-MPH (SMD, 0.32; 95% CI, 0.12 to 0.53). MPH-IR was not superior to atomoxetine (SMD, -0.04; 95% CI, -0.19 to 0.12). There was no significant difference in acceptability between atomoxetine and MPH (RR, 1.22; 95% CI, 0.87 to 1.71). Secondary: Not reported
Bloch et al.[123] (2009) ADHD medications	MA (11 trials) Children diagnosed with ADHD and Tourette's	N=77 Variable duration	Primary: ADHD severity (ADHD-RS, CADS-P, CADS-T, CTRS-R) and tic severity (YGTSS, STSSS, HMVTS, and GTSS) Secondary: Not reported	Primary: MPH, α-2 agonists, desipramine, and atomoxetine demonstrated efficacy in improving ADHD symptoms in children with co-morbid tics. α-2 agonists and atomoxetine significantly improved co-morbid tic symptoms. There was evidence that supratherapeutic doses of DXM worsened tics; however, there was no evidence that MPH worsened tic severity in the short term. Secondary: Not reported

Drug regimen abbreviations: AMP=mixed amphetamine salts, DEX=dextroamphetamine, DXM=dexmethylphenidate, ER=extended release, IR=immediate release, LDX=lisdexamfetamine, MPH=methylphenidate, OROS=osmotic-release oral system, SR=sustained release, XR=extended release
Study abbreviations: CI=confidence interval, DB=double blind, DR=dosing ranging, ES=extension study, FD=fixed dose, HR=hazard ratio, MA=meta-analysis, MC=multi-center, OL=open-label, OR=odds ratio, OS=observational study, PC=placebo-controlled, PG=parallel-group, PRO=prospective trial, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk, SA=single arm, SB=single blind, TB=triple blind, XO=crossover design

Other abbreviations: AAQoL=Adult ADHD quality of life scale, ADHD=attention deficit hyperactivity disorder, ADHD-RS=ADHD rating scale, AIM-A=ADHD impact module-adult, AISRS=Adult ADHD investigator system symptom report scale, ASRS=Adult self-rating scale, BFI=Brief Fatigue Inventory, BP=blood pressure, BRIEF=Behavior Rating Inventory of Executive Function, BRIEF-A=Behavior Rating Inventory of Executive Function-Adult Version, CAARS=Conner's adult ADHD rating scale, CAARS-Inv:SV=Conners' Adult ADHD Rating Scale–Investigator Rated: Screening Version, CAARS-Self:SV=Conners' Adult ADHD Rating Scale–Self Rated: Screening Version, CADS-P=Conners ADHD/DSM IV scale-parent version, CADS-T=Conners ADHD/DSM IV scale-teacher version, CANTAB-CRT=Cambridge Neuropsychological Test Automated Battery-Choice Reaction Time, CANTAB-SWM=Cambridge Neuropsychological Test Automated Battery-Working Memory and Strategy Performance, CASQ-P=Conner's abbreviated symptom questionnaire for parents, CASQ-T=Conner's abbreviated symptom questionnaire for teachers, CBC=Conner's behavior checklist, CGAS=Children's Global Assessment Scale, CGI=clinical global impression CGI-C=clinical global impression of change, CGI-I=clinical global impression of improvement, CGI-S=clinical global impression of severity, CHIP-CE=Child Health and Illness Profile-Child Edition, CPRS=Conners parent rating scale, CHQ=child health questionnaire, CHQ-PF50=Child Health Questionnaire-Parent Form, CPRS=Conners parent rating scale, CPRS-R=Conners parent rating scale—revised, CPRS-R:S=Conners parent rating scale: short form, CPRS-R:L=Conners' parent rating scale-revised: long form, CPT=Continuous performance test, CSHQ=Children's Sleep Habits Questionnaire, CTRS-R=Conners teacher rating scale–revised, CTRS-R: S=Conners teacher rating scale-revised: short form, DBP=diastolic blood pressure, DSST=Digit Symbol Substitution Task/Coding Test, EESC=Expression and Emotion Scale for Children, FBIM=Family Burden of Illness Module, HAMA=Hamilton Anxiety Rating Scale, GEC=global executive composite, GTSS=Global tic severity scale, $HAMD_{17}$=Hamilton 17-item Depression Rating scale, HMVTS=Hopkins motor/vocal tic scale, HR=heart rate, HSPP=Harter Self-Perception Profile, I/O=inattention/overactivity, JAMES=Joint Attention Measure from the EScs (Early and Social Communication Scale), LS=least square, MI=myocardial infarction, O/D=oppositional/defiance, ODD=oppositional defiant disorder, PDD=pervasive developmental disorders, PERMP=permanent product measure of performance, PGA=parent global assessment, PSQ=parental satisfaction questionnaire, Q-LES-Q=quality of life, enjoyment, and satisfaction questionnaire, SAICA=Social Adjustment Scale for Children and Adolescents, SBP=systolic blood pressure, SD=standard deviation, SDS=Sheehan disability scale, SF-36=36-item Short Form Health Survey, SERS=side effect ratings scale, SKAMP=Swanson, Kotkin, Agler, M-Flynn, and Pelham, SKAMP-A=SKAMP-Attention, SKAMP-D=SKAMP-Deportment, SMD=standard mean difference, SNAP=Swanson, Nolan and Pelham, SNAP-ODD=Swanson, Nolan and Pelham-oppositional defiant disorder, SNAP-P=Swanson, Nolan and Pelham-parent rating scale, SNAP-T=Swanson, Nolan and Pelham-teacher rating scale, SSERS=Stimulant Side Effects Rating Scale, STAI=State and trait anxiety inventory, STSSS=Shapiro Tourette syndrome severity scale, TOVA=test of variables of attention, WFIS=Weiss Functional Impairment Scale, WRAADDS=Wender-Reimherr Adult Attention-Deficit Disorder Scale, YGTSS=Yale global tic severity scale, YQOL-R=Youth quality of life-research version

Additional Evidence

Dose Simplification
Once-daily formulations increase patient compliance and eliminate the need for medication use during school. Prescribing immediate-release stimulants that require dosing during school hours can be problematic, especially with controlled drugs which have the potential for abuse. A few studies have compared immediate-release formulations with extended-release products. Lage et al. evaluated a pharmacy claims database to assess medication compliance among patients who took methylphenidate three times daily compared to those taking an extended-release product (Concerta®).[124] The investigators found better compliance in patients taking the extended-release product, less likelihood of switching medications, and a lower probability of discontinuing the medication. The use of the extended-release product was associated with a lower rate of emergency-room visits and fewer physician visits.

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

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

IX. Cost

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

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

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

Rx=prescription

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

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

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

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

X. Conclusions

The central nervous system agents that are included in this review are approved to treat attention deficit hyperactivity disorder (ADHD).[4-23] The cerebral stimulants are classified as Schedule II (amphetamines and methylphenidate derivatives) controlled substances. Atomoxetine, extended-release clonidine and extended-release guanfacine are not cerebral stimulants; therefore, they are not classified as controlled substances. There is at least one short-acting, intermediate-acting and long-acting central nervous system agent available in a generic formulation.

Guidelines recommend the use of an agent approved by the Food and Drug Administration (FDA) for the initial pharmacologic treatment of ADHD and they do not give preference to one agent over another.[3,24,25] The central nervous system agents have been shown to be effective for the treatment of ADHD in numerous clinical trials.[24,35-39,40,44,46,47,62,65-67,69,70,72-74,76-78,84,85,89,89,92-96,98-106,108-113,116] Although comparative trials have been conducted, it is difficult to interpret the results of these studies due to design flaws (small sample size, short duration, crossover design, variable outcomes, etc.).[35-39,50-56,64,98-104,107-109,116] Extended-release clonidine and extended-release guanfacine are approved for the treatment of ADHD as monotherapy and as adjunctive therapy to stimulants.[4,20,63,79,80]

There are several factors to take into consideration when selecting a pharmacologic agent for the treatment of children and adolescents with ADHD. This includes the presence of comorbid conditions, patient/family preference, storage/administration at school, history of substance abuse, drug diversion, pharmacokinetics and adverse events.[3,25,26] The advantage of a once-daily formulation is that the medication does not need to be taken during school hours, as is the case with the immediate-release formulations. Administration of medications during school hours, especially Schedule II controlled substances, can be difficult since the medication must be administered by a licensed school nurse. Atomoxetine, extended-release clonidine and extended-release guanfacine are not controlled substances, which may make it preferable to the stimulants in certain situations.

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

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

XI. Recommendations

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

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Wakefulness Promoting Agents
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I. Overview

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

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

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

The wakefulness promoting agents that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. In terms of duration of action, modafinil and armodafinil are both long-acting agents while sodium oxybate is a short-acting agent.[5-7] Modafinil is currently the only wakefulness promoting agent that is available generically. The agents in this class were last reviewed in August 2012 as part of the Cerebral Stimulants/Agents Used for Attention Deficit Hyperactivity Disorder therapeutic class review.

Table 1. Wakefulness Promoting Agents Included in this Review

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

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

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the wakefulness promoting agents are summarized in Table2.

Table 2. Treatment Guidelines Using the Wakefulness Promoting Agents

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

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

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

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

III. Indications

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

Table 3. FDA-Approved Indications for the Wakefulness Promoting Agents[4-7,9-11]

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

IV. Pharmacokinetics

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

Table 4. Pharmacokinetic Parameters of the Wakefulness Promoting Agents[4-7,9-11]

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

V. Drug Interactions

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

Table 5. Significant Drug Interactions with the Wakefulness Promoting Agents[9]

Generic Name(s)	Significance Level	Interaction	Mechanism
Armodafinil, modafinil	1	Contraceptives, oral	Armodafinil or modafinil may cause induction of gastrointestinal and hepatic metabolism of oral contraceptives. Pharmacologic effects of oral contraceptives may be decreased.

Generic Name(s)	Significance Level	Interaction	Mechanism
Sodium oxybate	1	Barbiturates	Concurrent use of sodium oxybate and barbiturates may result in an increase in sleep duration and central nervous system depression.
Sodium oxybate	1	Benzodiazepines	Concurrent use of sodium oxybate and benzodiazepines may result in an increase in sleep duration and central nervous system depression.
Sodium oxybate	1	Central nervous system depressants	Concurrent use of sodium oxybate and central nervous system depressants may result in an increase in sleep duration and central nervous system depression.
Sodium oxybate	1	Buspirone	Concurrent use of sodium oxybate and buspirone may result in an increase in sleep duration and central nervous system depression.
Sodium oxybate	1	Zolpidem	Concurrent use of sodium oxybate and zolpidem may result in an increase in sleep duration and central nervous system depression.
Armodafinil, modafinil	2	Midazolam, triazolam	Coadministration of armodafinil or modafinil may result in reduced midazolam or triazolam plasma levels.

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

VI. Adverse Drug Events

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

Table 6. Adverse Drug Events (%) Reported with the Wakefulness Promoting Agents [4-7,9-11]

Adverse Events	Armodafinil	Modafinil	Sodium Oxybate
Cardiovascular			
Angina	-	-	-
Cardiac arrhythmia	-	-	-
Chest pain	-	3	✔
Hypertension	-	3	6
Hypotension	-	-	-
Myocardial infarction	-	-	-
Palpitations	2	2	-
Pulse increase/decrease	1	-	-
Raynaud's phenomenon	-	-	-
Sudden death	-	-	-
Systolic blood pressure increased	✔	-	-
Tachycardia	-	2	<1
Vasodilation	-	2	-
Central Nervous System			
Abnormal dreams	-	-	3 to 9

Adverse Events	Armodafinil	Modafinil	Sodium Oxybate
Aggressive behavior	-	-	-
Agitation	1	1	✔
Anxiety	4	5 to 21	3 to 6
Ataxia	-	-	✔
Attention disturbance	1	-	3 to 9
Cerebral arteritis	-	-	-
Cerebral occlusion	-	-	-
Chills	-	-	✔
Confusion	-	-	3 to 6
Depression	1 to 3	2	6
Disorientation	-	-	6
Dizziness	3 to 8	5	17
Drowsiness	-	-	-
Dyskinesia	-	1	-
Emotional instability	-	-	-
Fatigue/lethargy	2	-	≤6
Fever	1	-	-
Hallucinations	-	-	-
Headache	14 to 28	34	22
Hyperkinesia	-	1	-
Hypertonia	-	1	-
Insomnia	4 to 6	3 to 21	5
Jittery feeling	-	-	-
Labile affect	-	-	-
Mania	-	✔	-
Migraine	1	-	-
Nervousness	1	7	✔
Neuroleptic malignant syndrome	-	-	-
Nightmare	-	-	3 to 6
Overstimulation	-	1	-
Paresthesia	1	2	-
Psychotic episodes	-	✔	-
Restlessness	-	-	-
Seizures	-	-	✔
Sleep disorder	-	-	3 to 6
Sleep paralysis	-	-	3 to 11
Sleep walking	-	-	6
Somnolence	-	2	8
Suicidal ideation	-	-	✔
Syncope	-	-	✔
Tic	-	-	-
Tourette's exacerbation	-	-	-
Toxic psychosis	-	-	-
Tremor	1	1	✔
Vertigo	-	1	-
Dermatological			
Alopecia	-	-	-
Application site reaction	-	-	-
Dermatitis	1	-	-
Diaphoresis	-	1	3 to 11
Erythema	-	-	-
Erythema multiforme	-	✔	-
Exfoliative dermatitis	-	-	-
Hair loss	-	-	-

Adverse Events	Armodafinil	Modafinil	Sodium Oxybate
Herpes simplex	-	1	-
Hyperhidrosis	1	-	3 to 6
Rash	1 to 4	<1	✔
Stevens-Johnson syndrome	✔	✔	-
Toxic epidermal necrolysis	-	-	-
Urticaria	-	-	-
Gastrointestinal			
Abdominal pain	2	-	3 to 11
Anorexia	1	4	-
Appetite decreased	1	-	-
Bruxism	-	-	-
Constipation	1	2	✔
Diarrhea	3 to 5	6	6 to 8
Dry mouth	2 to 7	4	-
Dyspepsia	2	5	3
Fecal incontinence	-	-	<1
Flatulence	-	1	✔
Mouth ulceration	-	1	-
Nausea	7 to 14	11	21
Stomach cramps	-	-	-
Thirst	-	1	-
Unpleasant taste	-	1	-
Vomiting	1	-	8
Weight increase	-	-	✔
Weight loss	-	-	-
Genitourinary			
Abnormal urine	-	1	-
Enuresis	-	-	3 to 17
Erectile disturbance	-	-	-
Hematuria	-	1	-
Libido decreased	-	-	✔
Polyuria	1	-	-
Pyuria	-	1	-
Urinary incontinence	-	-	7
Hematologic			
Agranulocytosis	-	✔	-
Anemia	-	-	-
Eosinophilia	-	1	-
Leukopenia	-	-	-
Pancytopenia	✔	-	-
Thrombocytopenic purpura	-	-	-
Hepatic			
Hepatic coma	-	-	-
Liver function test abnormalities	✔	2	-
Musculoskeletal			
Arthralgia	-	-	-
Back pain	-	6	-
Hypoesthesia	-	-	6
Myalgia	-	-	✔
Myasthenia	-	-	3 to 6
Weakness	-	-	6 to 8
Respiratory			
Bronchitis	-	-	✔
Cough	-	-	✔

Adverse Events	Armodafinil	Modafinil	Sodium Oxybate
Dyspnea	1	-	✔
Epistaxis	-	1	-
Lung disorder	-	2	-
Nasal congestion	-	-	-
Nasopharyngitis	-	-	8
Pharyngitis	-	4	-
Pharyngolaryngeal pain	-	-	-
Respiratory tract infection	-	-	3
Rhinitis	-	7	8
Sinusitis	-	-	-
Special Senses			
Abnormal vision	-	1	-
Accommodation difficulties	-	1	-
Amblyopia	-	1	6
Blurred vision	-	1	3
Dry eyes	-	-	-
Eye pain	-	1	-
Mydriasis	-	-	-
Tinnitus	-	-	6
Other			
Accidental injury	-	-	-
Allergic contact sensitization	-	-	✔
Anaphylaxis	✔	✔	-
Dysmenorrhea	-	-	3 to 6
Ear pain	-	-	✔
Edema	-	1	-
Flu-like syndrome	1	4	✔
Growth suppression	-	-	-
Hypersensitivity reactions	-	✔	✔
Necrotizing vasculitis	-	-	-
Pain	1	-	3
Pallor	-	-	✔
Thirst	1	-	✔
Viral infection	-	-	6

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

Table 7. Boxed Warning for Sodium Oxybate[7]

WARNING
Sodium oxybate is a gamma hydroxybutyrate, a known drug of abuse. Abuse has been associated with some important central nervous system adverse reactions, including death. Even at recommended doses, use has been associated with confusion, depression, and other neuropsychiatric reactions. Reports of respiratory depression occurred in clinical trials. Almost all of the patients who received sodium oxybate during clinical trials were receiving central nervous system stimulants. Important central nervous system adverse reactions associated with abuse of sodium oxybate include respiratory depression, seizure, and profound decreases in level of consciousness, with instances of coma and death. For reactions that occurred outside of clinical trials, in people taking sodium oxybate for recreational purposes, the circumstances surrounding the reactions often are unclear (e.g., dose of sodium oxybate taken, the nature and amount of alcohol or any concomitant drugs). Sodium oxybate is available through the Xyrem® Success Program, using a centralized pharmacy (1-866-997-3688). The Success Program provides educational materials to the prescriber and the patient explaining the

WARNING
risks and proper use of sodium oxybate and the required prescription form. Once it is documented that the patient has read and/or understands the materials, the drug will be shipped to the patient. The Xyrem® Success Program also recommends patient follow-up every three months. Health care providers are expected to report all serious adverse reactions to the manufacturer.

VII. Dosing and Administration

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

Table 8. Usual Dosing Regimens for the Wakefulness Promoting Agents[4-7,9-11]

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

VIII. Effectiveness

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

Table 9. Comparative Clinical Trials with the Wakefulness Promoting Agents

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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Armodafinil demonstrated significantly greater improvements in quality of episodic secondary memory compared to placebo at the final visit (P<0.05). Armodafinil 250 mg and the combined group demonstrated significantly greater improvement in speed of memory compared to placebo at the final visit (P<0.05). Differences in the change from baseline on the ESS were statistically significant in favor of each armodafinil group compared to placebo at weeks eight (P<0.01 for all comparisons) and 12 (P<0.01) and at the final visit (150 mg/day, -4.1; P=0.0044, 250 mg/day, -3.8; P=0.0015, and combined group, -3.9; P=0.0006). At the final visit, 21% of patients in the armodafinil 150 mg/day group (P=0.0312) and 28% of patients in the armodafinil 250 mg/day group (P=0.0023) had an ESS score <10, compared to only 7% of patients in the placebo group. Improvements in global fatigue were significantly greater with armodafinil compared to placebo at the final visit (150 mg/day, -1.5; P=0.0007; 250 mg/day, -1.3; P=0.0018; combined group, -1.4; P=0.0002; placebo, -0.3). Headache, nausea, dizziness, and decreased appetite were the most commonly reported adverse events with armodafinil.
U.S. Modafinil in Narcolepsy Group[13] (1998) Modafinil 200 to 400 mg daily vs	DB, MC, PC, RCT Adults 18 to 68 years of age diagnosed with narcolepsy	N=283 9 weeks	Primary: ESS Secondary: MSLT, MWT, CGI-C	Primary: Both modafinil treatment groups reduced mean ESS scores and subjective sleepiness at each time point (weeks three, six, and nine) compared to the placebo group (P<0.001). The two modafinil groups did not differ from each other. Secondary: Mean sleep latency for MSLT significantly increased in both modafinil groups compared to the placebo group (P<0.001). Modafinil groups did not differ from each other.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				Mean sleep latencies for MWT significantly increased in each of the modafinil groups compared to the placebo group (P<0.001). The two modafinil groups did not differ from each other. There were significantly more patients with improved CGI-C scores in each of the modafinil groups compared to the placebo group (P<0.005), but the number of patients did not differ between modafinil groups.
U.S. Modafinil in Narcolepsy Group[14] (2000) Modafinil 200 to 400 mg daily vs placebo	DB, MC, PC, RCT Adults 17 to 67 years of age diagnosed with narcolepsy	N=271 9 weeks	Primary: MWT, CGI-C Secondary: MSLT, ESS	Primary: MWT improved for both modafinil groups vs the placebo group (P<0.001) at each follow-up visit (weeks three, six, nine). The percent of patients with improvement in CGI-C scores at week nine were as follows: modafinil 200 mg, 58%; modafinil 400 mg, 61%; and placebo, 38% (P<0.03). Secondary: MSLT increased by 5.1 minutes with modafinil 400 mg vs 3.5 minutes with placebo (P<0.001). The impact of the 200 mg modafinil dose was not significant. Mean ESS scores were reduced by both treatment groups (P<0.001) vs the placebo group.
Broughton et al.[15] (1997) Modafinil 200 to 400 mg daily vs placebo	MC, PC, RCT, XO Patients 27 to 59 years of age diagnosed with narcolepsy	N=75 6 weeks	Primary: MWT results, patient assessed sleepiness Secondary: ESS	Primary: MWT (sleep latency) increased by 40% with modafinil 200 mg (P<0.002) and by 54% with modafinil 400 mg (P<0.001) compared to placebo. There was not a significant difference between modafinil groups. Both modafinil groups significantly decreased the patient assessed mean number of involuntary sleep and somnolence episodes by 24% in the 200 mg group and 26% in the 400 mg group as compared to the placebo group (P<0.013 and P<0.007). Secondary: ESS was significantly decreased in modafinil 200 mg (P<0.018) and modafinil 400 mg (P<0.0009) groups compared to the placebo group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Billiard et al.[16] (1994) Modafinil 100 mg in the morning and 200 mg at noon (or vice versa) vs placebo	DB, MC, PC, RCT, XO Patients 27 to 54 years of age diagnosed with narcolepsy	N=50 12 weeks	Primary: Results of sleep logs, CGI Secondary: MWT	Primary: In the patient sleep logs, the number of episodes of sleepiness and duration of daytime total sleep time were significantly reduced in the modafinil groups compared to the placebo group (P=0.05, P=0.0002). The CGI scores were not statistically significantly different between the modafinil group and the placebo group (P=0.19). Secondary: MWT scores were significantly improved in the modafinil group compared to the placebo group (P<0.05).
Boivin et al.[17] (1993) Modafinil 200 mg in morning and 100 mg at noon vs placebo	DB, PC, RCT, XO Patients 31 to 61 years of age with a history of EDS, cataplexy, at least two sleep onset REM periods and MSLT less than five minutes	N=10 12 weeks	Primary: Subjectively assessed sleepiness, FCRTT, PLM, nocturnal sleep organization Secondary: Not reported	Primary: Subjective sleepiness was significantly reduced in the modafinil group compared to the placebo group (P<0.05) based on home questionnaires. Modafinil significantly reduced the number of gaps and % of error at the FCRTT (P<0.05), but did not significantly reduce the mean reaction time over placebo (P=0.08). Modafinil did not statistically significantly decrease PLMs over placebo (P=0.06). Modafinil did not display negative effects on any of the nocturnal sleep parameters measured (P value not significant). Secondary: Not reported
Thorpy et al.[18] (2003) Modafinil 200 to 400 mg/day	OL, RCT Adults 17 to 65 years of age diagnosed with narcolepsy who had been receiving MPH for EDS for a	N=40 5 weeks	Primary: ESS, tolerability Secondary: Not reported	Primary: Mean ESS scores were <12 for all groups at the end of the study: 11.3 in the no-washout group, 8.2 for in the washout group, and 10.1 in the taper-down/titrate-up group. Headache was the most frequently reported adverse event during therapy, experienced by 42% of patients in the no-washout group, 36% of patients in the washout group, and 21% of patients in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	month			taper/titrate group. Secondary: Not reported
U.S. Xyrem Multicenter Study Group[19] (2004) <u>Phase One (Two weeks)</u> Continue sodium oxybate at the dose previously prescribed. <u>Phase Two (Two weeks)</u> Continue sodium oxybate treatment at previously prescribed dose vs conversion to placebo	DB treatment withdrawal study design (alternative to conventional DB, PC, RCT) Patients ≥16 years of age with narcolepsy or symptoms of narcolepsy who were previously stabilized on sodium oxybate 3 to 9 g/day	N=55 4 weeks	Primary: Cataplexy attacks, treatment-emergent adverse events Secondary: Not reported	Primary: During the two-week DB phase, the abrupt cessation of sodium oxybate therapy in the placebo study patients resulted in a significant increase in the number of cataplexy attacks (median, 21; P<0.001) compared to patients who remained on sodium oxybate (median, 0). Cataplexy attacks returned gradually with placebo study patients reporting a median of 4.2 and 11.7 cataplexy attacks during the first and second weeks, respectively. There were no symptoms of withdrawal reported by the study investigators. Secondary: Not reported
Xyrem International Study Group[20] (2005) Sodium oxybate 4.5 to 9 g/day administered at bedtime	DB, MC, PC, RCT Patients ≥16 years of age with narcolepsy or symptoms of narcolepsy	N=228 8 weeks	Primary: ESS, MWT, CGI-C Secondary: Not reported	Primary: Study patients displayed dose related decreases in median ESS scores and frequency of weekly inadvertent naps, which were significant at the 6 and 9 g doses (P<0.001 for each). Study patients treated with 9 g of sodium oxybate nightly displayed a significant median increase of >10 minutes in the MWT (P<0.001). Improvements in EDS were incremental in those study patients who

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				received concomitant stimulants alone. Significant improvements in the CGI-C were observed for each group treated with sodium oxybate (P≤0.001). The most common adverse events were mild to moderate and included nausea, dizziness, and enuresis, which seemed to be dose related. Other adverse events less common included feeling drunk, contusion, back pain, muscle cramp, somnolence, disturbance in attention, dysarthria, tremor, disorientation, sleepwalking, dyspnea, and snoring. Secondary: Not reported
Xyrem International Study Group[21] (2005) Sodium oxybate 4.5 to 9 g/day administered at bedtime vs placebo	DB, MC, PC, RCT Patients ≥16 years of age with narcolepsy or symptoms of narcolepsy	N=228 8 weeks	Primary: Narcolepsy symptoms, medication use, adverse events Secondary: Not reported	Primary: Compared to placebo, nightly doses of 4.5, 6, and 9 g of sodium oxybate for eight weeks resulted in significant decreases in weekly cataplexy attacks of 57.0 (P=0.003), 65.0 (P=0.002), and 84.7% (P<0.001), respectively. The decrease in cataplexy at the 4.5 g dose was significant compared to placebo at eight weeks of treatment (P=0.003). The reduction in the number of weekly cataplexy attacks was dependent on the length of time study patients received treatment and the amount of medication received. The weekly increase in sodium oxybate dose was associated with fewer adverse events than previously reported in double-blind sodium oxybate studies using fixed doses. The most common adverse events included nausea and dizziness, which demonstrated a clear dose–response relationship. Although greater than 5% of study patients reported emesis, this adverse event was not significantly different than placebo-treated patients. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Black et al.[22] (2010) Sodium oxybate 4.5 to 9 g/day administered at bedtime vs placebo	DB, PC, PG, RCT Patients ≥16 years of age with narcolepsy or symptoms of narcolepsy	N=228 8 weeks	Primary: Sleep architecture, narcolepsy symptoms and adverse events Secondary: Not reported	Primary: Following four (P<0.001) and eight weeks (P<0.001) of sodium oxybate treatment, study patients demonstrated significant dose-related increases in the duration of stage three and four sleep, reaching a median increase of 52.5 minutes in patients receiving 9 g nightly. Compared to placebo-treated patients, delta power was significantly increased in all treatment dose groups. Stage one sleep and the frequency of nocturnal awakenings were each significantly decreased at the 6 and 9 g/night doses. The changes in nocturnal sleep coincided with significant decreases in the severity and frequency of narcolepsy symptoms. The most common adverse events included nausea, headache, dizziness, nasopharyngitis, and enuresis with a statistical significant difference in nausea and dizziness compared to placebo. Adverse events were mild to moderate in severity and appeared to be dose-related as documented by study investigators. Secondary: Not reported
Weaver et al.[23] (2006) Sodium oxybate 4.5 to 9 g/day in two divided doses taken at bedtime and again 2.5 to 4 hours later vs placebo	DB, MC, RCT Patients 16 to 75 years of age with narcolepsy who were experiencing cataplexy and EDS with recurrent episodes for ≥3 months	N=285 4 weeks	Primary: FOSQ Secondary: Not reported	Primary: The nightly administration of sodium oxybate showed statistically significant dose-related improvements in functional status and quality of life as evidenced by the total FOSQ (P<0.001), as well as in the activity level (P<0.001), vigilance (P<0.001), general productivity (P=0.002), and social outcomes (P<0.001) subscales. Effect sizes escalated from small effects for the 6 g per day dose of sodium oxybate to large effects for the 9 g/day dose. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Wang et al.[24] (2009) Sodium oxybate	RETRO Patients receiving sodium oxybate	N=~26,000 68 months	Primary: Occurrence of abuse/misuse of sodium oxybate Secondary: Not reported	Primary: During the study period, 3,781 adverse event reports were reported to the manufacturer worldwide. Overall, there were no new significant safety findings from the postmarketing adverse event profile compared to what was reported in clinical trials described in the product prescribing information. Of those 26,000 patients, 0.2% reported ≥1 of the events studied. These included 10 cases (0.039%) meeting DSM-IV abuse criteria, four cases (0.016%) meeting DSM-IV dependence criteria, eight cases (0.031%, including three of the previous four) with withdrawal symptoms reported after discontinuation of sodium oxybate, two confirmed cases (0.008%) of sodium oxybate–facilitated sexual assault, eight cases (0.031%) of overdose with suicidal intent, 21 deaths (0.08%) in patients receiving sodium oxybate treatment with one death known to be related to sodium oxybate, and three cases (0.01%) of traffic accidents involving drivers taking sodium oxybate. During the study period, approximately 600,000 bottles of sodium oxybate were distributed, and five incidents (0.0009%) of diversion were reported. Secondary: Not reported
Black et al.[25] (2006) Sodium oxybate 6 to 9 g/day vs modafinil 200 to 600 mg/day vs	DB, MC, PC, RCT Patients ≥18 years of age with narcolepsy taking 200 to 600 mg of modafinil daily for the treatment of EDS	N=270 8 weeks	Primary: MWT Secondary: ESS, CGI-C	Primary: Following the switch from modafinil to placebo, the mean average daytime sleep latency on the MWT decreased from 9.74 minutes at baseline to 6.87 minutes after eight weeks (P<0.001). In the sodium oxybate group, there was no decrease in sleep latency, suggesting that this medication was as efficacious in treating EDS as previously administered modafinil. In the sodium oxybate plus modafinil group, there was an increase in daytime sleep latency from 10.43 to 13.15 minutes (P<0.001), suggesting that this combination of drugs produced an additive effect.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
sodium oxybate 6 to 9 g/day and modafinil 200 to 600 mg/day vs placebo				Secondary: The sodium oxybate group showed a decrease in median average EES scores, from 15 to 12 (P<0.001). The sodium oxybate plus modafinil group showed a decreased in median average EES scores from 15 to 11 (P<0.001). Treatment with sodium oxybate, alone (P=0.002) and together with modafinil (P=0.023), showed significant overall clinical improvements as compared to the placebo-treated study patients. The placebo and the modafinil-treated study patients demonstrated no significant change in symptoms.
Black et al.[26] (2009) Sodium oxybate 6 g/day vs modafinil 200 to 600 mg/day vs sodium oxybate 6 g/day and modafinil 200 to 600 mg/day vs placebo	DB, PC, RCT Patients ≥18 years of age with narcolepsy taking modafinil 200 to 600 mg/day for the treatment of EDS	N=278 8 weeks	Primary: Sleep architecture, MWT Secondary: Not reported	Primary: Following eight weeks of treatment, there was no significant change in total sleep time for any group. Significant changes in total non-REM sleep among patients receiving sodium oxybate and sodium oxybate plus modafinil included a median increase in Stage three and four sleep (43.5 and 24.25 minutes, respectively; P<0.001 for each) and delta power (P<0.001 for each) and significant decrease in the number of nocturnal awakenings in sodium oxybate (P=0.008) and sodium plus modafinil (P=0.014) treated study patients. No significant changes in PSG parameters were noted in patients treated with placebo or modafinil alone. Patients who had been randomized to placebo demonstrated a significant decrease in MWT sleep latency at eight weeks (P<0.001) once they had been switched to placebo following stable chronic modafinil treatment. A slight worsening of EDS indicated by increased ESS scores, was noted in placebo-treated patients (P=0.011) after stopping baseline modafinil, and ESS scores continued unchanged in the group that was randomized to continue modafinil treatment.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Sodium oxybate-treated patients and sodium oxybate plus modafinil-treated patients experienced significant improvements in ESS scores (P<0.001 for each). There was no change in ESS scores in the group maintained on modafinil alone. Secondary: Not reported
Obstructive Sleep Apnea				
Hirshkowitz et al.[27] (2007) Armodafinil 150 mg/day vs placebo	DB, MC, PC, RCT Patients 18 to 65 years of age with a diagnosis of OSA/hypopnea syndrome who complained of residual excessive sleepiness during CPAP therapy	N=263 12 weeks	Primary: MWT, CGI-C Secondary: CDR, ESS, BFI	Primary: Armodafinil significantly improved wakefulness compared to placebo. The mean MWT sleep latency increased from baseline by 2.3 minutes in the armodafinil group and decreased by 1.3 minutes in the placebo group (P=0.0003). Armodafinil significantly improved MWT sleep latency compared to placebo at each visit (P<0.01 for all). The proportion of patients with at least ‘‘minimal improvement’’ on the CGI-C scale was greater for armodafinil than placebo (71 vs 53%; P=0.0069). Secondary: As assessed on the CDR, armodafinil significantly improved the quality of episodic secondary memory compared to placebo. The quality of episodic secondary memory increased by 7.6 points from baseline to the final visit for patients in the armodafinil group and decreased by 7.0 points for those in the placebo group (P=0.0102). The mean change from baseline in ESS total score was significantly greater for patients receiving armodafinil than for those receiving placebo (P<0.01 for all). As assessed on the BFI, armodafinil significantly reduced global fatigue and worst fatigue in the past 24 hours at weeks four and 12 and at the final visit compared to placebo (P<0.05 for all).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Roth et al.[28] (2006) Armodafinil 150 to 250 mg/day vs placebo	DB, MC, PC, RCT Patients 18 to 65 years of age with a diagnosis of moderate OSA/ hypopnea syndrome and residual excessive sleepiness despite effective, regular, and stable use of CPAP treatment	N=395 12 weeks	Primary: MWT, CGI-C Secondary: ESS, CDR, BFI	Primary: The mean changes in MWT sleep latency across the first four tests were significantly greater in the armodafinil 150 mg/day, 250 mg/day, and combined groups compared to the placebo group at the final visit (P<0.001 for all). There was no difference between the two modafinil doses. The proportions of patients who had at least minimal improvement on the CGI-C were significantly greater in the armodafinil 150 mg/day, 250 mg/day, and combined groups compared to the placebo group (P<0.001 for all). There was no difference between the two modafinil doses. Secondary: The mean change in ESS total score was significantly greater in the armodafinil combined group compared to the placebo group at the final visit (P<0.001). Mean changes in global fatigue scores were significantly greater in the armodafinil combined group compared to the placebo group at all visits (P<0.05 for all). The mean change in score for worst fatigue during the past 24 hours was statistically greater in the armodafinil combined group compared to placebo at week eight (P<0.05). Mean changes in quality of episodic secondary memory score were significantly greater with armodafinil 150 and 250 mg/day compared to placebo at week four (both, P<0.05) and with armodafinil 250 mg/day vs placebo at week eight (P<0.01). No significant differences in speed of memory or power of attention were found between the armodafinil combined and placebo groups across the first four or last three sessions at any assessment. At weekeight8, mean changes in continuity of attention across the first four sessions were significantly greater in the armodafinil 150 mg/day,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				250 mg/day, and combined groups compared to the placebo group (P<0.05 for all). The most frequently reported adverse event was headache, occurring in 17.6% of patients in the armodafinil combined group and 8.5% of patients in the placebo group (P<0.05). The severity of adverse events was generally mild or moderate in patients receiving armodafinil (58.4%) or placebo (46.9%).
Krystal et al.[29] (2010) Armodafinil 200 mg/day vs placebo	DB, PC, PG, RCT Patients 18 to 65 years of age diagnosed with obstructive sleep apnea	N=249 18 months	Primary: CGI-C as related to sleepiness, mean change from baseline in MWT to mean sleep latency at final visit Secondary: ESS	Primary: The proportion of patients with least minimal improvement on CGI-C was significantly greater in the armodafinil group compared to the placebo group (69 vs 53%; P=0.012). Mean MWT sleep latency was increased following armodafinil (2.6 minutes) compared to placebo (1.1 minutes), but was not statistically significant (P=0.30). Secondary: Mean ESS scores were significantly reduced in study patients treated with armodafinil compared to patients treated with placebo (-6.3 vs -4.8; P=0.003). The most common adverse effects included headache, dry mouth and insomnia. Most adverse events were considered mild or moderate by the study investigator.
Black et al.[30] (2005) Modafinil 200 to 400 mg/day vs placebo	DB, MC, PC, RCT Adults 18 to 70 years of age with OSA/ hypopnea syndrome and having residual excessive sleepiness during CPAP therapy	N=305 12 weeks	Primary: MWT, ESS Secondary: CGI-C, FOSQ	Primary: Modafinil significantly improved mean sleep latency on the MWT compared to placebo (P<0.001). Modafinil significantly decreased the ESS scores compared to placebo (P<0.001). There were no significant differences in MWT or ESS scores seen between the two modafinil treatment groups (P>0.15 for each). Secondary: At the end of the study, modafinil had significant improvements in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				CGI-C compared to placebo (P<0.001). Modafinil improved mean FOSQ scores compared to placebo (P<0.02) for vigilance, general productivity, and activity level.
Weaver et al.[31] (2009) Modafinil 200 to 400 mg/day vs placebo	2 DB, MC, PC, RCT (Pooled analysis) Patients 24 to 76 years of age diagnosed with OSA and residual excessive sleepiness associated with CPAP	N=480 4 to 12 weeks	Primary: FOSQ Secondary: Not reported	Primary: After treatment with modafinil, there were greater improvements from baseline in the total FOSQ score (P<0.0001) as well as activity level (P=0.002), productivity level (P=0.007), intimacy and sexual relationships (P=0.01) and vigilance (P<0.001) compared to treatment with placebo. A greater proportion of patients who received modafinil were considered responders compared to patients who received placebo (45 vs 25%; P<0.001). Analysis based on the individual FOSQ questions demonstrated that 18 of the 30 questions increased at least one point for significantly more patients who received modafinil (P<0.05). Secondary: Not reported
Williams et al.[32] (2010) Modafinil 200 mg/day vs placebo	DB, RCT, XO Men diagnosed with OSA who were modafinil-naïve	N=21 2 days	Primary: Driving simulation, subjective sleepiness Secondary: Not reported	Primary: During CPAP withdrawal, severe sleep-disordered breathing was evident and administration of modafinil improved simulated driving performance (steering variability; P<0.0001, mean reaction time; P<0.0002, lapses on a current task; P<0.01), psychomotor vigilance task (mean one/reaction time and lapses, both P<0.0002), and subjective sleepiness (P<0.01). Secondary: Not reported
Shift Work Sleep Disorder				
Czeisler et al.[33] (2009) Armodafinil 150 mg daily	DB, MC, PC, RCT Patients 18 to 65 years of age who exhibited signs and	N=254 12 weeks	Primary: MSLT, CGI-C Secondary: KSS, CDR	Primary: Armodafinil improved mean nighttime sleep latency (2 to 8 AM) by 3.1 to 5.3 minutes compared to an increase of 0.4 to 2.8 minutes at in patients receiving placebo at the final visit (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
administered 30 to 60 minutes before the start of work shift vs placebo	symptoms of SWD of moderate or greater severity, as documented by a CGI-S rating of four or higher for sleepiness on work nights, including the commute to and from work			Of the patients who received armodafinil, 79% were rated as improved in the CGI-C ratings compared to 59% of the patients who received placebo at the final visit (P=0.001). Secondary: Patient-reported levels of sleepiness during the night shift on the KSS were reduced with armodafinil compared to placebo at all visits. Armodafinil improved most items assessed in the electronic diaries, including the maximum level of sleepiness during the night shift and commute home, and mean number of mistakes, accidents, or near misses compared to placebo. Armodafinil significantly improved the mean score for the quality of episodic secondary memory factor compared to placebo at each visit (P<0.001 at weeks four and eight; P=0.002 at week 12; P<0.001 at final visit) and during the first four tests on the final night shift (P=0.002 at 12:30 AM; P<0.001 at 2:30 AM; P=0.02 at 4:30 AM; P=0.006 at 6:30 AM). Armodafinil significantly improved speed of memory from baseline compared to placebo at week eight (armodafinil, -240.9 milliseconds; placebo, -6.5 milliseconds; P=0.02) and week 12 (armodafinil, -307.7 milliseconds; placebo, -115.2 milliseconds; P=0.01). However, this was not significant at the final visit (armodafinil, -257.2 milliseconds; placebo. -140.4 milliseconds; P=0.09). Armodafinil significantly improved mean power of attention at each study visit (P=0.005 at week four; P=0.006 at week eight; P=0.005 at week 12; P=0.001 at final visit) and during the first four tests on the final night shift compared to placebo (P=0.002 at 12:30 AM; P=0.006 at 2:30 AM; P=0.004 at 4:30 AM; P=0.03 at 6:30 AM). Continuity of attention improved at the final visit in patients who received armodafinil compared to those who received placebo (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Adverse events included headache, nausea, nasopharyngitis and anxiety. Most adverse events were considered mild or moderate by the investigator.
Tembe et al.[34] (2011) Armodafinil 150 mg administered one hour prior to night shift vs modafinil 200 mg administered one hour prior to night shift	DB, MC, RCT Patients 18 to 60 years of age suffering from excessive sleepiness associated with SWD	N=211 12 weeks	Primary: Proportion of patients showing ≥2 grades of improvement (responder) based on SSS in both groups Secondary: Improvement in mean SSS grades, compliance, patients' as well as physicians' global assessment for efficacy and safety	Primary: Responder rates with armodafinil (72.12%) and modafinil (74.29%) were comparable (P=0.76). Secondary: Armodafinil and modafinil significantly improved mean sleepiness grades as compared to baseline (P<0.0001). At the end of therapy, compliance in both modafinil group (99.31%) and armodafinil group (99.13%) was found to be comparable (P=0.63). Both physicians' and patients' assessment of efficacy was comparable among the treatment groups. Adverse events were similar with modafinil (40.57%) and armodafinil (42.87%; P=0.78). The most commonly treatment-emergent adverse events reported were mild to moderate in severity and included headache, nausea, and dry mouth.
Erman et al (abstract)[35] (2012) Armodafinil 150 mg administered one hour prior to night shift vs placebo	DB, MC, PC, PG, RCT Patients 18 to 65 years of age suffering from excessive sleepiness associated with SWD	N=383 6 weeks	Primary: SDS-M and FOSQ-10 Secondary: Not reported	Primary: Patients treated with armodafinil experienced significantly greater improvements in SDS-M composite scores at final visit compared to patients treated with placebo (-6.8 vs -4.5, respectively; P=0.0027). Patients in the armodafinil treatment group demonstrated a greater improvement in total FOSQ-10 score from baseline to six weeks compared to placebo (3.6 vs 2.7; P=0.0351); however, there was no difference between treatments at the final visit (3.4 vs 2.7; P=0.0775). Secondary: Not reported
Erman et al[36] (2011) Armodafinil 150	DB, MC, PC, RCT Patients 18 to 65 years of age	N=383 6 weeks	Primary: CGI-C Secondary:	Primary: Significantly more patients treated with armodafinil experienced an improvement in CGI-C compared to placebo at three weeks (78 vs 51%; P<0.0001) and at six weeks (80 vs 56%; P<0.0001). Similarly,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg administered one hour prior to night shift vs placebo	suffering from excessive sleepiness associated with SWD		GAF and KSS	more patients treated with armodafinil experienced an improvement in late-in-shift CGI-C at the final visit compared to placebo (77 vs 57%; P<0.0001). At the final visit, most patients in the armodafinil group were categorized as 'much improved' (33%) or 'very much improved' (24%) on the late-in-shift CGI-C rating scale. For patients treated with placebo, 38% had 'no change' in their condition compared to only 19% of patients in the armodafinil group. Secondary: The mean (±SD) improvement from baseline in GAF score at the final visit was significantly greater in the armodafinil group compared to the placebo group (9.4 vs 5.0; P<0.0001). Improvements in GAF scores were also significantly greater for armodafinil-treated patients at three weeks (6.9 vs 3.7; P<0.0001) and six weeks (9.8 vs 4.9; P<0.0001) compared to patients treated with placebo. A higher proportion of patients treated with armodafinil had GAF scores greater than 70 ("normal function") at each visit, with almost twice as many patients receiving armodafinil reaching GAF scores greater than 70 at final visit compared to placebo (51 vs 28%; P value not reported). The improvements in KSS scores from baseline to the final visit were significantly greater for armodafinil-treated patients compared to patients receiving placebo (-2.8 vs -1.8; P<0.0001). The KSS scores were also significantly improved in the armodafinil group compared to the placebo group at three weeks (-2.6 vs -1.6; P<0.0001) and six weeks (-2.9 vs -1.8; P<0.0001).
Czeisler et al.[37] (2005) Modafinil 200 mg daily administered 30 to 60 minutes before the start of work shift	DB, MC, PC, RCT Adults 18 to 60 years of age diagnosed with SWD and worked each month at least five night shifts for ≤12 hours,	N=204 3 months	Primary: MSLT, CGI-C, Psychomotor Vigilance Test Secondary: Not reported	Primary: The modafinil group produced a significant increase in overall mean MSLT from 2.1 minutes at baseline to 3.8 minutes at endpoint compared to the placebo change of 2.04 to 2.37 minutes (P=0.002). The modafinil group significantly improved the CGI-C test scores with 74% of the patients rated as at least minimally improved compared to 36% in the placebo group (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	with ≥6 hours or worked between 10 PM and 8 AM and at least three shifts occurring consecutively			The modafinil group produced a significant decrease in mean number of lapses of attention during the Psychomotor Vigilance Test from baseline vs the placebo group (P=0.005). Secondary: Not reported
Miscellaneous				
Black et al.[38] (2010) Armodafinil 100 to 250 mg/day (OSA) or 100 to 250 mg/night 30 minutes to one hour before night shift but no later than 23:00 (SWD)	DB, MC, OL Men and women 18 to 65 years of age with a diagnosis of OSA, SWD, or narcolepsy	N=743 ≥12 months	Primary: Tolerability and efficacy (CGI-C, ESS, BFI) Secondary: Not reported	Primary: Discontinuations due to adverse events occurred in 13% of study patients during the initial study period. Most adverse events were mild to moderate in severity and included headache (25%), nasopharyngitis (17%), and insomnia (14%). Small increases were observed in BP (3.6/2.3 mm Hg), HR (6.7 beats per minute) across all study patient groups with most of the changes occurring by month three. Greater improvement, compared to baseline, on the CGI-C was reported in the three study groups (75 to 92%) at the final visit with the SWD group reporting the greatest improvement. Study patients reported significant improvement at the final visit by 65% with treated OSA (95% CI, 60.2 to 68.9), 88% with SWD (95% CI, 81.3 to 93.9), and 62% with narcolepsy (95% CI, 54.2 to 69.8). Armodafinil improved wakefulness, measured by the ESS, in the treated OSA and narcolepsy groups, at all follow-up visits compared to baseline. The level of fatigue and its impact on daily activities was consistently reduced from baseline, at all visits, in each of the study groups, measured by BFI scores. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Schwartz et al.[39] (2010) Armodafinil 100 to 250 mg/day (OSA and narcolepsy) or 100 to 250 mg/day 30 minutes to one hour before the start of night shift but no later than 23:00 (SWD)	MC, OL Patients 18 to 65 years of age who had a complaint of excessive sleepiness associated with OSA, SWD, or narcolepsy	N=328 12 months	Primary: CGI, ESS, adverse events Secondary: Not reported	Primary: At the final visit, 80% (95% CI, 74.1 to 86.7) of patients with OSA and 84% (95% CI, 72.7 to 94.8) of patients with narcolepsy were rated with the CGI-I scale as at least minimally improved with regard to overall clinical condition. Armodafinil improved EES scores in study patients treated with OSA (-7.3; 95% CI, -8.39 to -6.30) and narcolepsy (-4.7; 95% CI, -7.41 to -1.93). A total of 98% (95% CI, 95.2 to 100.0) of patients with SWD were rated as improved with regard to sleepiness during night shifts, including the commute to and from work. Across the diagnosis groups, the most commonly occurring adverse event was headache (14 to 24%). The adverse event was mild to moderate in severity as noted by the study investigators. Secondary: Not reported
Jean-Pierre et al.[40] (2010) Modafinil 200 mg/day vs placebo	DB, MC, PC, RCT Patients ≥18 years of age diagnosed with cancer with a survival expectancy >6 months	N=877 4.5 years	Primary: BFI question 3, ESS, POMS-DD Secondary: Not reported	Primary: Patients with severe fatigue at baseline benefited from modafinil (P=0.033) whereas patients with mild (P=0.09) to moderate (P=0.41) fatigue did not benefit from modafinil as compared to placebo. Daytime sleepiness improved significantly in the modafinil group (P=0.002). Modafinil had no statistically significant effect on depression (P>0.05). Secondary: Not reported
Orlikowski et al.[41] (2009) Modafinil 300	DB, MC, PC, RCT Patients ≥18 years of age diagnosed	N=28 2.5 years	Primary: MWT Secondary:	Primary: At four weeks, the mean MWT score was 16.4 minutes in the modafinil group and 15.8 minutes in the placebo group (P=0.71).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/day vs placebo	with myotonic muscular dystrophy type one experiencing hypersomnia		MSLT, ESS, global assessment (patient and physician), HAMD, SF-36	Secondary: There were no significant differences between the treatment groups in MSLT latency, ESS or treatment efficacy scores. There were no significant differences between the groups in disturbances of personality and mood or quality-of-life. A total of eight patients reported at least one adverse event, including digestive, neurologic and skin symptoms. The adverse events were considered mild or moderate by the study investigator.

Study abbreviations: DB=double blind, CI=confidence interval, MC=multi-center, OL=open-label, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial, RETRO=retrospective, SD=standard deviation, XO=crossover design
Other abbreviations: BFI=Brief Fatigue Inventory, CDR=Cognitive Drug Research, CGI-C=clinical global impression of change, CGI-S=clinical global impression of severity, CPAP=continuous positive airway pressure, DSM-IV=Diagnostic and Statistical Manual of Mental Disorders Fourth Edition, EDS=excessive daytime sleepiness, ESS=Epworth sleep scale, FCRTT=four-choice reaction time test, FOSQ=Functional outcomes of sleep questionnaire, GAF=Global Assessment of Functioning, $HAMD_{17}$=Hamilton 17-item Depression Rating scale, KSS=Karolinska Sleepiness Scale, MPH=methylphenidate, MSLT=multiple sleep latency test, MWT=maintenance of wakefulness test, OSA=obstructive sleep apnea, PLM=periodic leg movements, POMS-DD=depression-dejection subscale of profile of mood states, PSG=Polysomnogram, REM=rapid eye movement, SDS-M=modified Sheehan Disability Scale, SF-36=36-item Short Form Health Survey, SSS=Stanford sleepiness score, SWD=shift work disorder

Additional Evidence

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

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

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

IX. Cost

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

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

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

Rx=prescription

Table 10. Relative Cost of the Wakefulness Promoting Agents

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

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

X. Conclusions

The central nervous system agents that are included in this review are approved to improve wakefulness in patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnea and shift work sleep disorder.[5-7,9-11] Armodafinil and modafinil are Schedule IV controlled substances. Sodium oxybate is a central nervous system depressant and is classified as a Schedule III controlled substance. Armodafinil and modafinil are long-acting agents while sodium oxybate is a short-acting agent. Modafinil is currently the only generically available wakefulness promoting agent.

The American Academy of Sleep Medicine guidelines for the treatment of narcolepsy state that amphetamines, methylphenidate, modafinil and sodium oxybate are all effective for the treatment of narcolepsy.[1] Modafinil is also recommended as one of several initial treatment options for individuals with excessive sleepiness due to obstructive sleep apnea and shift work sleep disorder.[3,4] Armodafinil was approved by the Food and Drug

Administration in June 2007 and is not addressed in the available guidelines. Armodafinil, modafinil and sodium oxybate have been shown to be more effective than placebo in patients with narcolepsy, obstructive sleep apnea and shift work sleep disorder[12-22,25-33,37]

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

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

XI. Recommendations

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

XII. References

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Anxiolytics, Sedatives and Hypnotics – Barbiturates
AHFS Class 282404
May 14, 2014

I. Overview

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

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

The barbiturates that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Phenobarbital is available in a generic formulation. This class was last reviewed in August 2012.

Table 1. Barbiturates Included in this Review

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

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

II. Evidence-Based Medicine and Current Treatment Guidelines

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

Table 2. Treatment Guidelines Using the Barbiturates

Clinical Guideline	Recommendation(s)

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

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

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

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

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

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

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

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

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

*Agent not available in the United States.

III. Indications

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

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

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

†Oral formulation.
§Parenteral formulation.

IV. Pharmacokinetics

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

Table 4. Pharmacokinetic Parameters of the Barbiturates[1-7]

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

V. Drug Interactions

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

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

Generic Name(s)	Significance Level	Interaction	Mechanism
Barbiturates (amobarbital, butabarbital, phenobarbital, secobarbital)	1	Anticoagulants	Barbiturates reduce the effects of anticoagulants through increased metabolic clearance of anticoagulants, probably caused by induction of hepatic microsomal enzymes.
Barbiturates (amobarbital, butabarbital,	1	Estrogens	Induction of hepatic microsomal enzymes by barbiturates increases elimination of estrogenic substances, decreasing plasma

Generic Name(s)	Significance Level	Interaction	Mechanism
phenobarbital, secobarbital)			concentrations. Oral contraceptive-induced water retention may exacerbate seizures. Contraceptive failure has been reported.
Barbiturates (amobarbital, butabarbital, phenobarbital, secobarbital)	1	Hormonal contraceptives	Barbiturate induction of contraceptive-steroid hepatic metabolism and sex hormone-binding globulin synthesis combine to reduce effective concentrations of oral contraceptives and loss of oral contraceptive efficacy, possibly leading to unintended pregnancy.
Barbiturates (amobarbital, butabarbital, phenobarbital, secobarbital)	1	Dienogest	Barbiturates may increase hepatic metabolism and decrease the pharmacologic effects of dienogest. Menstrual irregularities (spotting, breakthrough bleeding, and amenorrhea) and pregnancy may occur.
Barbiturates (amobarbital, butabarbital, phenobarbital, secobarbital)	1	Sodium oxybate	Concurrent use of sodium oxybate and barbiturates may result in an increase in sleep duration and central nervous system depression.
Barbiturates (butabarbital)	1	Disulfiram	Coadministration of butabarbital and disulfiram may produce acute and severe alcohol intolerance. Induction of P-glycoprotein and CYP3A4 by phenobarbital may increase the metabolic elimination of direct factor Xa inhibitors.
Barbiturates (phenobarbital)	1	Direct factor Xa inhibitors	Plasma concentrations and pharmacologic effects of direct factor Xa inhibitors may be decreased by phenobarbital.
Barbiturates (phenobarbital)	1	Hepatitis C virus protease inhibitors	Plasma concentrations and pharmacologic effects of hepatitis C virus protease inhibitors may be decreased by phenobarbital. Induction of CYP3A4 by phenobarbital may increase the metabolic elimination of hepatitis C virus protease inhibitors.
Barbiturates (phenobarbital)	1	Brentuximab	Plasma concentrations and pharmacologic effects of brentuximab may be decreased by phenobarbital. Induction of CYP3A4 by phenobarbital may decrease the plasma concentrations of monomethyl auristatin E, the microtubule disrupting agent in brentuximab.
Barbiturates (phenobarbital)	1	Crizotinib	Plasma concentrations and pharmacologic effects of crizotinib may be decreased by phenobarbital. Induction of CYP3A4 by phenobarbital may increase the metabolic elimination of crizotinib.
Barbiturates (phenobarbital)	1	Lurasidone	Plasma concentrations and pharmacologic effects of lurasidone may be decreased by phenobarbital. Induction of CYP3A4 by phenobarbital may increase the metabolic elimination of lurasidone.
Barbiturates (phenobarbital)	1	Praziquantel	Praziquantel plasma concentrations may be decreased by phenobarbital. The antiparasitic effect of praziquantel may be decreased.

Generic Name(s)	Significance Level	Interaction	Mechanism
			Induction of cytochrome P450 3A4 isoenzymes by phenobarbital may increase the metabolic elimination of praziquantel.
Barbiturates (phenobarbital)	1	Ranolazine	Pharmacologic effects and plasma concentrations of ranolazine may be decreased by phenobarbital. Induction of cytochrome P450 3A4 isoenzymes by phenobarbital may increase the metabolic elimination of ranolazine.
Barbiturates (phenobarbital)	1	Rilpivirine	Plasma concentrations and pharmacologic effects of rilpivirine may be reduced by phenobarbital possibly resulting in loss of virologic response or resistance. Induction of cytochrome P450 3A4 isoenzymes by phenobarbital may increase the metabolic elimination of rilpivirine.
Barbiturates (phenobarbital)	1	Voriconazole	Plasma concentrations and pharmacologic effects of Voriconazole may be decreased by phenobarbital. Induction of cytochrome P450 3A4 isoenzymes by phenobarbital may increase the metabolic elimination of voriconazole.
Barbiturates (amobarbital, butabarbital, phenobarbital, secobarbital)	2	Corticosteroids	Decreased pharmacologic effects of the corticosteroid may be observed, with possible exacerbation of the disease being treated, due to stimulation of corticosteroid metabolism secondary to barbiturate induction of liver enzymes.
Barbiturates (amobarbital, butabarbital, phenobarbital, secobarbital)	2	Cabazitaxel	Plasma concentrations and pharmacologic effects cabazitaxel may be decreased by barbiturates.
Barbiturates (amobarbital, butabarbital, phenobarbital, secobarbital)	2	Clozapine	Clozapine plasma concentrations may be reduced, possibly through induction of hepatic metabolism of clozapine, decreasing the pharmacologic effects.
Barbiturates (amobarbital, butabarbital, phenobarbital, secobarbital)	2	Doxycycline	Barbiturates may increase the hepatic metabolism of doxycycline via stimulation of microsomal enzymes. The coadministration of a barbiturate with doxycycline may decrease the half-life and serum levels of doxycycline, possibly resulting in a decreased therapeutic effect.
Barbiturates (amobarbital, butabarbital, phenobarbital, secobarbital)	2	Estradiol valerate	Plasma concentrations and pharmacologic effects of estradiol valerate may be decreased by barbiturates. Induction of CYP3A4 isoenzymes by barbiturates may increase the metabolic elimination of estradiol valerate.
Barbiturates (amobarbital, butabarbital, phenobarbital, secobarbital)	2	Methoxyflurane	Barbiturates appear to stimulate degradation of methoxyflurane, perhaps to nephrotoxic metabolites. Enhanced renal toxicity may occur.

Generic Name(s)	Significance Level	Interaction	Mechanism
Barbiturates (amobarbital, butabarbital, phenobarbital, secobarbital)	2	Metronidazole	Barbiturate induction of metronidazole metabolism resulting in more rapid elimination and lower serum concentrations may cause therapeutic failure of metronidazole.
Barbiturates (amobarbital, butabarbital, phenobarbital, secobarbital)	2	Quinidine	Barbiturates appear to produce decreased quinidine serum concentrations and a decreased quinidine elimination half-life, possibly because of an increased metabolic clearance of quinidine.
Barbiturates (amobarbital, butabarbital, phenobarbital, secobarbital)	2	Tacrolimus	Plasma concentrations and pharmacologic effects of tacrolimus may be decreased, due to increased hepatic metabolism of tacrolimus via CYP3A4.
Barbiturates (amobarbital, butabarbital, phenobarbital, secobarbital)	2	Theophylline	Decreased theophylline levels may possibly result in reduced therapeutic effects. Barbiturates may induce cytochrome P450, stimulating theophylline metabolism and increasing clearance.
Barbiturates (amobarbital, butabarbital, phenobarbital, secobarbital)	2	Ulipristal	Plasma concentrations and pharmacologic effects of ulipristal may be decreased by barbiturates. Coadministration of butabarbital with ulipristal may reduce the efficacy of ulipristal.
Barbiturates (butabarbital)	2	Cephalosporins	The combination of butabarbital and cephalosporins may produce acute alcohol intolerance.
Barbiturates (butabarbital)	2	Furazolidone	The combination of butabarbital and furazolidone may produce acute alcohol intolerance.
Barbiturates (phenobarbital)	2	Aromatase inhibitors	Plasma concentrations and pharmacologic effects of aromatase inhibitors may be decreased by phenobarbital. Induction of cytochrome P450 3A4 isoenzymes by phenobarbital may increase the metabolic elimination of aromatase inhibitors.
Barbiturates (phenobarbital)	2	Epothilones	The pharmacologic effects of epothilones may be decreased by strong CYP3A4 inducers, such as phenobarbital. Induction of cytochrome P450 3A4 isoenzymes by phenobarbital may increase the metabolic elimination of epothilones.
Barbiturates (phenobarbital)	2	Human immunodeficiency virus protease inhibitors	Plasma concentrations and pharmacologic effects of human immunodeficiency virus protease inhibitors may be decreased by phenobarbital. Induction of CYP3A4 isoenzymes by barbiturates may increase the metabolic elimination of human immunodeficiency virus protease inhibitors.
Barbiturates (phenobarbital)	2	Mammalian target of rapamycin inhibitors	Induction of CYP34A isoenzymes by phenobarbital may increase the metabolic elimination and decrease pharmacological of mammalian target of rapamycin inhibitors.
Barbiturates (phenobarbital)	2	Non-nucleoside reverse	Induction of CYP34A isoenzymes by phenobarbital may increase the metabolic

Generic Name(s)	Significance Level	Interaction	Mechanism
		transcriptase inhibitors	elimination and decrease pharmacological of non-nucleoside reverse transcriptase inhibitors.
Barbiturates (phenobarbital)	2	Tyrosine kinase receptor inhibitors	Induction of CYP34A isoenzymes by phenobarbital may increase the metabolic elimination of tyrosine kinase receptor inhibitors. Concomitant use is not recommended.
Barbiturates (phenobarbital)	2	Vasopressin receptor antagonists	Plasma concentrations and pharmacologic effects of vasopressin receptor antagonists may be decreased by phenobarbital. Induction of CYP3A4 isoenzymes by barbiturates may increase the metabolic elimination of vasopressin receptor antagonists.
Barbiturates (phenobarbital)	2	Deferasirox	Plasma concentrations and pharmacologic effects of deferasirox may be decreased by phenobarbital. Induction of UDP-glucuronosyltransferase by phenobarbital may increase the metabolic elimination of deferasirox.
Barbiturates (phenobarbital)	2	Dronedarone	Plasma concentrations and pharmacologic effects of dronedarone may be decreased by phenobarbital. Induction of cytochrome P450 3A4 isoenzymes by phenobarbital may increase the metabolic elimination of dronedarone.
Barbiturates (phenobarbital)	2	Erlotinib	Plasma concentrations of Erlotinib may be decreased by coadministration of phenobarbital. The potential for reduced therapeutic effects of erlotinib should be considered. Induction of cytochrome P450 3A4 isoenzymes by phenobarbital may increase the metabolic elimination of erlotinib.
Barbiturates (phenobarbital)	2	Imatinib	Plasma concentrations and pharmacologic effects of imatinib may be decreased by phenobarbital. Induction of CYP3A4 isoenzymes by barbiturates may increase the metabolic elimination of imatinib.
Barbiturates (phenobarbital)	2	Ivacaftor	Plasma concentrations and pharmacologic effects of ivacaftor may be decreased by phenobarbital. Induction of CYP3A4 isoenzymes by barbiturates may increase the metabolic elimination of ivacaftor.
Barbiturates (phenobarbital)	2	Maraviroc	Induction of CYP3A4 isoenzymes by long-acting barbiturates may increase the metabolic elimination of maraviroc and decrease its pharmacologic effects.
Barbiturates (phenobarbital)	2	Mifepristone	Plasma concentrations and pharmacologic effects of mifepristone may be decreased by phenobarbital. Induction of CYP3A4 isoenzymes by barbiturates may increase the metabolic elimination of mifepristone.
Barbiturates (phenobarbital)	2	Roflumilast	Plasma concentrations and pharmacologic effects of roflumilast may be decreased by

Generic Name(s)	Significance Level	Interaction	Mechanism
			phenobarbital. Induction of CYP3A4 isoenzymes by barbiturates may increase the metabolic elimination of roflumilast.
Barbiturates (phenobarbital)	2	Ticagrelor	Plasma concentrations and pharmacologic effects of ticagrelor may be decreased by phenobarbital. Induction of CYP3A4 isoenzymes by barbiturates may increase the metabolic elimination of ticagrelor.
Barbiturates (phenobarbital)	2	Valproic acid	Valproic acid may decrease the hepatic metabolism of barbiturates. Plasma barbiturate concentrations may be elevated, increasing the pharmacologic and adverse effects.
Barbiturates (phenobarbital)	2	Vandetanib	Plasma concentrations and pharmacologic effects of vandetanib may be decreased by phenobarbital. Induction of CYP3A4 isoenzymes by barbiturates may increase the metabolic elimination of vandetanib.

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

VI. Adverse Drug Events

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

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

Adverse Events	Amobarbital	Butabarbital	Phenobarbital	Secobarbital
Cardiovascular				
Bradycardia	✔	✔	✔	-
Hypotension	✔	✔	✔	✔
Syncope	✔	✔	✔	-
Central Nervous System				
Abnormal thinking	✔	✔	-	-
Agitation	✔	✔	✔	-
Anxiety	✔	✔	✔	-
Ataxia	✔	✔	✔	-
Confusion	✔	✔	✔	✔
Central nervous system depression	✔	-	✔	✔
Central nervous system excitation	-	-	✔	-
Complex sleep-related activities	-	<1	-	✔
Depression	-	✔	-	✔
Dizziness	✔	✔	✔	✔
Drowsiness	-	-	✔	✔
Excitement	-	-	-	✔
Faint feeling	-	-	-	✔
Fever	✔	✔	-	✔
Hallucinations	✔	✔	✔	✔
Hangover effect	-	-	✔	✔
Headache	✔	✔	✔	✔
Hyperkinesia	✔	✔	✔	-
Impaired judgment	-	-	✔	-
Insomnia	✔	✔	✔	✔
Lethargy	-	-	✔	-
Lightheadedness	-	-	-	✔

Adverse Events	Amobarbital	Butabarbital	Phenobarbital	Secobarbital
Nervousness	✔	✔	✔	✔
Nightmares	✔	✔	✔	✔
Psychiatric disturbances	✔	✔	-	-
Somnolence	✔	1 to 3	✔	-
Dermatological				
Exfoliative dermatitis	-	✔	✔	✔
Injection site reaction	✔	-	-	-
Rash	-	✔	✔	✔
Stevens-Johnson syndrome	-	✔	✔	✔
Urticaria	-	-	-	✔
Gastrointestinal				
Constipation	✔	✔	✔	✔
Nausea	✔	✔	✔	✔
Vomiting	✔	✔	✔	✔
Hematologic				
Agranulocytosis	-	✔	✔	✔
Megaloblastic anemia	✔	✔	✔	✔
Thrombocytopenia	-	✔	✔	✔
Thrombophlebitis	-	✔	✔	✔
Respiratory				
Apnea	✔	✔	✔	✔
Atelectasis	✔	-	-	-
Hypoventilation	✔	✔	✔	-
Laryngospasm	-	-	✔	✔
Respiratory depression	-	✔	✔	✔
Other				
Anaphylaxis	-	✔	-	✔
Angioedema	✔	✔	-	✔
Dependence	-	✔	-	-
Gangrene	-	-	✔	-
Hypersensitivity reaction	✔	✔	-	-
Liver damage	✔	✔	-	-
Oliguria	-	-	✔	-
Pain at injection site	-	-	✔	✔

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

VII. Dosing and Administration

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

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

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Amobarbital	Preanesthetic: Injection: 65 to 500 mg administered intramuscularly or intravenously two to three times daily Hypnotic (short-term treatment of insomnia): Injection: 65 to 200 mg administered intramuscularly or intravenously at bedtime	Preanesthetic: Injection: 65 to 500 mg administered intravenously Hypnotic (short-term treatment of insomnia): Injection: six to 12 years of age, 65 to 500 mg administered intravenously Sedative (sedation):	Injection: 500 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Sedative (sedation): Injection: 30 to 50 mg administered intramuscularly or intravenously two to three times daily	Injection: six years of age and older, 30 to 50 mg administered intramuscularly or intravenously two to three times daily	
Butabarbital	Hypnotic (short-term treatment of insomnia): Elixir, tablet: 50 to 100 mg at bedtime Sedative (sedation): Elixir, tablet: 15 to 30 mg administered three to four times daily	Safety and efficacy in children have not been established.	Elixir: 30 mg/5 mL Tablet: 30 mg 50 mg
Phenobarbital	Acute convulsions: Injection: 20 to 320 mg intramuscularly or intravenously, repeated in six hours as necessary, maximum 600 mg/24 hours Anticonvulsant: Elixir: 60 to 200 mg/day Tablet: 50 to 100 mg two or three times daily Hypnotic (short-term treatment of insomnia): Elixir: 100 to 200 mg/day at bedtime, up to maximum 400 mg in 24 hours Injection, tablet: 100 to 320 mg at bedtime, up to maximum 600 mg in 24 hours for injection and 400 mg in 24 hours for tablet Preanesthetic: Injection: 100 to 200 mg intramuscularly 60 to 90 minutes before surgery Sedative (sedation): Elixir, tablet: 30 to120 mg/day in two to three divided doses, up to maximum 400 mg in 24 hours Injection: 30 to 120 mg/day in two to three divided doses intramuscularly or intravenously	Anticonvulsant: Elixir: 3 to 6 mg/kg/day Injection: 4 to 6 mg/kg/day for seven to 10 days to blood level of 10 to 15 µg/mL or 10 to 15 mg/kg/day intramuscularly or intravenously Tablet: 15 to 50 mg two or three times daily Preanesthetic: Injection: 1 to 3 mg/kg intramuscularly or intravenously 60 to 90 minutes prior to procedure Sedative (sedation): Tablet: 6 mg/kg/day in three divided doses Status epilepticus: Injection: 15 to 20 mg/kg intravenously over 10 to 15 minutes	Elixir: 20 mg/5 mL Injection: 65 mg/mL 130 mg/mL Tablet: 15 mg 16.2 mg 30 mg 32.4 mg 60 mg 64.8 mg 97.2 mg 100 mg
Secobarbital	Hypnotic (short-term treatment of insomnia): Capsule: 100 mg at bedtime Preanesthetic: Capsule: 200 to 300 mg one to two hours before surgery	Preanesthetic: Capsule: 2 to 6 mg/kg one to two hours before surgery, maximum dose of 100 mg	Capsule: 100 mg

VIII. Effectiveness

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

Table 8. Comparative Clinical Trials with the Barbiturates

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

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

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

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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Treiman et al.[26] (1998) Phenobarbital 15 mg/kg vs diazepam 0.15 mg/kg, followed by phenytoin 18 mg/kg vs lorazepam 0.1 mg/kg vs phenytoin 18 mg/kg	DB, MC, RCT Adults with overt or subtle generalized convulsive status epilepticus	N=518 5 years	Primary: Success (defined as cessation of all motor and electrical seizure activity within 20 minutes of start of drug infusion and no recurrence of seizure activity within the next 40 minutes), side effects, outcomes 30 days posttreatment Secondary: Not reported	Primary: For treatment success in overt status epilepticus, a significant difference overall in the frequency of success was found, reported as: lorazepam, 64.9%; phenobarbital, 58.2%; diazepam/phenytoin, 55.8%; and phenytoin, 43.6% (P<0.02 between all groups). For subtle status epilepticus, no significant differences were seen between treatment groups (P<0.18). Lorazepam showed significantly higher frequency of treatment success compared to phenytoin in a pairwise comparison of patients with overt status epilepticus (P<0.002). Pairwise comparisons among other individual treatments showed no significant differences. There were no significant differences among any of the treatment groups with respect to adverse effects or 30-day posttreatment outcomes. Secondary: Not reported
Miscellaneous				
Gerhardt et al.[27] (2011) Secobarbital 100 mg for one to two doses post-discharge vs placebo	DB, PC, RCT Patients 18 to 65 years of age who presented to the emergency department with a migraine (with or without aura); patients underwent standard treatment	N=50 1 day	Primary: Change in perceived headache pain using a 100 mm visual analog scale Secondary: Difference in self-reported headache resolution rate	Primary: The average change in reported headache pain for the placebo group was an increase of 3 mm (95% CI, −13 to 19 mm) at 24 hours after emergency department discharge. In the secobarbital group, the average change in reported headache pain was a decrease of 25 mm (95% CI, −13 to −38; P=0.01 vs placebo). Secondary: A total of 94% of patients receiving secobarbital self-reported partial or complete headache resolution (95 CI, 81 to 100) compared to 50% of patients receiving placebo (95% CI, 24 to 76; P=0.012). This translated to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	in the emergency department (intravenous fluids, antiemetics, ketorolac, and opiate rescue therapy as required)			a number needed to treat of 2.3 patients treated with secobarbital to affect one additional partial or complete headache resolution.

Drug regimen abbreviations: BID=twice daily, QD=once daily, QID=four times daily, TID=three times daily
Study abbreviations: DB=double-blind, MA=meta-analysis, MC=multicenter, OL=open-label, PC=placebo-controlled, RCT=randomized controlled trial, SB=single-blind, SR=systematic review, XO=crossover
Other abbreviations: CI=confidence interval, HR=hazard ratio

Additional Evidence

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

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

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

IX. Cost

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

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

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

Rx=prescription

Table 9. Relative Cost of the Barbiturates

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

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

X. Conclusions

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

Currently, there are no clinical guidelines that recommend the use of a barbiturate as first-line therapy for any condition in an outpatient setting.[9-18] There are few clinical trials available that directly compare the various agents. Studies suggest that the barbiturates are not as effective as other sedative-hypnotic agents.[19-27]

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

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

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

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

XI. Recommendations

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

XII. References

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Anxiolytics, Sedatives and Hypnotics – Benzodiazepines
AHFS Class 282408
May 14, 2014

I. Overview

The benzodiazepines are approved for the treatment of anxiety disorders and insomnia.[1-14] Anxiety disorders include generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder and social phobia.[15,16] The agents approved for the treatment of anxiety include alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, lorazepam and oxazepam.

The benzodiazepines that are approved solely for the treatment of insomnia include estazolam, flurazepam, quazepam, temazepam and triazolam. The key diagnostic feature of primary insomnia is difficulty initiating or maintaining sleep for at least one month, which causes marked distress or impairment in social, occupational, or other important areas of functioning.[15,16] Insomnia may be considered either an acute or chronic disorder (especially if associated with underlying illnesses).

Some of the benzodiazepines are also approved for the treatment of seizure disorders (monotherapy, adjunctive therapy, Lennox-Gastaut syndrome, and status epilepticus) and for the management of acute alcohol withdrawal. Midazolam is a unique product compared to the other benzodiazepines; it is used for the induction/maintenance of general anesthesia and as a sedative (e.g., preoperative, prior to diagnostic/radiologic procedures, and intensive care unit sedation).

Benzodiazepines potentiate the effects of gamma-aminobutyric acid and other inhibitory neurotransmitters.[1-14] Within the body, there are three major benzodiazepine receptor subtypes. Benzodiazepine receptor subtype-1 is located throughout the central nervous system and is thought to mediate the anxiolytic, sedative and anticonvulsant properties of the benzodiazepines. Benzodiazepine receptor subtype-2 is located in the cortex, hippocampus, striatum and spinal cord, and is believed to mediate muscle relaxation, central nervous system depression, as well as psychomotor impairment. Depression of the central nervous system may range from mild impairment of task performance to hypnosis.[1,2] Benzodiazepine receptor subtype-3 is located throughout the body and glial cells, and is believed to contribute to tolerance and withdrawal when activated.[1,2] The benzodiazepines are mechanistically similar; however, they differ with regards to their pharmacokinetic properties.[17] This includes onset, duration of action and metabolism. Benzodiazepines with an active parent compound and rapid onset of action may produce euphoria and are more likely to be abused.

The benzodiazepines that are included in this review are listed in Table 1. Prior to January 1, 2014 benzodiazepines were an excludable/optional drug class in accordance with the Omnibus Budget Reconciliation Act of 1990 (OBRA 90). This review encompasses all dosage forms and strengths, regardless of coverage status. All of the benzodiazepines are available in a generic formulation, with the exception of quazepam. This class was last reviewed in August 2012.

Table 1. Benzodiazepines Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Alprazolam	extended-release tablet, oral concentrate, orally disintegrating tablet, tablet	Niravam®*, Xanax®*, Xanax XR®*	alprazolam, alprazolam ER, alprazolam ODT
Chlordiazepoxide	capsule	N/A	chlordiazepoxide
Clonazepam	orally disintegrating tablet, tablet	Klonopin®*	clonazepam
Clorazepate	tablet	Tranxene T-Tab®*	clorazepate
Diazepam	injection, oral concentrate, oral solution, rectal gel, tablet	Diastat®*, Diastat AcuDial®*	diazepam

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Estazolam	tablet	N/A	estazolam
Flurazepam	capsule	N/A	flurazepam
Lorazepam	injection, oral concentrate, tablet	Ativan®*	lorazepam
Midazolam	injection, oral syrup	N/A	midazolam
Oxazepam	capsule	N/A	oxazepam
Quazepam	tablet	Doral®	none
Temazepam	capsule	Restoril®*	temazepam
Triazolam	tablet	Halcion®*	triazolam

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

II. Evidence-Based Medicine and Current Treatment Guidelines

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

Table 2. Treatment Guidelines Using the Benzodiazepines

Clinical Guideline	Recommendation(s)

National Institute for Clinical Excellence: **Generalized Anxiety Disorder and Panic Disorder (With or Without Agoraphobia) in Adults (2011)**[19]	<u>Stepped care for people with generalized anxiety disorder (GAD)</u>
	• If a person with GAD chooses drug treatment, offer a selective serotonin reuptake inhibitor (SSRI), specifically sertraline.
	• If sertraline is ineffective, offer an alternative SSRI or a serotonin–noradrenaline reuptake inhibitor (SNRI), taking into account the following factors:
	  o Tendency to produce a withdrawal syndrome (especially with paroxetine and venlafaxine).
	  o The side-effect profile and the potential for drug interactions.
	  o The risk of suicide and likelihood of toxicity in overdose (especially with venlafaxine).
	  o The person's prior experience of treatment with individual drugs (particularly adherence, effectiveness, side effects, experience of withdrawal syndrome and the person's preference).
	• If the person cannot tolerate SSRIs or SNRIs, consider offering pregabalin.
	• Do not offer a benzodiazepine for the treatment of GAD in primary or secondary care except as a short-term measure during crises.
	• Do not offer an antipsychotic for the treatment of GAD in primary care.
	
	<u>Panic disorder general considerations</u>
	• Benzodiazepines are associated with a less effective outcome in the long term and should not be prescribed for panic disorder.
	• Sedating antihistamines or antipsychotics should not be prescribed for panic disorder.
	• Interventions with evidence for the longest duration of effect are listed in descending order, where preference of the patient should be taken into account:
	  o Psychological therapy (i.e., cognitive behavioral therapy, structured problem solving, psychoeducation).
	  o Pharmacological therapy (antidepressant therapy).
	  o Self-help interventions (i.e., bibliotherapy, support groups, exercise, cognitive behavioral therapy via a computer interface).
	• Antidepressants should be the only pharmacologic intervention used in the longer term.
	• Two types of medication are considered in the guideline for the treatment of panic disorder, tricyclic antidepressants (TCAs) and SSRIs.
	• Unless otherwise indicated, an SSRI (e.g., paroxetine, fluvoxamine, citalopram)

Clinical Guideline	Recommendation(s)
	licensed for panic disorder should be offered. If an SSRI is not suitable or there is no improvement after a 12-week course and if further medication is appropriate, imipramine or clomipramine may be considered. • If the patient is showing improvement, the medication should be continued for at least six months after optimal dose is reached, after which the dose may be tapered slowly over an extended period of time to minimize the risk of discontinuation/withdrawal symptoms.
American Psychiatric Association: **Practice Guideline for the Treatment of Patients with Panic Disorder, Second Edition (2009)**[20]	• SSRIs, SNRIs, TCAs, and benzodiazepines have demonstrated efficacy in numerous controlled trials and are recommended for treatment of panic disorder. • Because SSRIs, SNRIs, TCAs, and benzodiazepines appear roughly comparable in their efficacy for panic disorder, selecting a medication involves considerations of side effects, pharmacological properties, potential drug interactions, prior treatment history, and comorbid medical and psychiatric conditions. • The relatively favorable safety and side effect profile of SSRIs and SNRIs makes them the best initial choice for many patients with panic disorder. • There is no evidence of differential efficacy between the SSRIs, although differences in the side-effect profile (e.g., potential for weight gain, discontinuation-related symptoms), half-life, propensity for drug interactions, and availability of generic formulations may be clinically relevant. They are safer than TCAs and monoamine oxidase inhibitors. They are rarely lethal in overdose and have few serious effects on cardiovascular function. • Venlafaxine extended release has been shown to be effective for panic disorder. It is generally well tolerated and has a side effect profile similar to the SSRIs. No systematic data are currently available supporting the use of duloxetine, in panic disorder, although its mechanism of action suggests it might be an effective agent. • Although TCAs are effective, the side effects and greater toxicity in overdose limit their acceptability to patients and clinical utility. Given the equivalency of TCAs in treating depression, there is little reason to expect other TCAs to work less well for panic disorder. TCAs that are more noradrenergic (e.g., desipramine, maprotiline) may be less effective than agents that are more serotonergic. • SSRIs, SNRIs, and TCAs are all preferable to benzodiazepines as monotherapies for patients with comorbid depression or substance use disorders. Benzodiazepines may be especially useful adjunctively with antidepressants to treat residual anxiety symptoms. • Benzodiazepines may be preferred for patients with very distressing or impairing symptoms in whom rapid symptom control is critical. The benefit of more rapid response to benzodiazepines must be balanced against the possibilities of troublesome side effects and physiological dependence that may lead to difficulty discontinuing the medication. • MAOIs appear effective for panic disorder but, because of their safety profile, they are generally reserved for patients who have failed to respond to several first-line treatments. • Neither trazodone nor nefazodone can be recommended as a first-line treatment for panic disorder. There is minimal support for the use of trazodone in panic disorder and it appears less effective than imipramine and alprazolam. There are a few small, uncontrolled studies showing benefits of nefazodone in some patients with panic disorder; however, its use has been limited by concerns about liver toxicity. • Bupropion was effective in one small trial and ineffective in another. It cannot be recommended as a first line treatment for panic disorder. • Other medications with less empirical data may be considered as monotherapies or adjunctive treatments for panic disorder when patients have failed to respond

Clinical Guideline	Recommendation(s)
	to several standard treatments or based on other individual circumstances.

American Academy of Child and Adolescent Psychiatry: **Practice Parameter for the Assessment and Treatment of Children and Adolescents with Anxiety Disorders (2007)**[21]	• A multimodal treatment approach for children and adolescents with anxiety disorders should consider education of the parents and the child about the anxiety disorder, consultation with school personnel and primary care physicians, cognitive-behavioral interventions, psychodynamic psychotherapy, family therapy, and pharmacotherapy.
	• Treatment of childhood anxiety disorders of mild severity should begin with psychotherapy.
	• Valid reasons for combining medication and treatment with psychotherapy include the following:
	  o Need for acute symptom reduction in a moderately to severely anxious child.
	  o A comorbid disorder that requires concurrent treatment.
	  o Partial response to psychotherapy and potential for improved outcome with combined treatment.
	• SSRIs have emerged as the medication of choice in the treatment of childhood anxiety disorders.
	• When anxiety disorder symptoms are moderate or severe or impairment makes participation in psychotherapy difficult, or psychotherapy results in a partial response, treatment with medication is recommended.
	• No controlled studies are available for medication treatment of childhood-onset panic disorder. The use of a SSRI in adolescents with panic disorder has shown significant improvement in panic symptoms.
	• Controlled trials have established the safety and efficacy of short-term treatment with SSRIs for childhood anxiety disorders; however, the benefits and risks of long-term use of SSRIs have not been studied. It is recommended that clinicians consider a medication-free trial for children who have a significant reduction in anxiety or depressive symptoms on an SSRI and maintain stability in these symptoms for one year.
	• There is no empirical evidence that a particular SSRI is more effective than another for treatment of childhood anxiety disorders. The choice is often based on side effects, duration of action, or positive response to a particular SSRI in a first-degree relative with anxiety.
	• The risk-benefit ratio for a medication trial needs to be carefully assessed because cognitive-behavioral therapy has been shown to be effective and long-term side effects of medications have not been studied in youths.
	• The safety and efficacy of medications other than SSRIs for the treatment of childhood anxiety disorders have not been established.
	• Noradrenergic antidepressants (venlafaxine and TCAs), buspirone, and benzodiazepines have been suggested as alternatives to be used alone or in combination with the SSRIs.
	• Data are limited in childhood anxiety disorders to guide treatment with combinations of medications when a single medication is not effective in managing anxiety symptoms. Comorbid diagnoses are strongly considered in selection of medication.
	• Preliminary findings from controlled trials of extended-release venlafaxine in the treatment of youths with GAD and social phobia suggest it may be well tolerated and effective relative to placebo.
	• Controlled trials with TCAs for pediatric anxiety disorders have shown conflicting results and have not established efficacy for this use.
	• Buspirone may be an alternative to SSRIs for GAD in youths, but there are no published controlled trials.
	• Benzodiazepines have not shown efficacy in controlled trials in childhood anxiety disorders despite established benefit in adult trials. They are used as an adjunct short-term treatment with SSRIs to achieve rapid reduction in severe

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	anxiety symptoms that may permit initiation of the exposure phase of cognitive-behavioral therapy. Clinicians should use benzodiazepines cautiously because of the possibility of developing dependency.
American Academy of Child and Adolescent Psychiatry: **Practice Parameter for the Assessment and Treatment of Children and Adolescents With Obsessive-Compulsive Disorder (2012)**[22]	• The psychiatric assessment of children and adolescents should routinely screen for the presence of obsessions and/or compulsions or repetitive behaviors. • If screening suggests obsessive-compulsive symptoms, clinicians should fully evaluate the child using the DSM-IV-TR criteria and scalar assessment. • A complete psychiatric evaluation should be performed, including information from all available sources and compromising standard elements of history and a mental state examination, with attention to the presence of commonly occurring comorbid psychiatric disorders. • It is possible that three out of four children with obsessive-compulsive disorder (OCD) meet criteria for at least one comorbid diagnosis, and these children have lower response rates to CBT than children without comorbid diagnoses. • Identification of MDD and bipolar disorder is very important before initiating treatment with a SSRI. • Comorbid eating disorders are infrequent in younger children; however, comorbid eating disorders become more prevalent in adolescents. • A full medical, developmental, family and school history should be included with the psychiatric history and examination. • CBT is the first-line treatment for mild to moderate OCD in children, whenever possible. • For moderate to severe OCD, medication is indicated in addition to CBT. • Serotonin reuptake inhibitors (SRIs) are the first-line medications recommended for OCD in children, including clomipramine (a TCA) and certain SSRIs (fluoxetine, fluvoxamine, paroxetine and sertraline). • There is no SRI that is proven to be more efficacious over another. • The modality of assigned treatment should be guided by empirical evidence on the moderators and predictors of treatment response. • Multimodal treatment with CBT and medication is recommended if CBT fails to achieve a clinical response after several months or in more severe cases. • Medication augmentation strategies are reserved for treatment-resistant cases in which impairments are deemed moderate in at least one important domain of function despite adequate monotherapy. • Adding clomipramine to an SSRI is a useful medication augmentation strategy. • Augmenting with an atypical neuroleptic is also a strategy employed by experts (e.g. haloperidol and risperidone combined) based on studies in adults with OCD; however, controlled data for the use of atypical antipsychotics in children with OCD does not exist. • A minimum of two adequate SSRI trials or an SSRI and clomipramine trial is recommended before atypical augmentation. • Empirically validated medication and psychosocial treatments for comorbid disorders should be considered.
American Psychiatric Association: **Practice Guideline for the Treatment of Patients with Obsessive-Compulsive Disorder (2007)**[23]	<u>General considerations</u> • OCD is a chronic illness which typically waxes and wanes. • Patients who have symptoms interfering with daily functioning should be treated. • Clinical remission and recovery may not always occur and will not occur rapidly. • Goals of treatment include improving symptoms, patient functioning, and quality of life. <u>Initial treatment options</u> • The choice of treatment depends on the patient's ability to comply with therapy, whether psychotherapy, pharmacotherapy, or both. • First-line treatments include cognitive-behavioral therapy, SRIs, or a combination of the two. The choice depends on past treatment history, comorbid

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	psychiatric conditions, severity of symptoms, and functional limitations. • Cognitive-behavioral therapy or SRI therapy may be used alone or in combination, and combination therapy may be considered in patients who do not respond fully to monotherapy, those with severe symptoms, those with comorbid psychiatric illnesses for which an SRI is indicated, or in patients who wish to limit SRI exposure. • All SRIs appear to be equally effective, though patients may respond to agents differently. • Prescribers should consider the safety, side effects, FDA warnings, drug interactions, past response to treatment, and comorbid medical conditions when choosing a medication for treatment. • Most patients do not experience a significant improvement until four to six weeks after treatment initiation, and some may ultimately respond after as many as 10 to 12 weeks. • Patients not responding after 10 to 12 weeks may respond to a higher dose of the same medication. <u>Changing treatments and pursuing sequential treatment trials</u> • Augmentation strategies may be preferred to switching strategies in patients who have a partial response to the initial treatment. • Augmentation of SRIs with trials of different antipsychotic medications or with cognitive-behavioral therapy or augmentation of cognitive-behavioral therapy with an SRI. • Patients who do not respond to their first SRI may have their medication switched to a different SRI. A switch to venlafaxine is less likely to produce an adequate response. • For patients who have not benefitted from their first SSRI trial, a switch to mirtazapine can be considered. • After first- and second-line treatments and well-supported augmentation strategies have been exhausted, less well-supported treatment strategies may be considered. These include augmenting SRIs with clomipramine, buspirone, pindolol, riluzole, or once- weekly oral morphine sulfate. • Evidence for beneficial effects of benzodiazepines as monotherapy for OCD is limited to case reports with clonazepam and alprazolam. Modest doses of benzodiazepines may relieve anxiety and distress in OCD without directly diminishing the frequency or duration of obsessions or compulsions. Given their limited evidence for efficacy, benzodiazepines cannot be recommended as monotherapy for OCD, except in those rare individuals who are unable or unwilling to take standard anti-OCD medications.
American Academy of Child and Adolescent Psychiatry: **Practice Parameter for the Assessment and Treatment of Children and Adolescents With Posttraumatic Stress Disorder (2010)**[24]	• The psychiatric evaluation of children and adolescents should routinely include questions about traumatic experiences and posttraumatic stress disorder (PTSD) symptoms. • If the evaluation indicates symptoms of PTSD, the clinician should formally determine if PTSD is present, the severity of PTSD symptoms and the degree of functional impairment. Caregivers should be included in the formal evaluation. • A differential diagnosis should be conducted in order to rule out diagnoses with symptoms that can mimic PTSD symptoms. • The treatment plan should be comprehensive in approach and should consider the severity of symptoms and impairment, as well as comorbid psychiatric conditions. • Trauma-focused psychotherapies should be considered first-line in children and adolescents with PTSD, including psychoanalytic, attachment and cognitive behavioral treatment models. • SSRIs can be considered for treatment of children and adolescents with PTSD. • The effect of SSRIs in children with PTSD may be more consistent with a

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	placebo effect. • Other medications such as clonidine and propranolol may be useful in decreasing symptoms of hyperarousal, and anticonvulsants may beneficial in treating PTSD symptoms other than avoidance. • Benzodiazepines have not been found to be beneficial in treating PTSD symptoms. • School-based accommodations are recommended for children with PTSD, especially in children with school-based trauma, such as bullying. • The use of restrictive, "rebirthing," binding or other coercive therapies are not recommended. • Screening for PTSD in the school or community should be conducted after traumatic events that affect significant numbers of children.
American Psychiatric Association: **Guideline Watch: Practice Guideline for the Treatment of Patients with Acute Stress Disorder and Posttraumatic Stress Disorder (2009)**[25]	• Meta-analyses and several randomized controlled trials published since 2004 support the greater efficacy of SSRIs and SNRIs over placebo for non-combat-related PTSD. • The evidence base for pharmacological intervention in combat-related PTSD has not been significantly augmented by recent studies. Studies suggest that SSRIs may not be recommended with the previous level of confidence for the treatment of PTSD in this particular population. Further research is needed to answer why these populations have been shown to have differential responses to SSRI treatment. • As described in the 2004 guideline, no significant differences among antidepressants, including the SSRIs, were found in the few head-to-head studies then available. Since that time, studies have been published comparing nefazodone and sertraline, venlafaxine and sertraline, the SNRI reboxetine and fluvoxamine, and fluoxetine, moclobemide, and tianeptine. These studies have generally demonstrated the greater efficacy of antidepressants to placebo but have done little to clarify the relative utility of these different antidepressants. • There is a relatively robust evidence basis for pharmacological treatment with antidepressant medications (particularly SSRIs and SNRIs for noncombat PTSD) as compared to other classes of medications. • Comparison of other treatments with the SSRIs and SNRIs is complicated by methodological differences in the available studies. SSRIs and SNRIs have mostly been studied in rigorous trials compared to placebo; other agents have been studied against "treatment as usual" or as augmentation agents in patients with refractory illness.
American Psychiatric Association: **Practice Guideline for the Treatment of Patients with Acute Stress Disorder and Posttraumatic Stress Disorder (2004)**[26]	• Goals of treatment for patients with PTSD and acute stress disorder (ASD) include lessening the severity of symptoms and preventing trauma-related comorbid conditions. • Clinical trial data and randomized studies are limited and difficult to perform. • Treatment includes pharmacotherapy, psychotherapy and supportive measures. • SSRIs are first-line therapy for PTSD and ASD and if found effective, treatment should be continued in order to continue to see benefit. • Second-line treatment agents include TCAs (specifically amitriptyline and imipramine, but not desipramine) and MAOIs. • Benzodiazepines should not be used as monotherapy, but may be effective as sedatives and anxiolytics. • Atypical antipsychotics may be necessary for patients experiencing psychotic symptoms. • Anticonvulsants (divalproex, carbamazepine, topiramate and lamotrigine) have produced mixed results for treating PTSD and ASD but may prove to be beneficial. • Limited data exists for the use of adrenergic inhibitors and their use is not part of the guideline at this time. • An adequate trial of therapy requires a minimum of three months of treatment. If

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	treatment is effective, it should be continued for up to 12 months or longer.

American Academy of Sleep Medicine: **Clinical Guideline for the Evaluation and Management of Chronic Insomnia in Adults (2008)**[27]	• The primary treatment goals are to improve sleep quality/quantity and to improve insomnia related daytime impairments.
	• Short-term hypnotic treatment should be supplemented with behavioral and cognitive therapies when possible.
	• When pharmacotherapy is utilized, the choice of a specific pharmacological agent should be directed by: symptom pattern, treatment goals, past treatment responses, patient preference, availability of other treatments, comorbid conditions, contraindications, concurrent medication interactions, and side effects.
	• For patients with primary insomnia, when pharmacologic treatment is utilized alone or in combination therapy, the recommended general sequence of medication trials is:
	  o Short-intermediate acting benzodiazepine receptor agonists or ramelteon.
	  o Alternate short-intermediate acting benzodiazepine receptor agonists or ramelteon if the initial agent has been unsuccessful.
	  o Sedating antidepressants, especially when used in conjunction with treating comorbid depression/anxiety. Examples of these include trazodone, amitriptyline, doxepin, and mirtazapine.
	  o Combined benzodiazepine receptor agonists or ramelteon and sedating antidepressant.
	  o Other sedating agents. Examples include anti-epilepsy medications (gabapentin, tiagabine) and atypical antipsychotics (quetiapine and olanzapine). These medications may only be suitable for patients with comorbid insomnia who may benefit from the primary action of these drugs as well as from the sedating effect.
	• Over-the-counter antihistamine or antihistamine/analgesic type drugs (over-the-counter "sleep aids"), as well as herbal and nutritional substances (e.g., valerian and melatonin), are not recommended in the treatment of chronic insomnia due to the relative lack of efficacy and safety data.
	• Older approved drugs for insomnia including barbiturates, barbiturate-type drugs and chloral hydrate are not recommended for the treatment of insomnia.
	• Pharmacological treatment should be accompanied by patient education regarding treatment goals, safety concerns, potential side effects and drug interactions, other treatment modalities (cognitive and behavioral treatments), potential for dosage escalation, and rebound insomnia.
	• Patients should be followed on a regular basis, every few weeks in the initial period of treatment when possible, to assess for effectiveness, possible side effects, and the need for ongoing medication.
	• Efforts should be made to employ the lowest effective maintenance dosage of medication and to taper medication when conditions allow. Medication tapering and discontinuation are facilitated by cognitive behavioral therapy for insomnia.
	• Chronic hypnotic medication may be indicated for long-term use in those with severe or refractory insomnia or chronic comorbid illness. Whenever possible, patients should receive an adequate trial of cognitive behavioral treatment during long-term pharmacotherapy.
	• Long-term prescribing should be accompanied by consistent follow-up, ongoing assessment of effectiveness, monitoring for adverse effects, and evaluation for new onset or exacerbation of existing comorbid disorders.
	• Long-term administration may be nightly, intermittent (e.g., three nights per week), or as needed.

National Institutes of Health: **Manifestations and**	<u>Behavioral and cognitive therapies</u> • Behavioral methods include relaxation training, stimulus control, and sleep restriction.

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Management of Chronic Insomnia in Adults (2005)[28]	• Cognitive therapy methods have been added to behavioral methods and include cognitive restructuring, in which anxiety-producing beliefs and erroneous beliefs about sleep and sleep loss are specifically targeted. • The combination of cognitive methods and behavioral methods has been found to be as effective as prescription medications for short-term treatment of chronic insomnia. The beneficial effects of cognitive-behavioral therapy may last well beyond the termination of active treatment. <u>Benzodiazepine receptor agonists</u> • Benzodiazepine receptor agonists include benzodiazepines (e.g., flurazepam, temazepam, and triazolam) as well as nonbenzodiazepine-structured anxiolytic agents acting at benzodiazepine receptors (e.g., eszopiclone, zaleplon, and zolpidem). • Benzodiazepine receptor agonists have been shown to be effective in the short-term management of insomnia. • The frequency and severity of the adverse effects are much lower for the newer benzodiazepine receptor agonists, most likely because these agents have shorter half-lives. • In the short term, abuse of the benzodiazepine receptor agonists is not a major problem, but problems associated with their long-term use require further study. • Barbiturates (e.g., phenobarbital) have been used in the treatment of insomnia, however, short-term and long-term studies are lacking; such drugs bear significant risks and are not recommended in the treatment of chronic insomnia. <u>Other prescription medications</u> • Other sedating medications have been used in the treatment of insomnia. These include barbiturates and antipsychotics. • Studies demonstrating the usefulness of these medications for either short- or long-term management of insomnia are lacking. • All of these agents have significant risks. Thus, their use in the treatment of chronic insomnia cannot be recommended. <u>Antidepressants</u> • Antidepressants (especially trazodone) are often prescribed for insomnia, although they are not FDA-approved for this purpose. • In short-term use, trazodone and doxepin have been shown to have some beneficial effects, but there are no studies on long-term use. • Data on other antidepressants (e.g., amitriptyline and mirtazapine) in individuals with chronic insomnia are lacking. • These guidelines were published prior to the FDA approval of ramelteon. <u>Nonprescription medications</u> • Antihistamines are the most commonly used over-the-counter treatments for chronic insomnia, but there is no systematic evidence for efficacy and there are significant concerns about risks of these medications. • Adverse effects include residual daytime sedation, diminished cognitive function, and delirium, the latter being of particular concern in the elderly. Other adverse effects include dry mouth, blurred vision, urinary retention, constipation, and risk of increased intraocular pressure in individuals with narrow angle glaucoma.
American Academy of Neurology: **Evidence-Based Guideline Update: Medical Treatment of Infantile Spasms:**	• To date, there is insufficient evidence to support the use of agents other than adrenocorticotropic hormone, and vigabatrin. • Low-dose adrenocorticotropic hormone should be considered as an alternative to high-dose adrenocorticotropic hormone for treatment of infantile spasms. • Adrenocorticotropic hormone or vigabatrin may be offered for short-term treatment of infantile spasms. Evidence suggests that adrenocorticotropic

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Report of the Guideline Development Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society (2012)[29]	hormone may be offered over vigabatrin. • There is insufficient evidence to recommend the use of dexamethasone, prednisolone and methylprednisolone as being as effective as adrenocorticotropic hormone for short-term treatment of infantile spasms. • The data is insufficient to recommend other therapies (valproic acid, vitamin B6, nitrazepam, levetiracetam, zonisamide, topiramate, the ketogenic diet, or novel/combination therapies) for the treatment of infantile spasms. • Hormonal therapy (adrenocorticotropic hormone or prednisolone) may be considered for use in preference to vigabatrin in infants with cryptogenic infantile spasms, to possibly improve developmental outcome. • A shorter lag time to treatment of infantile spasms with either hormonal therapy or vigabatrin may be considered to improve long-term cognitive outcomes.
Infantile Spasms Working Group: **Infantile Spasms: A U.S. Consensus Report (2010)**[30]	• To improve outcomes in infantile spasms, the goals include early recognition and diagnosis, short-term treatment with a first-line therapy, timely electroencephalography evaluation to assess treatment effectiveness and prompt treatment modification if indicated. • Effective treatment should produce both cessation of spasms and resolution of hypsarrhythmia on electroencephalography. • The dose of the chosen first-line agent should be adjusted to achieve the maximum effective dose in as short amount of time as clinically indicated. • There is insufficient evidence to recommend the best approach in events of relapse. Possible treatment options include using the previously effective agent and dose, using the previously effective agent at the maximum dose or using a new agent. • Adrenocorticotropic hormone is considered first-line therapy for infantile spasms. There is insufficient evidence to recommend the optimal dose and duration of treatment, although short duration is preferable to avoid adverse events. Treatment with the maximum dose of adrenocorticotropic hormone should be continued for two weeks followed by taper and evaluation of treatment response. • Vigabatrin is considered first-line therapy for infantile spasms, especially in patients with comorbid tuberous sclerosis complex. Vigabatrin should be initiated at 50 mg/kg/day and increased up to 100 to 150 mg/kg/day if indicated. Efficacy should be assessed within two weeks following dose titration. Responders to treatment may continue therapy for six to nine months, with continued ophthalmic evaluation. • No recommendations can be given with regard to oral corticosteroids in the treatment of infantile spasms. • Ketogenic diet may be considered as second-line therapy when first-line therapies fail or are inappropriate. • Patients with refractory spasms, concomitant partial seizures or focal abnormalities on the electroencephalography may be evaluated for surgery.
American Academy of Neurology/ American Epilepsy Society: **Efficacy and Tolerability of the New Antiepileptic Drugs I: Treatment of New Onset Epilepsy (2004)**[31]	• At this time, there are no studies that assessed the efficacy and tolerability of the new antiepileptic drugs (gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate and zonisamide) in adults with newly diagnosed (exclusively) idiopathic or symptomatic generalized epilepsy. • Lamotrigine can be included in the treatment options for children with newly diagnosed absence seizures. At this time, there is insufficient evidence to recommend use of gabapentin, levetiracetam, oxcarbazepine, tiagabine, topiramate and zonisamide in children with newly diagnosed (exclusively) idiopathic or symptomatic generalized epilepsy. • Patients with newly diagnosed partial or mixed seizure disorders who require treatment can be initiated on carbamazepine, gabapentin, lamotrigine, oxcarbazepine, phenobarbital, phenytoin, topiramate or valproic acid. The choice of drug will depend on individual patient characteristics. At this time, there is

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	insufficient evidence to determine effectiveness in newly diagnosed patients for levetiracetam, tiagabine and zonisamide.
American Academy of Neurology/ American Epilepsy Society: **Efficacy and Tolerability of the New Antiepileptic Drugs II: Treatment of Refractory Epilepsy (2004)**[32]	• Topiramate may be used for the treatment of refractory generalized tonic-clonic seizures in adults and children. At this time, there is insufficient evidence to recommend use of gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine or zonisamide for refractory generalized tonic-clonic seizures in adults and children. • Lamotrigine and topiramate may be used to treat drop attacks associated with Lennox Gastaut syndrome in adults and children. • Lamotrigine, oxcarbazepine and topiramate can be used as monotherapy in adults with refractory partial epilepsy. At this time, there is insufficient evidence to recommend use of gabapentin, levetiracetam, tiagabine or zonisamide in monotherapy for refractory partial epilepsy. • Gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate and zonisamide are appropriate treatment options as adjunctive therapy for refractory partial epilepsy in adults. • Gabapentin, lamotrigine, oxcarbazepine and topiramate may be used as adjunctive treatment of refractory partial seizures in children. At this time, there is insufficient evidence to recommend levetiracetam, tiagabine or zonisamide as adjunctive treatment of refractory partial seizures in children.
International League Against Epilepsy: **Updated International League Against Epilepsy Evidence Review of Antiepileptic Drug Efficacy and Effectiveness as Initial Monotherapy for Epileptic Seizures and Syndromes (2013)**[33]	Adults with partial onset seizures • Carbamazepine, levetiracetam, phenytoin, and zonisamide are established treatments as initial monotherapy for adults with newly diagnosed or untreated partial-onset seizures. Valproic acid is probably effective and gabapentin, lamotrigine, oxcarbazepine, phenobarbital, topiramate and vigabatrin are possibly effective for partial onset seizures. Clonazepam and primidone are potentially efficacious/effective. Children with partial-onset seizures • Oxcarbazepine is established as initial monotherapy for children with newly diagnosed or untreated partial-onset seizures. Carbamazepine, phenobarbital, phenytoin, topiramate, valproic acid and vigabatrin may be effective and clobazam, clonazepam, lamotrigine and zonisamide are potentially efficacious/ effective. Elderly adults with partial-onset seizures • Gabapentin and lamotrigine are effective as initial monotherapy for elderly adults with newly diagnosed or untreated partial-onset seizures. Carbamazepine may be effective and topiramate and valproic acid are potentially efficacious/effective. Adults with generalized-onset tonic-clonic seizures • Carbamazepine, lamotrigine, oxcarbazepine, phenobarbital, phenytoin, topiramate and valproic acid are possibly effective as initial monotherapy for adults with newly diagnosed or untreated generalized-onset tonic-clonic seizures. Gabapentin, levetiracetam and vigabatrin are potentially efficacious/effective. Carbamazepine and phenytoin may precipitate or aggravate generalized-onset tonic-clonic seizures. Children with generalized-onset tonic-clonic seizures • Carbamazepine, phenobarbital, phenytoin, topiramate and valproic acid are possibly effective for children with newly diagnosed or untreated generalized onset tonic-clonic seizures. Oxcarbazepine is potentially efficacious/effective. Carbamazepine and phenytoin may precipitate or aggravate generalized-onset tonic-clonic seizures.

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	Children with absence seizures • Ethosuximide and valproic acid are established treatments for children with newly diagnosed or untreated absence seizures. Lamotrigine is possibly efficacious/ effective as initial monotherapy. Gabapentin is inefficacious/ineffective for children with absence seizures. • Based on scattered reports, the following antiepileptic drugs may precipitate or aggravate absence seizures: carbamazepine, oxcarbazepine, phenobarbital, phenytoin, tiagabine and vigabatrin. No conclusion can be made about levetiracetam efficacy/effectiveness for absence seizures since the failed class III placebo-controlled trial was uninformative. Children with benign childhood epilepsy with centrotemporal spikes • Carbamazepine and valproic acid are possibly effective as initial monotherapy for children with benign childhood epilepsy with centrotemporal spikes. Gabapentin, levetiracetam, oxcarbazepine, and sulthiame* are potentially efficacious/effective. Juvenile myoclonic epilepsy • Topiramate and valproic acid are potentially efficacious/effective for patients with newly diagnosed juvenile myoclonic epilepsy. Carbamazepine, gabapentin, oxcarbazepine, phenytoin, tiagabine and vigabatrin may precipitate or aggravate absence seizures, myoclonic seizures, and in some cases generalized tonic-clonic seizures. There has been a report that lamotrigine may exacerbate seizures in juvenile myoclonic epilepsy.
National Institute for Clinical Excellence: **The Epilepsies: The Diagnosis and Management of the Epilepsies in Adults and Children in Primary and Secondary Care (2012)**[34]	Treatment of atonic or tonic seizures • First-line treatment in children, young people, and adults with tonic or atonic seizure: sodium valproate. • Offer lamotrigine as adjunctive treatment if sodium valproate is ineffective or not tolerated. • Discuss with a tertiary epilepsy specialist if adjunctive treatment is ineffective or not tolerated. Other antiepileptics that may be considered by the tertiary epilepsy specialist are rufinamide and topiramate. • Do not offer carbamazepine, gabapentin, oxcarbazepine, pregabalin, tiagabine or vigabatrin. Treatment of generalized tonic-clonic seizures • First-line treatment in children, young people, and adults with newly diagnosed focal seizures: sodium valproate. • Offer lamotrigine if sodium valproate is unsuitable. • Consider carbamazepine and oxcarbazepine. • Offer clobazam, lamotrigine, levetiracetam, sodium valproate, or topiramate as adjunctive treatment to all patients if first-line treatments are ineffective or not tolerated. • If there are absence or myoclonic seizures, or if juvenile myoclonic epilepsy is suspected, do not offer carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine, or vigabatrin. Treatment of infantile spasms • Discuss with, or refer to, a tertiary pediatric epilepsy specialist when an infant presents with infantile spasms. • Offer a steroid or vigabatrin as first-line treatment to infants with infantile spasms that are not due to tuberous sclerosis. • Offer vigabatrin as first-line treatment to infant with infantile spasms due to tuberous sclerosis. If vigabatrin is ineffective, offer a steroid.

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	Treatment of Lennox-Gastaut Syndrome • Discuss with, or refer to, a tertiary pediatric epilepsy specialist when a child presents with suspected Lennox-Gastaut syndrome. • Offer sodium valproate as first-line treatment to children with Lennox-Gastaut syndrome. • Offer lamotrigine as adjunctive treatment if first-line treatments are ineffective or not tolerated. • Discuss with a tertiary epilepsy specialist if adjunctive treatment is ineffective or not tolerated. Other antiepileptics that may be considered by the tertiary epilepsy specialist are rufinamide and topiramate. • Do not offer carbamazepine, gabapentin, oxcarbazepine, pregabalin, tiagabine or vigabatrin. • Only offer felbamate in centers providing tertiary epilepsy specialist care and when treatment with all of the antiepileptics listed above have proved ineffective or not tolerated. Treatment of myoclonic seizures • First-line treatment in children, young people, and adults with myoclonic seizures: valproate, unless unsuitable. • Consider levetiracetam or topiramate if sodium valproate is unsuitable or not tolerated. • Offer levetiracetam, sodium valproate, or topiramate as adjunctive treatment to all patients if first-line treatments are ineffective or not tolerated. • If adjunctive treatment is ineffective or not tolerated, discuss with, or refer to, a tertiary epilepsy specialist or consider clobazam, clonazepam, piracetam*, or zonisamide. • Do not offer carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin. Treatment of absence seizures • First-line treatment in children, young people, and adults with absence seizures: ethosuximide or sodium valproate. If there is a high risk of generalized tonic-clonic seizures, offer sodium valproate first, unless it is unsuitable. • Offer lamotrigine if ethosuximide and sodium valproate are unsuitable, ineffective, or not tolerated. • If two first-line antiepileptics are ineffective, consider a combination of two of these three antiepileptics as adjunctive treatment: ethosuximide, lamotrigine, or sodium valproate. • If adjunctive treatment is ineffective or not tolerated, discuss with, or refer to, a tertiary epilepsy specialist and consider clobazam, clonazepam, levetiracetam, topiramate or zonisamide. • Do not offer carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin. Treatment of focal seizures • First-line treatment in children, young people, and adults with newly diagnosed focal seizures: carbamazepine or lamotrigine. • Offer levetiracetam, oxcarbazepine, or sodium valproate if first-line treatments are unsuitable or not tolerated. If the first antiepileptic tried is ineffective, offer an alternative from the five antiepileptics noted above. • Consider adjunctive treatment if a second well-tolerated antiepileptic is ineffective. • For refractory focal seizures, offer carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate, or topiramate as adjunctive treatment to all patients with focal seizures if first-line treatments are

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

Clinical Guideline	Recommendation(s)
	• If adjunctive treatment is ineffective or not tolerated, discuss with, or refer to, a tertiary epilepsy specialist and consider clobazam, clonazepam, or zonisamide. • Do not offer carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin. Treatment of epilepsy with generalized tonic-clonic seizures only • First-line treatment in children, young people, and adults with epilepsy with generalized tonic-clonic seizures only: lamotrigine, sodium valproate. • Consider carbamazepine or oxcarbazepine. • Offer clobazam, lamotrigine, levetiracetam, sodium valproate, or topiramate as adjunctive treatment if first-line treatments are ineffective or not tolerated. Treatment of childhood absence epilepsy, juvenile absence epilepsy, or other absence epilepsy syndromes • First-line treatment in children, young people, and adults: ethosuximide, sodium valproate. • Offer lamotrigine if first-line treatments are unsuitable, ineffective, or not tolerated. • If two first-line antiepileptic drugs are ineffective, consider a combination of two of these three antiepileptic drugs adjunctive treatment: ethosuximide, lamotrigine, or sodium valproate. • If adjunctive treatment is ineffective or not tolerated, discuss with, or refer to, a tertiary epilepsy specialist and consider clobazam, clonazepam, levetiracetam, topiramate, or zonisamide. • Do not offer carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin.
European Federation of Neurological Societies: **Guideline on the Management of Status Epilepticus (2010)**[35]	Initial pharmacological treatment for generalized convulsive status epilepticus and non-convulsive status epilepticus • The preferred treatment is intravenous administration of lorazepam 0.1 mg/kg; however, depending on the patients' general medical condition, treatment can be started at a lower dose of 4 mg, to be repeated if seizures continue for >10 minutes after first injection. • If lorazepam is not available, diazepam 10 mg (route of administration not specified) directly followed by phenytoin (15 to 18 mg/kg) or equivalent fosphenytoin. • General management of refractory status epilepticus includes treatment in an intensive care unit. Pharmacological treatment for refractory generalized convulsive status epilepticus and subtle status epilepticus • Immediate infusions of anesthetic doses of midazolam, propofol or barbiturates are recommended due to the progressive risk of brain and systemic damage. • If midazolam is given, seizure suppression is recommended. This goal should be maintained for at least 24 hours. Simultaneous initiation of the chronic medication the patient with be treated with in the future should be initiated. • For elderly patients in whom intubation and artificial ventilation would not be justified, further non-anesthetizing anticonvulsants may be tried. Pharmacological treatment for refractory non-convulsive status epilepticus • Due to poor evidence and lack of any head-to-head trials, no recommendations can be made regarding which of the non-anaesthetizing anticonvulsants should be the drug of choice. • Recommendations include phenobarbital, valproic acid and levetiracetam. • If treatment regimen includes the administration of anesthetics, use the same protocol as refractory generalized convulsive status epilepticus.

Clinical Guideline	Recommendation(s)
Journal of Child Neurology: **Treatment of Pediatric Epilepsy: Expert Opinion (2005)**[36]	• 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.
National Institute for Health and Clinical Excellence: **Alcohol-Use Disorders. Diagnosis, Assessment and Management of Harmful Drinking and Alcohol Dependence (2011)**[37]	<u>Treatment for acute alcohol withdrawal</u> • Offer pharmacotherapy to treat the symptoms of acute alcohol withdrawal. • Consider offering a benzodiazepine or carbamazepine. • Clomethiazole may be offered as an alternative to a benzodiazepine or carbamazepine. <u>Management of delirium tremens</u> • Lorazepam is considered a first-line treatment option. • If symptoms persist or oral medication is declined, give parenteral lorazepam, haloperidol or olanzapine. <u>Management of alcohol withdrawal seizures</u> • In people with alcohol withdrawal seizures, consider offering a quick-acting benzodiazepine (e.g., lorazepam) to reduce the likelihood of further seizures. • Do not offer phenytoin to treat alcohol withdrawal seizures.
American Psychiatric Association: **Treatment of Patients with Substance Use Disorders, Second Edition (2007)**[38]	<u>Alcohol use disorders: treatment principles and alternatives</u> • The treatment of patients in moderate to severe withdrawal includes efforts to reduce central nervous system irritability and restore physiological homeostasis. • Management of alcohol withdrawal generally requires the use of thiamine and fluids, benzodiazepines, and occasionally other medications such as anticonvulsants, clonidine, or antipsychotic agents. • Once clinical stability is achieved, the tapering of benzodiazepines and other medications should be carried out as necessary. • Naltrexone may attenuate some of the reinforcing effects of alcohol; however, long-term data regarding efficacy are limited. • Acamprosate may also be an effective adjunctive medication in motivated patients who are receiving psychosocial treatment. • Disulfiram is an effective adjunct to a comprehensive treatment program for reliable, motivated patients whose drinking may be triggered by events that suddenly increase alcohol craving.

III. Indications

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

Table 3. FDA-Approved Indications for the Benzodiazepines (Drugs A to E)[1-14]

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

Indication	Alprazolam	Chlordiazepoxide	Clonazepam	Clorazepate	Diazepam	Estazolam
caused by upper motor neuron disorders, athetosis, and stiff-man syndrome						

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

Table 4. FDA-Approved Indications for the Benzodiazepines (Drugs F to T)[1-14]

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

*Injection formulation.
†Oral formulation(s).

IV. Pharmacokinetics

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

Table 5. Pharmacokinetic Parameters of the Benzodiazepines[1-14]

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

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

V. Drug Interactions

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

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

Generic Name(s)	Significance Level	Interaction	Mechanism
Benzodiazepines (clonazepam, clorazepate, diazepam, estazolam, flurazepam, lorazepam, midazolam, oxazepam, quazepam, temazepam, triazolam)	1	Clozapine	Delirium, sedation, sialorrhea, and ataxia may occur when certain benzodiazepines and clozapine are coadministered. Severe orthostatic hypotension and respiratory depression may occur.
Benzodiazepines (clonazepam, clorazepate, diazepam, estazolam, flurazepam, lorazepam, midazolam, oxazepam, quazepam,	1	Sodium oxybate	Concurrent use of sodium oxybate and benzodiazepines may result in an increase in sleep duration and central nervous system depression.

Generic Name(s)	Significance Level	Interaction	Mechanism
temazepam, triazolam)			
Benzodiazepines (clorazepate, diazepam, estazolam, flurazepam, midazolam, quazepam)	1	Protease inhibitors	Concurrent use may lead to severe sedation and respiratory depression due to inhibition of hepatic metabolism.
Benzodiazepines (diazepam, midazolam)	1	Azole antifungals	Increased and prolonged serum levels, central nervous system depression, and psychomotor impairment have been reported with benzodiazepines undergoing oxidative metabolism.
Benzodiazepines (diazepam)	1	Disulfiram	Coadministration of diazepam and disulfiram may produce acute and severe alcohol intolerance. Symptoms include flushing, headache, palpitations, tachycardia, dyspnea, hyperventilation, nausea, and vomiting. Hypotension and cardiovascular collapse may also occur.
Benzodiazepines (clorazepate, diazepam, estazolam, flurazepam, lorazepam, midazolam, oxazepam, quazepam, temazepam, triazolam)	2	Hydantoins	Serum hydantoin concentrations may be increased and phenytoin may increase the clearance of certain benzodiazepines.
Benzodiazepines (clonazepam, clorazepate, diazepam, estazolam, flurazepam, quazepam, temazepam, triazolam)	2	Disulfiram	Pharmacologic effects of certain benzodiazepines may be increased by disulfiram due to inhibition of benzodiazepine hepatic metabolism.
Benzodiazepines (clonazepam, clorazepate, diazepam, estazolam, flurazepam, midazolam, quazepam)	2	Omeprazole	Pharmacologic effects of certain benzodiazepines may be increased by omeprazole due to decreased hepatic oxidative metabolism. Toxicity may occur.
Benzodiazepines (clonazepam, clorazepate, diazepam, estazolam, flurazepam, midazolam, quazepam)	2	Nefazodone	Nefazodone may increase the pharmacologic effects of certain benzodiazepines due to CYP3A4 inhibition and decreased metabolic elimination. Impaired psychomotor performance and increased sedation may result from elevated benzodiazepine plasma concentrations.
Benzodiazepines (clonazepam, clorazepate, diazepam, estazolam,	2	Rifamycins	Pharmacologic effects of certain benzodiazepines may be decreased by rifamycins due to CYP3A4 induction and increased metabolic elimination.

Generic Name(s)	Significance Level	Interaction	Mechanism
flurazepam, midazolam, quazepam)			
Benzodiazepines (estazolam, midazolam)	2	Carbamazepine	The pharmacologic effects of certain benzodiazepines may be decreased due to CYP3A4 induction by carbamazepine.
Benzodiazepines (diazepam, estazolam, midazolam)	2	Macrolides and ketolides	Central nervous system depression and prolonged sedation have been reported with the concurrent use of benzodiazepines and macrolides/ketolides.
Benzodiazepines (clonazepam, diazepam, midazolam)	2	St. John's Wort	Plasma concentrations and pharmacologic effects of certain benzodiazepines may be decreased by St. John's wort. Reductions in the therapeutic efficacy of benzodiazepines may occur due to induction of CYP3A4 by St. John's wort and increased elimination of the benzodiazepine.
Benzodiazepines (diazepam, midazolam)	2	Diltiazem	Increased central nervous system depression and prolonged effects have been observed with the use of diltiazem and certain benzodiazepines. Diltiazem may increase plasma concentrations of midazolam due to CYP3A4 inhibition.
Benzodiazepines (diazepam, midazolam)	2	Voriconazole	Plasma concentrations and pharmacologic effects of diazepam may be increased by voriconazole, leading to prolonged sedative effects. Inhibition of cytochrome CYP3A4 isoenzymes by voriconazole may decrease the metabolic elimination of diazepam.
Benzodiazepines (clonazepam)	2	Valproic acid	Toxicity of clonazepam may be increased, while the therapeutic effects of both drugs may be reduced (increased seizure risk).
Benzodiazepines (diazepam)	2	Cephalosporins	The combination of cephalosporins and diazepam may produce acute alcohol intolerance. Symptoms include flushing, headache, palpitations, tachycardia, dyspnea, hyperventilation and nausea and vomiting. Hypotensive episodes also have been reported.
Benzodiazepines (diazepam)	2	Furazolidone	This combination may produce acute alcohol intolerance in some patients. Symptoms include flushing, palpitations, tachycardia, dyspnea, hyperventilation, as well as nausea and vomiting.
Benzodiazepines (diazepam)	2	Metronidazole	This combination may produce alcohol intolerance reactions.
Benzodiazepines (lorazepam)	2	Narcotic analgesics	This combination may interact synergistically thus reducing the dosages needed for amnesia and analgesia. The hemodynamic status of some patients may deteriorate unexpectedly when these agents are coadministered.
Benzodiazepines (midazolam)	2	Vasopressin receptor antagonists	Plasma concentrations of midazolam may be increased by vasopressin receptor antagonists.
Benzodiazepines	2	Delavirdine	Inhibition of CYP3A4 by delavirdine may

Generic Name(s)	Significance Level	Interaction	Mechanism
(midazolam)			decrease the metabolic elimination of certain benzodiazepines. Plasma concentrations and pharmacologic effects of certain benzodiazepines may be increased by delavirdine. Adverse effects, including the potential for serious cardiac arrhythmias, may result.
Benzodiazepines (midazolam)	2	Efavirenz	Pharmacologic and toxic effects of midazolam may be increased by efavirenz due to inhibition of CYP2C9, 2C19 and 3A4 by efavirenz.

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

VI. Adverse Drug Events

The most common adverse drug events reported with the benzodiazepines are listed in Tables 7 to 8. The boxed warnings for midazolam are listed in Tables 9 to 10. The benzodiazepines share a number of similar adverse drug events. The most common adverse events are central nervous system-related, including ataxia, confusion, drowsiness, dizziness and lightheadedness.[1-14] Long-acting benzodiazepines, or benzodiazepines with active metabolites, may have a higher incidence of residual daytime sedation and cognitive/psychomotor impairment. This may be more pronounced in elderly patients or patients with impaired elimination of benzodiazepines. Complex behaviors such as "sleep driving", as well as other behaviors, have been reported in patients who are not fully awake after taking a sedative-hypnotic.[1,2]

Misuse and dependence are a concern with the use of benzodiazepines. The risk of dependence increases with long-term therapy, high daily dose, use of high potency and rapid-onset benzodiazepines, history of substance abuse, chronic physical illness, chronic sleep disorders, and dysthymic or personality disorders.[39,40] Withdrawal symptoms may occur when benzodiazepines are discontinued, especially if therapy is abruptly stopped. Symptoms may include relapse of anxiety disorder or rebound/withdrawal syndromes. Withdrawal may occur within hours of discontinuation of a short-acting benzodiazepine or as late as one to two weeks with the use of long-acting agents. Factors that can predict the severity of withdrawal symptoms include long-term therapy, high daily dose, short benzodiazepine half-life, rapid taper rate and concomitant substance abuse.[39,41]

Table 7. Adverse Drug Events (%) Reported with the Benzodiazepines (Drugs A to E)[1-14]

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

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

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

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

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

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

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

Table 8. Adverse Drug Events (%) Reported with the Benzodiazepines (Drugs F to T)[1-14]

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

Adverse Events	Flurazepam	Lorazepam	Midazolam	Oxazepam	Quazepam	Temazepam	Triazolam
Central Nervous System							
Abnormal thinking	-	-	-	-	✔	-	-
Agitation	-	-	<1	-	✔	-	-
Akathisia	-	1 to 10	-	-	-	-	-
Amnesia	-	1 to 10	<1	-	✔	<1	<1
Anxiety	-	-	-	-	✔	1 to 10	-
Apathy	-	-	-	-	✔	-	-
Apprehension	✔	-	-	-	-	-	-
Ataxia	✔	1 to 10	-	✔	✔	<1	5
Coma	✔	-	-	-	-	-	-
Complex sleep-related behavior	-	-	-	-	✔	<1	<1
Confusion	✔	1 to 10	-	-	✔	1 to 10	<1
Delirium	-	-	<1	-	-	-	-
Depression	✔	1 to 10	-	-	✔	-	<1
Disinhibition	-	<1	-	-	-	-	-
Disorientation	-	1 to 10	-	-	-	-	-
Dizziness	✔	1 to 10	-	✔	2	1 to 10	8
Dream abnormalities	-	-	-	-	-	-	<1
Drowsiness	✔	-	1 to 10	✔	12	1 to 10	14
Dysesthesia	-	-	-	-	-	-	<1
Dystonia	-	-	-	-	✔	-	-
Euphoria	✔	<1	<1	-	✔	1 to 10	<1
Faintness	✔	-	-	-	-	-	-
Fatigue	-	<1	-	-	2	1 to 10	<1
Hallucinations	✔	-	<1	-	✔	-	-
Hangover effect	✔	-	-	-	-	1 to 10	-
Headache	✔	1 to 10	1 to 10	✔	5	1 to 10	10
Hyperkinesia	-	-	-	-	✔	-	-
Hypokinesia	-	-	-	-	✔	-	-
Incoordination	-	-	-	-	✔	-	-
Irritability	✔	-	-	-	✔	-	-
Lethargy	-	-	-	-	-	1 to 10	-
Lightheadedness	✔	-	-	-	-	-	5
Malaise	-	-	-	-	✔	-	-
Memory impairment	✔	-	-	✔	✔	-	<1
Nervousness	✔	-	-	-	✔	-	5
Nightmares	-	-	-	-	✔	-	<1

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

Adverse Events	Flurazepam	Lorazepam	Midazolam	Oxazepam	Quazepam	Temazepam	Triazolam
Vomiting	✔	-	1 to 10	-	-	<1	5
Weight changes	✔	1 to 10	-	-	-	-	-
Xerostomia	✔	-	-	-	2	-	<1
Genitourinary							
Impotence	-	-	-	-	✔	-	-
Incontinence	-	-	-	✔	✔	-	-
Libido changes	-	-	-	✔	✔	1 to 10	<1
Decreased libido	-	-	-	-	✔	-	-
Menstrual irregularities	-	<1	-	✔	✔	-	-
Urinary retention	-	-	-	-	✔	-	-
Hematologic							
Blood dyscrasias	-	<1	-	✔	-	<1	-
Granulocytopenia	✔	-	-	-	-	-	-
Leukopenia	✔	-	-	✔	-	-	-
Hepatic							
Aspartate aminotransferase increased	✔	-	-	-	-	-	-
Alkaline phosphatase increased	✔	-	-	-	-	-	-
Alanine aminotransferase increased	✔	-	-	-	-	-	-
Bilirubin increased	✔	-	-	-	-	-	-
Hepatic dysfunction	-	-	-	✔	-	-	-
Jaundice	✔	-	-	✔	✔	-	-
Musculoskeletal							
Asthenia	-	<1	-	-	-	-	-
Dysarthria	✔	-	-	✔	✔	1 to 10	<1
Joint pain	✔	-	-	-	-	-	-
Muscle spasticity	-	-	-	-	✔	-	-
Myoclonic jerks	-	-	1 to 10	-	-	-	-
Weakness	✔	1 to 10	-	-	✔	1 to 10	<1
Respiratory							
Apnea	✔	1 to 10	-	-	-	-	-
Bronchospasm	-	-	<1	-	-	-	-
Cough	-	-	1 to 10	-	-	-	-
Dyspnea	✔	-	-	-	-	-	-
Hyperventilation	-	1 to 10	-	-	-	-	-
Laryngospasm	-	-	<1	-	-	-	-
Nasal congestion	-	1 to 10	-	-	-	-	-
Respiratory rate decreased	-	-	>10	-	-	-	-

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

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

Table 9. Boxed Warning for Midazolam Injection[1]

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

Table 10. Boxed Warning for Midazolam Syrup[1]

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

VII. Dosing and Administration

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

Table 11. Usual Dosing Regimens for the Benzodiazepines[1-14]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Alprazolam	Management of anxiety disorders, short-term relief of symptoms of anxiety: Oral concentrate (IR), orally disintegrating tablet (IR), tablet (IR): initial, 0.25 to 0.5 mg orally three times daily; may be increased to achieve a maximum therapeutic effect at every three to four days; maximum, 4 mg/day Treatment of panic disorder, with or without agoraphobia: Oral concentrate (IR), orally disintegrating tablet (IR), tablet (IR): initial, 0.5 mg orally three times daily; may increase dosage up to 1 mg every three to four days; usual dosage range is 1 to 10 mg/day Tablet (ER): initial, 0.5 to 1 mg orally in the morning; may increase dosage by up to 1 mg/day every three to four days; usual dosage range is 3 to 6 mg/day; maximum, 10 mg/day	Safety and efficacy in children have not been established.	Oral concentrate (IR): 1 mg/mL Orally disintegrating tablet (IR): 0.25 mg 0.5 mg 1 mg 2 mg Tablet (ER): 0.5 mg 1 mg 2 mg 3 mg Tablet (IR): 0.25 mg 0.5 mg 1 mg 2 mg
Chlordiazepoxide	Acute alcohol withdrawal: Capsule: initial, 50 to 100 mg, followed by repeated doses as needed; maximum, 300 mg/day Management of anxiety disorders, short-term relief of symptoms of anxiety: Capsule: mild-to-moderate symptoms, 5 or 10 mg three to four times daily; severe symptoms, 20 or 25 mg three to four times daily Preoperative apprehension/ anxiety: Capsule: 5 to 10 mg three to four times daily on days preceding surgery	Management of anxiety disorders, short-term relief of symptoms of anxiety ≥6 years of age: Capsule: 5 mg two to four times daily; may be increased to 10 mg two to three times daily	Capsule: 5 mg 10 mg 25 mg
Clonazepam	Treatment of panic disorder, with or without agoraphobia: Orally disintegrating tablet,	Management of patients with absence seizures who failed succinimides, monotherapy	Orally disintegrating tablet: 0.125 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	tablet: initial, 0.25 mg twice daily; increase by 0.125 to 0.25 mg twice daily every three days; maximum, 4 mg/day Management of patients with absence seizures who failed succinimides, monotherapy or adjunctive treatment of Lennox-Gastaut syndrome, akinetic and myoclonic seizures: Orally disintegrating tablet, tablet: initial, 1.5 mg/day divided into three doses; increase daily by 0.5 to 1 mg/day every three days; maximum, 20 mg/day	or adjunctive treatment of Lennox-Gastaut syndrome, akinetic and myoclonic seizures: Orally disintegrating tablet, tablet: ≤10 years of age (≤30 kg), 0.01 to 0.03 mg/kg/day divided two to three times daily; increase by 0.25 to 0.5 mg/day every three days; maximum, 0.2 mg/kg/day; >10 years of age (>30 kg): Initial, 1.5 mg/day divided into three doses; increase by 0.5 to 1 mg/day every three days; maximum, 20 mg/day	0.25 mg 0.5 mg 1 mg 2 mg Tablet: 0.5 mg 1 mg 2 mg
Clorazepate	Acute alcohol withdrawal: Tablet: day one: 30 mg initially, then 30 to 60 mg in divided doses for the remainder of the day; say two: 45 to 90 mg/day in divided doses; day three: 22.5 to 45 mg/day in divided doses; day four: 15 to 30 mg/day in divided doses; day five and thereafter: 7.5 to 15 mg/day in divided doses until the patient's condition is stable; maximum, 90 mg/day Management of anxiety disorders, short-term relief of symptoms of anxiety: Tablet: 15 to 60 mg/day in divided doses; usual daily dose is 30 mg/day; may be administered in a single dose at bedtime. Adjunct in partial seizures: Tablet: 7.5 mg three times daily; may increase dose by 7.5 mg/week; maximum, 90 mg/day	Adjunct in partial seizures: Tablet: nine to 12 years of age, 7.5 mg twice daily; increase by 7.5 mg/week; maximum, 60 mg/day; >12 years of age: 7.5 mg three times daily; increase by 7.5 mg/week; maximum, 90 mg/day	Tablet 3.75 mg 7.5 mg 15 mg
Diazepam	Acute alcohol withdrawal: Injection: initial, 10 mg IM/IV, then 5 to 10 mg in three to four hours, if necessary Oral concentrate, oral solution, tablet: 10 mg three to four times during the first 24 hours, reducing to 5 mg three to four times daily as needed	Management of anxiety disorders, short-term relief of symptoms of anxiety: Oral concentrate, oral solution, tablet: ≥6 months of age, 1 to 2.5 mg three to four times daily; increase gradually as needed and tolerated	Injection : 5 mg/mL Oral concentrate: 5 mg/mL Rectal gel: 2.5 mg 5-7.5-10 mg 12.5-15-17.5-20 mg

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

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	disorders: Oral: 2 to 10 mg two to four times daily Rectal gel: 0.2 mg/kg; may repeat in four4 to 12 hours Adjunct in status epilepticus and severe recurrent seizures: Injection: initial, 5 to 10 mg (IV preferred); may be repeated at 10 to 15 minute intervals; maximum, 30 mg		
Estazolam	Short-term management of insomnia: Tablet: 1 to 2 mg at bedtime	Safety and efficacy in children have not been established.	Tablet: 1 mg 2 mg
Flurazepam	Short-term management of insomnia: Capsule: 15 to 30 mg at bedtime	Safety and efficacy in children have not been established.	Capsule: 15 mg 30 mg
Lorazepam	Management of anxiety disorders, short-term relief of symptoms of anxiety: Oral concentrate, tablet: 2 to 3 mg/day divided into two to three daily doses Preanesthetic medication, producing sedation, relief of anxiety, and a decreased ability to recall events related to the day of surgery: Injection: 0.05 mg/kg IM two to three hours before procedure; maximum, 4 mg; 0.044 mg/kg or 2 mg IV (whichever is less); maximum, 0.05 mg/kg or 4 mg Treatment of status epilepticus: Injection: 4 mg IV; may repeat dose in 10 to 15 minutes if needed	Safety and efficacy in children have not been established.	Injection: 2 mg/mL 4 mg/mL Oral concentrate: 2 mg/mL Tablet: 0.5 mg 1 mg 2 mg
Midazolam	Induction of anesthesia, before administration of other anesthetic agents: Injection: unpremedicated patients, 0.3 to 0.35 mg/kg IV; premedicated patients, 0.15 to 0.35 mg/kg IV Sedation/anxiolysis/amnesia prior to or during diagnostic, therapeutic, or endoscopic procedures (amnesia maintenance): Injection: incremental	Preoperative sedation/anxiolysis/amnesia: Injection: non-neonatal: 0.1 to 0.15 mg/kg IM, six months to five years of age, 0.05 to 0.1 mg/kg IV; six to 12 years of age, 0.025 to 0.05 mg/kg IV; 12 to 16 years of age: refer to adult dosing Syrup: 0.25 to 1 mg/kg; maximum, 20 mg Sedation of intubated and	Injection: 1 mg/mL 5 mg/mL 5 mg/5 mL Syrup: 2 mg/mL

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	injections of approximately 25% of the induction dose should be given in response to signs of lightening of anesthesia and repeated as necessary Preoperative sedation/ anxiolysis/amnesia: Injection: 0.07 to 0.08 mg/kg IM administered up to one hour before surgery; IV dosage must be individualized and titrated; some patients may respond to as little as 1 mg; no more than 2.5 mg should be given over a period of at least two minutes Sedation/anxiolysis/amnesia prior to or during diagnostic, therapeutic, or endoscopic procedures (continuous infusion): Injection: 0.01 to 0.05 mg/kg IV loading dose, followed by a continuous IV infusion at a rate of 0.02 to 0.10 mg/kg/hr	mechanically ventilated patients as a component of anesthesia or during treatment in a critical care setting: Injection: <32 weeks, continuous IV infusion at a rate of 0.03 mg/kg/hr; ≥32 weeks, continuous IV infusion at a rate of 0.06 mg/kg/hour; non-neonatal, 0.05 to 0.2 mg/kg IV loading dose, followed by a continuous IV infusion at a rate of 0.06 to 0.12 mg/kg/hr	
Oxazepam	Acute alcohol withdrawal: Capsule: 15 to 30 mg three to four times daily Management of anxiety disorders, short-term relief of symptoms of anxiety: Capsule: mild-to-moderate symptoms: 10 to 15 mg three to four times daily; severe symptoms: 15 to 30 mg three to four times daily	Safety and efficacy in children <6 years of age have not been established. Absolute dosage for patients six to 12 years of age is not established. Management of anxiety disorders, short-term relief of symptoms of anxiety: Capsule: mild-to-moderate symptoms: 10 to 15 mg three to four times daily; severe symptoms: 15 to 30 mg three to four times daily	Capsule: 10 mg 15 mg 30 mg
Quazepam	Short-term management of insomnia: Tablet: 7.5 to 15 mg at bedtime	Safety and efficacy in children have not been established.	Tablet: 15 mg
Temazepam	Short-term management of insomnia: Capsule: 7.5 to 30 mg at bedtime	Safety and efficacy in children have not been established.	Capsule: 7.5 mg 15 mg 22.5 mg 30 mg
Triazolam	Short-term management of insomnia: Tablet: 0.25 mg at bedtime	Safety and efficacy in children have not been established.	Tablet: 0.125 mg 0.25 mg

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

VIII. Effectiveness

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

Table 12. Comparative Clinical Trials with the Benzodiazepines

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Alcohol Withdrawal				
Holbrook et al.[42] (1999) Benzodiazepines (chlordiazepoxide, diazepam, oxazepam, lorazepam) vs alternative active treatments (bromocriptine, carbamazepine, chlorpromazine, clonidine, doxepin, ethanol, hydroxyzine, paraldehyde, propranolol, thiamine) vs placebo	MA Patients being treated for acute alcohol withdrawal	N=1,286 (11 trials) Variable duration	Primary: Improvement of withdrawal symptoms, therapeutic success (CIWA-Ar score ≤10), adverse events, dropout rates Secondary: Not reported	Primary: In three studies with a similar outcome measures, the benzodiazepines were rated as more efficacious compared to placebo in relieving the symptoms of alcohol withdrawal within the first two days of withdrawal (OR, 3.28; 95% CI, 1.30 to 8.28). There were no significant differences in efficacy between individual benzodiazepines. In the nine trials that compared benzodiazepines with alternative active agents, there was no evidence of better efficacy of any alternative agent over a benzodiazepine. Three studies reported the number of adverse events and found no significant difference between benzodiazepines and the alternative treatments examined (OR, 0.67; 95% CI, 0.34 to 1.32). Data on study dropout rates were combined from five trials and indicated that fewer patients in the benzodiazepines group compared to the alternative treatment group dropped out within the first seven days of treatment (OR, 0.68; 95% CI, 0.47 to 0.97). Secondary: Not reported
Ntais et al.[43] (2005) Benzodiazepines alone or in	MA Patients with alcohol dependence who experienced	N=4,051 Variable duration	Primary: Severity of overall alcohol withdrawal syndrome, alcohol withdrawal	Primary: Compared to placebo, there was a benefit with the benzodiazepines against alcohol withdrawal seizures (P=0.01). Benzodiazepines had similar success rates as other drugs and offered a

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
combination with other agents vs alternate benzodiazepines vs other agents (e.g., anticonvulsants) vs placebo	alcohol withdrawal		seizures, alcohol withdrawal delirium Secondary: Adverse events, discontinuation due to adverse events, withdrawal rate, mortality	benefit for seizure control against non-anticonvulsants (P=0.02), but not against anticonvulsants (95% CI, 0.46 to 8.65). Data on other comparisons were limited preventing informative quantitative synthesis for the various outcomes. Secondary: Compared to placebo, the number of withdrawals per arm tended to be less common among patients receiving benzodiazepine (P=0.22). No patients discontinued due to side effects in the benzodiazepine group and one patient discontinued treatment for this reason in the placebo group. No patients died in either the benzodiazepine groups or placebo groups. In those studies that compared benzodiazepines to other agents, there were no between-group differences in number of withdrawals per arm (P=0.54 for comparison with other drugs and P=0.75 for comparison with anticonvulsants). Two out of 901 benzodiazepine-treated patients died compared to five out of 1,275 patients receiving other agents. Patients receiving benzodiazepines had a higher incidence of side effects compared to patients receiving other agents (P=0.16) or anticonvulsants (P=0.47), though NS.
Kumar et al.[44] (2009) Lorazepam 8 mg/day (2 mg in the morning, 2 mg in the afternoon, 4 mg at night) for 2 days; the dose was reduced by 2 mg/day every 2 days vs	DB, RCT Male inpatients in a state of moderately severe, uncomplicated alcohol withdrawal	N=100 12 days	Primary: Withdrawal severity and changes in the CIWA-Ar scale Secondary: Not reported	Primary: There was no significant difference in withdrawal severity between patients receiving lorazepam or chlordiazepoxide at baseline or at any time during the study. Using an 11-item alcohol-withdrawal checklist, irritability (2.9 vs 0.4%; P<0.001), dizziness (0.9 vs 0.0%; P<0.001), and brisk reflexes (0.8 vs 0.2%; P<0.02) were more common with lorazepam than with chlordiazepoxide. Palpitations were more common with chlordiazepoxide than with lorazepam (0.9 vs 0.0%, respectively; P<0.001). The incidence of the remaining items (depressed mood, impaired concentration, anorexia, insomnia, fever, and gait ataxia) did not differ between the two groups. There were no symptoms of benzodiazepine withdrawal recorded during

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
chlordiazepoxide 80 mg/day (20 mg in the morning, 20 mg in the afternoon, 40 mg at night) for 2 days; the dose was reduced by 20 mg per day every 2 days Dosing was down-titrated to zero across 8 treatment days.				the last four days of the study, nor were there impairing adverse events reported during this period. Secondary: Not reported
Anxiety Disorders				
Martin et al.[45] (2007) Alprazolam, diazepam, lorazepam vs placebo	MA Patients with generalized anxiety disorder	N=2,326 (23 trials) 2 to 24 weeks	Primary: Withdrawals for any reason and withdrawals due to adverse events Secondary: Withdrawals due to lack of efficacy	Primary: The RR of withdrawal for any reason was 0.78 (95% CI, 0.62 to 1.00; P=0.05) in favor of benzodiazepines. The RR of withdrawal due to adverse events was 1.54 (95% CI, 1.17 to 2.03; P=0.002) indicating an increased risk for the benzodiazepine group. Secondary: The RR of withdrawal due to lack of efficacy was 0.29 (95% CI, 0.18 to 0.45; P<0.00001) in favor of benzodiazepines.
Moylan et al.[46] (2011) Alprazolam vs benzodiazepines	MA Patients ≥18 years of age with panic disorder or agoraphobia with panic attacks	N=631 (8 trials) Variable duration	Primary: PAF, HAM-A, proportion of panic attack-free patients, adverse events Secondary: Not reported	Primary: There was no significant difference in mean PAF improvement between alprazolam and other benzodiazepines (WMD in PAF of 0.6 panic attacks/week; 95% CI, -0.3 to 1.6). There was no difference in mean HAM-A improvement between alprazolam and other benzodiazepines (WMD, 0.8 points; 95% CI, -0.5 to 2.1). There was no significant difference between alprazolam and other

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				benzodiazepines in the proportion of panic-attack free patients (RR, 1.1; 95% CI, 0.9 to 1.4). The most commonly reported adverse effect was sedation. There was no significant difference in the dropout rates due to adverse effects. There was no clinically significant difference in tolerability between alprazolam and comparative benzodiazepine. Secondary: Not reported
Mitte et al.[47] (2005) Benzodiazepines vs azaspirones vs placebo	MA Patients with generalized anxiety disorder	N=12,053 (48 trials) Variable duration	Primary: Anxiety (HAM-A), depression (HAM-D) Secondary: Not reported	Primary: Active treatment reduced both anxiety and depression symptoms better than placebo. There were no significant differences in efficacy between the benzodiazepines and azaspirones (P=NS). Significantly fewer patients in the benzodiazepine group dropped out of the study (20.5 vs 30.7%; P<0.05). Secondary: Not reported
Blanco et al.[48] (2003) Benzodiazepines, SSRIs, MAOIs, RIMAs, β-blockers, gabapentin, buspirone vs placebo	MA Patients with social anxiety disorder	N=2,954 (23 trials) 6 to 20 weeks	Primary: Outcome data on the LSAS or a categorical measure of status Secondary: CGI score	Primary: In terms of LSAS, no statistical difference was detected between medications or medication groups. Secondary: In terms of responders, effect sizes of each medication group were: benzodiazepines (16.61), brofaromine (6.96), phenelzine (4.10), gabapentin (3.78), SSRIs (3.22), atenolol (1.36), and moclobemide (1.27). No statistical differences were detected between these medications or medication groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
van Balkom et al.[49] (1997) Benzodiazepines vs antidepressants vs psychological panic management vs exposure in vivo vs placebo	MA Patients with panic disorder (with or without agoraphobia)	N=5,011 (106 trials) Variable duration	Primary: Panic, agoraphobia, depression, and general anxiety Secondary: Not reported	Primary: Antidepressants, psychological panic management and antidepressants/ exposure in vivo demonstrated significant improvement in the reduction of panic, agoraphobia, depression, and anxiety compared to a control conditions. High-potency benzodiazepines showed significant improvement in panic, agoraphobia, and anxiety compared to control conditions. There were no significant differences between the treatments for panic disorder. Antidepressant test groups had significant improvements compared to other treatments except exposure in vivo in agoraphobia. A significantly greater improvement was noted in antidepressant/exposure in vivo compared to exposure in vivo alone and psychological panic management/exposure in vivo in treatment of depression and anxiety. Secondary: Not reported
Chessick et al.[50] (2006) Benzodiazepines vs azaspirones The MA also compared the azaspirones to hydroxyzine, kava kava, placebo, venlafaxine and psychotherapy, but	MA Patients with generalized anxiety disorder	N=5,908 (36 trials) 4 to 14 weeks	Primary: HAM-A, patient acceptability Secondary: Not reported	Primary: Using the HAM-A, lorazepam (WMD, 1.1; 95% CI, 0.29 to 1.91; P=0.008) and alprazolam (WMD, 1.1; 95% CI, 0.28 to 1.92; P=0.009) were more effective than buspirone, but diazepam was comparable in efficacy to buspirone (WMD, -0.20; 95% CI, -7.45 to 7.05; P=0.96). Significantly fewer participants dropped out on benzodiazepine therapy compared to buspirone (RR, 1.24; 95% CI, 1.01 to 1.52; P=0.04). Patients receiving buspirone reported less drowsiness (P<0.00001), fatigue (P=0.00001), nervousness (P=0.0006), depression (P<0.00001), insomnia (P=0.01) and sleep problems (P=0.02) compared to benzodiazepines. Patients receiving benzodiazepines reported less nausea (P=0.03) and dizziness (P=0.02) compared to buspirone. In the trial that discontinued either diazepam or buspirone at either six or

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
only the results from studies comparing the azaspirones to the benzodiazepines are reported in this review.				12 weeks, neither group had worsening symptoms of anxiety but those on diazepam did show withdrawal symptoms at six weeks compared to those on buspirone (P<0.001). In the one extension trial with a taper off, 25% of patients on ipsapirone showed rebound anxiety symptoms compared to 40% of patients on lorazepam (P<0.001). Secondary: Not reported
Insomnia				
Holbrook et al.[51] (2000) Benzodiazepines vs zopiclone, diphenhydramine, glutethimide, promethazine, cognitive behavioral therapy, placebo	MA Patients with insomnia	N=2,672 (45 trials) 1 day to 6 weeks	Primary: Sleep latency, total sleep duration, adverse effects, dropout rates, cognitive function decline Secondary: Not reported	Primary: Using sleep records, benzodiazepines demonstrated a decrease in sleep latency by 4.2 minutes compared to placebo (95% CI, -0.7 to 9.2). Benzodiazepines demonstrated a significant increase in sleep duration compared to placebo by 61.8 minutes (95% CI, 37.4 to 86.2). Benzodiazepines were more likely to be associated with complaints of daytime drowsiness (OR, 2.4; 95% CI, 1.8 to 3.4) and dizziness/ lightheadedness (OR, 2.6; 95% CI, 0.7 to 10.3) compared to placebo. No difference was observed in dropout rates between the two groups. Pooled results from three trials indicated there was no significant difference between benzodiazepines and zopiclone in sleep latency, but benzodiazepine therapy may lead to a longer sleep by 23.1 minutes (95% CI, 5.6 to 40.6). There was no significant difference in adverse events among the treatment groups (OR, 1.5; 95% CI, 0.8 to 2.9). Comparisons between benzodiazepines and antihistamines did not detect any significant differences on sleep outcomes. Triazolam was found to be more effective in reducing sleep latency early in one trial, but efficacy decreased by the second week of treatment. Behavioral therapy efficacy was maintained throughout the nine-week follow-up.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Smith et al.[52] (2002) Benzodiazepines or benzodiazepine receptor agonists vs behavioral treatment vs placebo	MA Patients with primary insomnia for ≥1 month	N=470 (21 trials) 1 to 10 weeks	Primary: Sleep latency, TST, number of awakenings, wake time after sleep onset, and sleep quality before and after treatment Secondary: Not reported	Primary: Sleep latency was reduced by 30% with pharmacological treatment compared to 43% with behavioral interventions. Pharmacotherapy increased TST by 12% compared to 6% with behavior therapy. Both pharmacotherapy and behavior therapy reduced number of awakenings per night by one. Wake time after sleep onset was reduced by 46% with pharmacotherapy and by 56% with behavior therapy. Pharmacotherapy improved sleep quality by 20% compared to 28% with behavior therapy. Overall, there were no differences in TST, number of awakenings, wake time after sleep onset, and sleep quality between benzodiazepine receptor agonists and behavioral therapy. The behavioral therapy group had a greater reduction in latency to sleep onset than the group that took the benzodiazepine receptor agonists (95% CI, 0.17 to 1.04). Secondary: Not reported
Nowell et al.[53] (1997) Benzodiazepines or benzodiazepine receptor agonists vs placebo	MA Adults <65 years of age with chronic insomnia	N=1,894 (22 trials) 4 to 35 days	Primary: Sleep latency, TST, number of awakenings, sleep quality 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Buscemi et al.[54] (2007) Benzodiazepines, non-benzodiazepines, antidepressants vs placebo	MA Adults with chronic insomnia	105 trials 1 night to 6 months	Primary: Sleep latency, WASO, sleep efficiency, sleep quality, TST, adverse events Secondary: Not reported	Primary: Sleep latency assessed by PSG was significantly decreased for benzodiazepines (WMD, -10.0 minutes; 95% CI, -16.6 to -3.4), non-benzodiazepines (WMD, -12.8 minutes; 95% CI, -16.9 to -8.8) and antidepressants (WMD, -7.0 minutes; 95% CI, -10.7 to -3.3). Sleep latency assessed by sleep diaries was also significantly improved for benzodiazepines (WMD, -19.6 minutes; 95% CI, -23.9 to -15.3), non-benzodiazepines (WMD, -17.0 minutes; 95% CI, -20.0 to -14.0) and antidepressants (WMD, -12.2 minutes; 95% CI, -22.3 to -2.2). MA for WASO, sleep efficiency, sleep quality and TST measured by PSG and sleep diary were statistically significant and favored benzodiazepines and non-benzodiazepines vs placebo with the exception of PSG studies measuring WASO and TST, which were marginally nonsignificant. In contrast, PSG results significantly favored antidepressants vs placebo, but sleep diary results were fewer and non-significantly favored antidepressants for WASO and non-significantly favored placebo for TST. Indirect comparisons between benzodiazepines and non-benzodiazepines resulted in no significant difference in sleep latency; however, benzodiazepines were associated with more adverse events. Indirect comparisons between benzodiazepines and antidepressants resulted in no significant difference in sleep latency or adverse events. Indirect comparisons between non-benzodiazepines and antidepressants resulted in a significantly greater sleep latency assessed by PSG but not by sleep diary for non-benzodiazepines. There was no significant difference in adverse events. All drug groups had a statistically significant higher risk of harm compared to placebo, although the most commonly reported adverse events were minor. The adverse events most commonly reported in these studies were headache, drowsiness, dizziness and nausea. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Glass et al.[55] (2008) Temazepam 15 mg for 2 weeks vs diphenhydramine 50 mg for 2 weeks vs placebo for 2 weeks	DB, PC, RCT, XO Elderly patients ≥70 years of age with primary insomnia	N=20 6 weeks	Primary: Subjective assessments of sleep recorded on sleep diaries Secondary: Morning-after psychomotor impairment (using the DSST and the MTT); morning-after memory impairment (using free-recall)	Primary: There was a significant difference in sleep quality scores with temazepam compared to diphenhydramine and placebo (both P<0.05). There was a significant difference in sleep-onset latency and TST with temazepam compared to placebo (P<0.05). There was a significant difference in the number of awakenings with diphenhydramine and temazepam compared to placebo (both P<0.05). Secondary: There were no changes in the DSST or the MTT scores with any treatment. No treatment effects could be detected on the memory assessment performed.
Piccione et al.[56] (1980) Triazolam 0.25 mg vs triazolam 0.50 mg vs chloral hydrate 250 mg vs chloral hydrate 500 mg vs	DB, XO Elderly patients >60 years of age with insomnia	N=27 5 days	Primary: Efficacy (questionnaire with subjective estimates of sleep latency, TST, number of awakenings, overall quality of sleep), side effects Secondary: Not reported	Primary: The patients' global evaluation of effectiveness indicated that triazolam 0.25 and 0.50 mg improved sleep more than placebo (both P<0.05), while chloral hydrate 250 and 500 mg were not better than placebo. Triazolam 0.50 mg, but not 0.25 mg, was significantly better than chloral hydrate 250 mg (P<0.01) and 500 mg (P<0.05) in the global evaluation of effectiveness. There was no significant difference in sleep latency, TST and number of awakenings between placebo and either dose of chloral hydrate. Triazolam 0.25 mg significantly decreased sleep latency and increased TST compared to placebo (both P<0.05). Triazolam 0.50 mg significantly decreased the number of awakenings compared to placebo (P<0.01). Patients estimated their TST to be longer following the use of triazolam 0.25 mg as compared to chloral hydrate 250 or 500 mg (both P<0.05). There were no significant differences in reported side effects between the active treatments and placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				Secondary: Not reported
Okawa et al.[57] (1978) Secobarbital 100 mg vs triazolam 0.5 mg vs placebo	DB, RCT, XO (two trials) Patients 18 to 60 years of age with a history of insomnia and two of the following: onset of sleep longer than 30 minutes, duration of sleep six hours or less, or experiencing three or more awakenings	N=76 2 nights	Primary: Patient preference questionnaire, success (defined as sleep onset in 30 minutes or less and sleep duration of six hours or more), adverse effects Secondary: Not reported	Primary: One trial compared triazolam to placebo and involved 19 patients. Sixteen patients preferred triazolam over placebo and three expressed no preference (P<0.001). Triazolam demonstrated greater efficacy over placebo in overall sleep (P<0.001), onset (P<0.001), duration (P<0.002) and number of awakenings (P<0.002). Triazolam was determined to be significantly more successful in 15 of 19 patients (P<0.004). No difference in next-morning alertness was noted between the two study groups. Seven patients receiving active treatment experienced mild-to-moderate adverse effects, with dizziness, drowsiness and headache as the most frequently reported. In comparison, three of the patients in the placebo group experienced mild-to-moderate side effects. The second trial was a combined study of 57 patients comparing triazolam and secobarbital. The results of the patient preference questionnaire were analyzed and showed a significant preference for triazolam (41 patients) over secobarbital (10 patients), with six having no preference for either agent (P<0.001). Significant improvement was seen with triazolam compared to secobarbital (P<0.001) in sleep onset, duration of sleep and number of awakenings. Feelings of alertness the next morning did not differ between treatment groups. Success was established in 73% of triazolam treated patients whereas only 30% of the secobarbital treated patients were determined successful (P<0.001). Thirteen patients in the secobarbital group reported adverse effects ranging from drowsiness and restlessness to dry mouth. More patients on triazolam reported side effects. Secondary: Not reported
Seizures				
Pavlidou et al.[58] (2006) Diazepam 0.33 mg/kg every 8	PRO, RCT Children 6 months to 3 years of age who experienced a	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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
hours rectally for 1 day, followed by every 12 hours on day 2 vs no treatment	first febrile seizure			Secondary: Not reported
Treiman et al.[59] (1998) Phenobarbital 15 mg/kg vs diazepam 0.15 mg/kg, followed by phenytoin 18 mg/kg vs lorazepam 0.1 mg/kg vs phenytoin 18 mg/kg	DB, MC, RCT Adults with overt or subtle generalized convulsive status epilepticus	N=518 5 years	Primary: Success (defined as cessation of all motor and electrical seizure activity within 20 minutes of start of drug infusion and no recurrence of seizure activity within the next 40 minutes), side effects, outcomes 30 days posttreatment Secondary: Not reported	Primary: For treatment success in overt status epilepticus, a significant difference overall in the frequency of success was found, reported as: lorazepam, 64.9%; phenobarbital, 58.2%; diazepam/phenytoin, 55.8%; and phenytoin, 43.6% (P<0.02 between all groups). For subtle status epilepticus, no significant differences were seen between treatment groups (P<0.18). Lorazepam showed significantly higher frequency of treatment success compared to phenytoin in a pairwise comparison of patients with overt status epilepticus (P<0.002). Pairwise comparisons among other individual treatments showed no significant differences. There were no significant differences among any of the treatment groups with respect to adverse effects or 30-day posttreatment outcomes. Secondary: Not reported
Appleton et al.[60] (2002) Lorazepam intravenous or rectally (dose not specified)	MA Children 1 month to 16 years of age with acute tonic-clonic convulsions	N=102 1 year	Primary: Efficacy (cessation of the presenting convulsion, seizure recurrence within 24 hours of initial termination, need	Primary: Administration of one to two intravenous doses stopped the convulsion in 70% of lorazepam-treated patients compared to 65% of patients receiving intravenous diazepam (RR, 1.09; 95% CI, 0.77 to 1.54). A single dose of rectal lorazepam stopped the convulsion in all children (6/6), compared to 6/19 children treated with rectal diazepam (RR, 3.17; 95% CI, 1.63 to 6.14).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs diazepam intravenous or rectally (dose not specified)			for additional drugs), safety (adverse events, admission to intensive care unit) Secondary: Not reported	Approximately 22% of intravenous lorazepam-treated children and 35% of intravenous diazepam-treated children experienced a further convulsion within 24 hours after presentation (RR, 0.63; 95% CI, 0.27 to 1.46). Approximately 4% of patients receiving intravenous lorazepam compared to 15% of patients receiving intravenous diazepam required additional antiepileptic drugs to terminate the presenting seizure (RR, 0.25; 95% CI, 0.03 to 2.03). The incidence of respiratory depression occurring in the lorazepam-treated group was 4% compared to 21% in the diazepam-treated group (RR, 0.18; 95% CI, 0.02 to 1.37). Secondary: Not reported
Miscellaneous				
Leufkens et al.[61] (2007) Alprazolam XR 1 mg vs alprazolam IR 1 mg vs placebo	DB, PC, XO Healthy individuals 20 to 45 years of age	N=18 Up to 5.5 hours after administration	Primary: Comparison of effects on actual driving ability (as assessed in a standard on-the-road driving test) measured by SDLP in centimeters) Secondary: Comparison of effects on cognitive and psychomotor functioning related to driving in a controlled laboratory setting	Primary: Both drug formulations significantly increased SDLP (P<0.001 for both IR and XR). However, mean SDLP after alprazolam XR was significantly lower than alprazolam IR (23.44 vs 27.68 cm, respectively; P<0.001). SDLP increased with approximately 8 cm in the IR group and 4 cm in the XR group as compared to placebo (19.5 cm with placebo; P<0.001 for both comparisons). No overall differences were found between placebo and either formulation of alprazolam in terms of mean speed and speed variability. Ten driving tests were terminated prematurely due to patients being too drowsy to continue (7/18 rides in the IR group and 3/18 rides in the XR group). Secondary: In terms of the divided attention task, performance was significantly impaired at 1 (P<0.001), 2.5 (P<0.001), and 5.5 hours (P<0.01) after administration of alprazolam IR 1 mg. The effects of the XR preparation were less severe than the IR formulation at one hour (P<0.05) and at 2.5 hours (P<0.5) but no longer at 5.5 hours postdose. A significant

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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 one hour postdose; however, there was a significant difference at 2.5 and 5.5 hours (P<0.05 for both). In terms of the stop signal task, relative to placebo, the go reaction time was significantly longer after alprazolam IR (P<0.001) but not after alprazolam XR. In terms of the word learning test, placebo-drug comparisons demonstrated a significant impairing effect of alprazolam IR at one hour after administration but not with alprazolam XR.
Hindmarch et al.[62] (2006) Flurazepam 30 mg vs zolpidem modified release 6.25 mg vs zolpidem modified release 12.5 mg vs placebo	DB, RCT, XO Healthy volunteers ≥65 years of age	N=24 Single dose treatment	Primary: Psychometric tests performed 8 hours after study medication (CFF, CRT, word recall, CTT, DSST), subjective evaluation of sleep (LSEQ), safety, pharmacokinetics (zolpidem modified release only) Secondary: Not reported	Primary: There were no significant differences in psychometric tests between the zolpidem modified release treatment groups and placebo (P>0.05). Psychometric performance was significantly impaired with flurazepam compared to placebo for all tests with the exception of the DSST (P=0.0526). Ease of falling asleep and sleep quality were significantly improved with both doses of zolpidem modified release and with flurazepam (all P<0.05). Neither zolpidem modified release, nor flurazepam, modified perception of well-being on awakening. The frequency of adverse events was similar in all four treatment conditions. None of the adverse events was serious or led to withdrawal from the study. The plasma concentration ratio was 1.96 between the two doses of zolpidem modified release, which is consistent with dose linearity. Secondary: Not reported
Johnson et al.[63] (2006)	DB, XO Adults with a	N=14 18 days	Primary: Subject-rated measures (drug	Primary: Triazolam showed dose-related effects on subject-rated, observer-rated, and motor and cognitive performance measures.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Triazolam 0.25, 0.5 or 0.75 mg vs ramelteon 16, 80 or 160 mg vs placebo	history of sedative abuse		liking, street value, pharmacological classification), observer-rated measures (sedation, impairment), motor and cognitive performance (balance task, DSST, word recall) Secondary: Not reported	Compared to placebo, all doses of ramelteon showed no significant effect on any of the subjective effect measures, including those related to potential for abuse (all P>0.05). In the pharmacological classification, 79% of patients identified the highest dose of ramelteon as placebo. Compared to placebo, ramelteon had no effect at any dose on any observer-rated or motor and cognitive performance measure (all P>0.05). Secondary: Not reported

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

Additional Evidence

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

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

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

IX. Cost

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

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

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

Rx=prescription

Table 13. Relative Cost of the Benzodiazepines

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

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

X. Conclusions

The benzodiazepines are approved for the treatment of anxiety disorders and for the short-term treatment of insomnia.[1-14] In addition, some of the agents are approved for the treatment of seizure disorders, acute alcohol withdrawal, as muscle relaxants, and for the induction/maintenance of general anesthesia. The benzodiazepines are mechanistically similar; however, they differ with regards to their pharmacokinetic properties (e.g., onset and duration of action).[17,18] All of the benzodiazepines are available in a generic formulation, with the exception of quazepam.

The benzodiazepines that are approved for the treatment of anxiety include alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, lorazepam and oxazepam. The American Psychiatric Association recommends the initial use of either a serotonin-norepinephrine reuptake inhibitor (SNRI) or a selective serotonin reuptake inhibitor (SSRI) for the treatment of panic disorder due to their favorable safety and tolerability profiles.[20] However, benzodiazepines may be preferred for patients with very distressing or impairing symptoms in whom rapid symptom control is critical. They can be used concurrently with antidepressants to help control symptoms until the antidepressant takes effect, which is then followed by a slow tapering of the benzodiazepine.[20] For the long-term treatment of generalized anxiety disorder, the National Institute for Health and Clinical Excellence recommends the use of an SSRI as first-line therapy.[20] Benzodiazepines should only be used as a short-term measure during crises.[33] Benzodiazepines have been shown to be more effective than placebo, and have demonstrated similar efficacy compared to agents in other classes for the treatment of anxiety disorders.[20,47-50,45] Guidelines do not give preference to one particular benzodiazepine over another. The risk of adverse events and physiological dependence must be considered when using the benzodiazepines.[21] Benzodiazepines are not recommended as monotherapy for the treatment of obsessive-compulsive disorder or posttraumatic stress disorder.[23-26]

Several benzodiazepines are approved for the short-term treatment of insomnia, including estazolam, flurazepam, quazepam, temazepam and triazolam. The American Academy of Sleep Medicine recommends the use of a short/intermediate-acting benzodiazepine, benzodiazepine receptor agonist, or ramelteon for the initial treatment of insomnia.[27] They do not give preference to one agent over another. Symptom pattern, treatment goals, past treatment responses, patient preference, comorbid conditions, contraindications, drug interactions and adverse events should be considered when selecting a specific agent.[27] The frequency and severity of adverse events may be lower with benzodiazepine receptor agonists (e.g., eszopiclone, zaleplon and zolpidem) due to their shorter half-lives.[26,28] Hypnotic treatments should be combined with behavioral and cognitive therapies.[27] Patients should be followed every few weeks during the initial treatment period to assess for effectiveness, adverse events and the need for ongoing medication. Chronic use of hypnotic medications may be necessary in those individuals with severe/refractory insomnia or for those with chronic comorbid illnesses.[27] Results from clinical trials demonstrate that the benzodiazepines are effective for the short-term treatment of insomnia.[27,28,50,53,54]

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

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

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

XI. Recommendations

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

XII. References

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Anxiolytics, Sedatives and Hypnotics – Miscellaneous
AHFS Class 282492
May 14, 2014

I. Overview

The miscellaneous anxiolytics, sedatives, and hypnotics are used primarily for the treatment of anxiety disorders and insomnia. Anxiety disorders include generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder and social phobia.[1] The agents approved for the treatment of anxiety include buspirone, hydroxyzine and meprobamate.[2-5] The exact mechanism of action of buspirone is unknown. It lacks anticonvulsant, muscle relaxant or sedative properties, which are seen with other agents. The anxiolytic effects of hydroxyzine may be due to a suppression of activity in key regions of the subcortical area of the central nervous system. Meprobamate has been shown to have effects at multiple sites in the central nervous system, including the thalamus and limbic system.

The key diagnostic feature of primary insomnia is difficulty initiating or maintaining sleep for at least one month, which causes marked distress or impairment in social, occupational, or other important areas of functioning.[1] Insomnia may be classified as transient (one to three nights), short-term (three nights to one month) or chronic ($\geq$1 month) based upon the duration of symptoms.[6] Eszopiclone, zaleplon and zolpidem are approved for the treatment of insomnia.[7-13] These agents are considered benzodiazepine receptor agonists; however, they are more selective than traditional benzodiazepines when binding to the $GABA_A$ receptor complex. Compared to the benzodiazepines, they have a more rapid onset, shorter duration of action, and a lower risk of tolerance, dependence and abuse. They are classified as Schedule IV controlled substances by federal regulation.[7-13] Ramelteon is a melatonin receptor agonist, which is also approved for the treatment of insomnia.[14] It is more selective for the melatonin type 1 (MT_1) and type 2 (MT_2) receptors as compared to the type 3 (MT_3) receptor in the suprachiasmatic nucleus of the hypothalamus.[14] The MT_1 and MT_2 receptors are thought to be involved in the maintenance of the circadian rhythm underlying the normal sleep-wake cycle. Ramelteon is not a controlled substance. Discontinuation after chronic administration did not produce withdrawal signs and it does not appear to produce physical dependence.[14]

Some of the miscellaneous agents are also approved for the management of acute alcohol withdrawal, for use as a sedative (e.g., preoperative, prior to procedures, and in intubated or mechanically ventilated patients), for the management of nausea/vomiting from surgical/diagnostic procedures, and for the treatment of pruritus. Dexmedetomidine is a selective $alpha_2$-adrenergic agonist with sedative properties.[15] Droperidol is a butyrophenone antipsychotic. The antiemetic effect is due to the blockade of dopamine stimulation of the chemoreceptor trigger zone.[2-4] Other effects include alpha-adrenergic blockade, peripheral vascular dilation, and reduction of the pressor effect of epinephrine.

Since the last review Intermezzo® (zolpidem) a sublingual zolpidem formulation, was approved by the Food and Drug Administration (FDA) for the as needed treatment of insomnia when a middle of the night awakening is followed by difficultly returning to sleep.[13] This is the first medication to be approved for this indication.[16] Intermezzo® (zolpidem) provides a lower dose of zolpidem compared to other zolpidem agents. Furthermore, the agent is formulated as a sublingual tablet that employs a proprietary binary buffer system. This buffer system is theorized to increase salivary pH and facilitate the rapid sublingual absorption of the drug across the oral mucosa by conversion of the medication to its lipophilic form.[13]

In January 2013, the FDA released new recommendations that the dose of zolpidem be lowered due to new data suggesting that blood levels in some patients may be high enough the morning after use to impair activities that require alertness, including driving. Women appear to be more susceptible, as they eliminate zolpidem more slowly than men.[17]

The FDA required the manufacturers of Ambien®, Ambien CR®, Edluar®, and Zolpimist® to lower the recommended dose. The recommended dose of zolpidem for women should be lowered from 10 to 5 mg for immediate-release products (Ambien®, Edluar®, and Zolpimist®) and from 12.5 to 6.25 mg for extended-release

products (Ambien CR®). For men, the labeling should recommend that health care professionals consider prescribing the lower doses—5 mg for immediate-release products and 6.25 mg for extended-release products.[17]

The miscellaneous anxiolytics, sedatives, and hypnotics that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. All of the products are available in a generic formulation, with the exception of dexmedetomidine and ramelteon. This class was last reviewed in August 2012.

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

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Buspirone	tablet	N/A	buspirone
Dexmedetomidine	injection	Precedex®	none
Droperidol	injection	N/A	droperidol
Eszopiclone	tablet	Lunesta®*	eszopiclone
Hydroxyzine	capsule, injection, syrup, tablet	Vistaril®*	hydroxyzine
Meprobamate	tablet	N/A	meprobamate
Ramelteon	tablet	Rozerem®	none
Zaleplon	capsule	Sonata®*	zaleplon
Zolpidem	extended-release tablet, oral spray, sublingual tablet, tablet	Ambien®*, Ambien CR®*, Edluar®, Intermezzo®, Zolpimist®	zolpidem

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

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the miscellaneous anxiolytics, sedatives, and hypnotics are summarized in Table 2.

Table 2. Treatment Guidelines Using the Miscellaneous Anxiolytics, Sedatives, and Hypnotics

Clinical Guideline	Recommendation(s)

National Institute for Clinical Excellence: **Generalized Anxiety Disorder and Panic Disorder (With or Without Agoraphobia) in Adults (2011)**[18]	<u>Stepped care for people with generalized anxiety disorder (GAD)</u>
	• If a person with GAD chooses drug treatment, offer a selective serotonin reuptake inhibitor (SSRI), specifically sertraline.
	• If sertraline is ineffective, offer an alternative SSRI or a serotonin–noradrenaline reuptake inhibitor (SNRI), taking into account the following factors:
	  o Tendency to produce a withdrawal syndrome (especially with paroxetine and venlafaxine).
	  o The side-effect profile and the potential for drug interactions.
	  o The risk of suicide and likelihood of toxicity in overdose (especially with venlafaxine).
	  o The person's prior experience of treatment with individual drugs (particularly adherence, effectiveness, side effects, experience of withdrawal syndrome and the person's preference).
	• If the person cannot tolerate SSRIs or SNRIs, consider offering pregabalin.
	• Do not offer a benzodiazepine for the treatment of GAD in primary or secondary care except as a short-term measure during crises.
	• Do not offer an antipsychotic for the treatment of GAD in primary care.
	
	<u>Panic disorder general considerations</u>
	• Benzodiazepines are associated with a less effective outcome in the long term and should not be prescribed for panic disorder.
	• Sedating antihistamines or antipsychotics should not be prescribed for panic disorder.

Clinical Guideline	Recommendation(s)

	• Interventions with evidence for the longest duration of effect are listed in descending order, where preference of the patient should be taken into account:
	  o Psychological therapy (i.e., cognitive behavioral therapy, structured problem solving, psychoeducation).
	  o Pharmacological therapy (antidepressant therapy).
	  o Self-help interventions (i.e., bibliotherapy, support groups, exercise, cognitive behavioral therapy via a computer interface).
	• Antidepressants should be the only pharmacologic intervention used in the longer term.
	• Two types of medication are considered in the guideline for the treatment of panic disorder, tricyclic antidepressants (TCAs) and SSRIs.
	• Unless otherwise indicated, an SSRI (e.g., paroxetine, fluvoxamine, citalopram) licensed for panic disorder should be offered. If an SSRI is not suitable or there is no improvement after a 12-week course and if further medication is appropriate, imipramine or clomipramine may be considered.
	• If the patient is showing improvement, the medication should be continued for at least six months after optimal dose is reached, after which the dose may be tapered slowly over an extended period of time to minimize the risk of discontinuation/withdrawal symptoms.

American Psychiatric Association: **Practice Guideline for the Treatment of Patients with Panic Disorder, Second Edition (2009)**[19]	• SSRIs, SNRIs, TCAs, and benzodiazepines have demonstrated efficacy in numerous controlled trials and are recommended for treatment of panic disorder. • Because SSRIs, SNRIs, TCAs, and benzodiazepines appear roughly comparable in their efficacy for panic disorder, selecting a medication involves considerations of side effects, pharmacological properties, potential drug interactions, prior treatment history, and comorbid medical and psychiatric conditions. • The relatively favorable safety and side effect profile of SSRIs and SNRIs makes them the best initial choice for many patients with panic disorder. • There is no evidence of differential efficacy between the SSRIs, although differences in the side-effect profile (e.g., potential for weight gain, discontinuation-related symptoms), half-life, propensity for drug interactions, and availability of generic formulations may be clinically relevant. They are safer than TCAs and monoamine oxidase inhibitors (MAOI). They are rarely lethal in overdose and have few serious effects on cardiovascular function. • Venlafaxine extended release has been shown to be effective for panic disorder. It is generally well tolerated and has a side effect profile similar to the SSRIs. No systematic data are currently available supporting the use of duloxetine, in panic disorder, although its mechanism of action suggests it might be an effective agent. • Although TCAs are effective, the side effects and greater toxicity in overdose limit their acceptability to patients and clinical utility. Given the equivalency of TCAs in treating depression, there is little reason to expect other TCAs to work less well for panic disorder. TCAs that are more noradrenergic (e.g., desipramine, maprotiline) may be less effective than agents that are more serotonergic. • SSRIs, SNRIs, and TCAs are all preferable to benzodiazepines as monotherapies for patients with comorbid depression or substance use disorders. Benzodiazepines may be especially useful adjunctively with antidepressants to treat residual anxiety symptoms. • Benzodiazepines may be preferred for patients with very distressing or impairing symptoms in whom rapid symptom control is critical. The benefit of more rapid response to benzodiazepines must be balanced against the possibilities of troublesome side effects and physiological dependence that

Clinical Guideline	Recommendation(s)
	may lead to difficulty discontinuing the medication. • MAOIs appear effective for panic disorder but, because of their safety profile, they are generally reserved for patients who have failed to respond to several first-line treatments. • Neither trazodone nor nefazodone can be recommended as a first-line treatment for panic disorder. There is minimal support for the use of trazodone in panic disorder and it appears less effective than imipramine and alprazolam. There are a few small, uncontrolled studies showing benefits of nefazodone in some patients with panic disorder; however, its use has been limited by concerns about liver toxicity. • Bupropion was effective in one small trial and ineffective in another. It cannot be recommended as a first line treatment for panic disorder. • Other medications with less empirical data may be considered as monotherapies or adjunctive treatments for panic disorder when patients have failed to respond to several standard treatments or based on other individual circumstances.

American Academy of Child and Adolescent Psychiatry:
Practice Parameter for the Assessment and Treatment of Children and Adolescents with Anxiety Disorders (2007)[20]
	• A multimodal treatment approach for children and adolescents with anxiety disorders should consider education of the parents and the child about the anxiety disorder, consultation with school personnel and primary care physicians, cognitive-behavioral interventions, psychodynamic psychotherapy, family therapy, and pharmacotherapy.
	• Treatment of childhood anxiety disorders of mild severity should begin with psychotherapy.
	• Valid reasons for combining medication and treatment with psychotherapy include the following:
	  o Need for acute symptom reduction in a moderately to severely anxious child.
	  o A comorbid disorder that requires concurrent treatment.
	  o Partial response to psychotherapy and potential for improved outcome with combined treatment.
	• SSRIs have emerged as the medication of choice in the treatment of childhood anxiety disorders.
	• When anxiety disorder symptoms are moderate or severe or impairment makes participation in psychotherapy difficult, or psychotherapy results in a partial response, treatment with medication is recommended.
	• No controlled studies are available for medication treatment of childhood-onset panic disorder. The use of a SSRI in adolescents with panic disorder has shown significant improvement in panic symptoms.
	• Controlled trials have established the safety and efficacy of short-term treatment with SSRIs for childhood anxiety disorders; however, the benefits and risks of long-term use of SSRIs have not been studied. It is recommended that clinicians consider a medication-free trial for children who have a significant reduction in anxiety or depressive symptoms on an SSRI and maintain stability in these symptoms for one year.
	• There is no empirical evidence that a particular SSRI is more effective than another for treatment of childhood anxiety disorders. The choice is often based on side effects, duration of action, or positive response to a particular SSRI in a first-degree relative with anxiety.
	• The risk-benefit ratio for a medication trial needs to be carefully assessed because cognitive-behavioral therapy has been shown to be effective and long-term side effects of medications have not been studied in youths.
	• The safety and efficacy of medications other than SSRIs for the treatment of childhood anxiety disorders have not been established.
	• Noradrenergic antidepressants (venlafaxine and TCAs), buspirone, and benzodiazepines have been suggested as alternatives to be used alone or in

Clinical Guideline	Recommendation(s)
	combination with the SSRIs. • Data are limited in childhood anxiety disorders to guide treatment with combinations of medications when a single medication is not effective in managing anxiety symptoms. Comorbid diagnoses are strongly considered in selection of medication. • Preliminary findings from controlled trials of extended-release venlafaxine in the treatment of youths with GAD and social phobia suggest it may be well tolerated and effective relative to placebo. • Controlled trials with TCAs for pediatric anxiety disorders have shown conflicting results and have not established efficacy for this use. • Buspirone may be an alternative to SSRIs for GAD in youths, but there are no published controlled trials. • Benzodiazepines have not shown efficacy in controlled trials in childhood anxiety disorders despite established benefit in adult trials. They are used as an adjunct short-term treatment with SSRIs to achieve rapid reduction in severe anxiety symptoms that may permit initiation of the exposure phase of cognitive-behavioral therapy. Clinicians should use benzodiazepines cautiously because of the possibility of developing dependency.
American Academy of Child and Adolescent Psychiatry: **Practice Parameter for the Assessment and Treatment of Children and Adolescents With Obsessive-Compulsive Disorder (2012)**[21]	• The psychiatric assessment of children and adolescents should routinely screen for the presence of obsessions and/or compulsions or repetitive behaviors. • If screening suggests obsessive-compulsive symptoms, clinicians should fully evaluate the child using the Diagnostic and Statistical Manual of Mental Disorders-IV-TR criteria and scalar assessment. • A complete psychiatric evaluation should be performed, including information from all available sources and compromising standard elements of history and a mental state examination, with attention to the presence of commonly occurring comorbid psychiatric disorders. • It is possible that three out of four children with obsessive-compulsive disorder (OCD) meet criteria for at least one comorbid diagnosis, and these children have lower response rates to cognitive behavioral therapy than children without comorbid diagnoses. • Identification of major depressive disorder and bipolar disorder is very important before initiating treatment with a SSRI. • Comorbid eating disorders are infrequent in younger children; however, comorbid eating disorders become more prevalent in adolescents. • A full medical, developmental, family and school history should be included with the psychiatric history and examination. • Cognitive behavioral therapy is the first-line treatment for mild to moderate OCD in children, whenever possible. • For moderate to severe OCD, medication is indicated in addition to cognitive behavioral therapy. • Serotonin reuptake inhibitors (SRIs) are the first-line medications recommended for OCD in children, including clomipramine (a TCA) and certain SSRIs (fluoxetine, fluvoxamine, paroxetine and sertraline). • There is no SRI that is proven to be more efficacious over another. • The modality of assigned treatment should be guided by empirical evidence on the moderators and predictors of treatment response. • Multimodal treatment with cognitive behavioral therapy and medication is recommended if cognitive behavioral therapy fails to achieve a clinical response after several months or in more severe cases. • Medication augmentation strategies are reserved for treatment-resistant cases in which impairments are deemed moderate in at least one important domain of function despite adequate monotherapy. • Adding clomipramine to an SSRI is a useful medication augmentation

Clinical Guideline	Recommendation(s)
	strategy. • Augmenting with an atypical neuroleptic is also a strategy employed by experts (e.g. haloperidol and risperidone combined) based on studies in adults with OCD; however, controlled data for the use of atypical antipsychotics in children with OCD does not exist. • A minimum of two adequate SSRI trials or an SSRI and clomipramine trial is recommended before atypical augmentation. • Empirically validated medication and psychosocial treatments for comorbid disorders should be considered.
American Psychiatric Association: **Practice Guideline for the Treatment of Patients with Obsessive-Compulsive Disorder (2007)**[22]	General considerations • OCD is a chronic illness which typically waxes and wanes. • Patients who have symptoms interfering with daily functioning should be treated. • Clinical remission and recovery may not always occur and will not occur rapidly. • Goals of treatment include improving symptoms, patient functioning, and quality of life. Initial treatment options • The choice of treatment depends on the patient's ability to comply with therapy, whether psychotherapy, pharmacotherapy, or both. • First-line treatments include cognitive-behavioral therapy, SRIs, or a combination of the two. The choice depends on past treatment history, comorbid psychiatric conditions, severity of symptoms, and functional limitations. • Cognitive-behavioral therapy or SRI therapy may be used alone or in combination, and combination therapy may be considered in patients who do not respond fully to monotherapy, those with severe symptoms, those with comorbid psychiatric illnesses for which an SRI is indicated, or in patients who wish to limit SRI exposure. • All SRIs appear to be equally effective, though patients may respond to agents differently. • Prescribers should consider the safety, side effects, Food and Drug Administration (FDA) warnings, drug interactions, past response to treatment, and comorbid medical conditions when choosing a medication for treatment. • Most patients do not experience a significant improvement until four to six weeks after treatment initiation, and some may ultimately respond after as many as 10 to 12 weeks. • Patients not responding after 10 to 12 weeks may respond to a higher dose of the same medication. Changing treatments and pursuing sequential treatment trials • Augmentation strategies may be preferred to switching strategies in patients who have a partial response to the initial treatment. • Augmentation of SRIs with trials of different antipsychotic medications or with cognitive-behavioral therapy or augmentation of cognitive-behavioral therapy with an SRI. • Patients who do not respond to their first SRI may have their medication switched to a different SRI. A switch to venlafaxine is less likely to produce an adequate response. • For patients who have not benefitted from their first SSRI trial, a switch to mirtazapine can be considered. • After first- and second-line treatments and well-supported augmentation strategies have been exhausted, less well-supported treatment strategies may be considered. These include augmenting SRIs with clomipramine, buspirone,

Clinical Guideline	Recommendation(s)
	pindolol, riluzole, or once- weekly oral morphine sulfate. • Evidence for beneficial effects of benzodiazepines as monotherapy for OCD is limited to case reports with clonazepam and alprazolam. Modest doses of benzodiazepines may relieve anxiety and distress in OCD without directly diminishing the frequency or duration of obsessions or compulsions. Given their limited evidence for efficacy, benzodiazepines cannot be recommended as monotherapy for OCD, except in those rare individuals who are unable or unwilling to take standard anti-OCD medications.
American Academy of Child and Adolescent Psychiatry: **Practice Parameter for the Assessment and Treatment of Children and Adolescents With Posttraumatic Stress Disorder (2010)**[23]	• The psychiatric evaluation of children and adolescents should routinely include questions about traumatic experiences and posttraumatic stress disorder (PTSD) symptoms. • If the evaluation indicates symptoms of PTSD, the clinician should formally determine if PTSD is present, the severity of PTSD symptoms and the degree of functional impairment. Caregivers should be included in the formal evaluation. • A differential diagnosis should be conducted in order to rule out diagnoses with symptoms that can mimic PTSD symptoms. • The treatment plan should be comprehensive in approach and should consider the severity of symptoms and impairment, as well as comorbid psychiatric conditions. • Trauma-focused psychotherapies should be considered first-line in children and adolescents with PTSD, including psychoanalytic, attachment and cognitive behavioral treatment models. • SSRIs can be considered for treatment of children and adolescents with PTSD. • The effect of SSRIs in children with PTSD may be more consistent with a placebo effect. • Other medications such as clonidine and propranolol may be useful in decreasing symptoms of hyperarousal, and anticonvulsants may beneficial in treating PTSD symptoms other than avoidance. • Benzodiazepines have not been found to be beneficial in treating PTSD symptoms. • School-based accommodations are recommended for children with PTSD, especially in children with school-based trauma, such as bullying. • The use of restrictive, “rebirthing,” binding or other coercive therapies are not recommended. • Screening for PTSD in the school or community should be conducted after traumatic events that affect significant numbers of children.
American Psychiatric Association: **Guideline Watch: Practice Guideline for the Treatment of Patients with Acute Stress Disorder and Posttraumatic Stress Disorder (2009)**[24]	• Meta-analyses and several randomized controlled trials published since 2004 support the greater efficacy of SSRIs and SNRIs over placebo for non-combat-related PTSD. • The evidence base for pharmacological intervention in combat-related PTSD has not been significantly augmented by recent studies. Studies suggest that SSRIs may not be recommended with the previous level of confidence for the treatment of PTSD in this particular population. Further research is needed to answer why these populations have been shown to have differential responses to SSRI treatment. • As described in the 2004 guideline, no significant differences among antidepressants, including the SSRIs, were found in the few head-to-head studies then available. Since that time, studies have been published comparing nefazodone and sertraline, venlafaxine and sertraline, the SNRI reboxetine and fluvoxamine, and fluoxetine, moclobemide, and tianeptine. These studies have generally demonstrated the greater efficacy of antidepressants to placebo but have done little to clarify the relative utility of these different antidepressants.

Clinical Guideline	Recommendation(s)
	• There is a relatively robust evidence basis for pharmacological treatment with antidepressant medications (particularly SSRIs and SNRIs for noncombat PTSD) as compared to other classes of medications. • Comparison of other treatments with the SSRIs and SNRIs is complicated by methodological differences in the available studies. SSRIs and SNRIs have mostly been studied in rigorous trials compared to placebo; other agents have been studied against "treatment as usual" or as augmentation agents in patients with refractory illness.
American Psychiatric Association: **Practice Guideline for the Treatment of Patients with Acute Stress Disorder and Posttraumatic Stress Disorder (2004)**[25]	• Goals of treatment for patients with PTSD and acute stress disorder include lessening the severity of symptoms and preventing trauma-related comorbid conditions. • Clinical trial data and randomized studies are limited and difficult to perform. • Treatment includes pharmacotherapy, psychotherapy and supportive measures. • SSRIs are first-line therapy for PTSD and acute stress disorder and if found effective, treatment should be continued in order to continue to see benefit. • Second-line treatment agents include TCAs (specifically amitriptyline and imipramine, but not desipramine) and MAOIs. • Benzodiazepines should not be used as monotherapy, but may be effective as sedatives and anxiolytics. • Atypical antipsychotics may be necessary for patients experiencing psychotic symptoms. • Anticonvulsants (divalproex, carbamazepine, topiramate and lamotrigine) have produced mixed results for treating PTSD and acute stress disorder but may prove to be beneficial. • Limited data exists for the use of adrenergic inhibitors and their use is not part of the guideline at this time. • An adequate trial of therapy requires a minimum of three months of treatment. If treatment is effective, it should be continued for up to 12 months or longer.

American Academy of Sleep Medicine:
Clinical Guideline for the Evaluation and Management of Chronic Insomnia in Adults (2008)[26]
	• The primary treatment goals are to improve sleep quality/quantity and to improve insomnia related daytime impairments.
	• Short-term hypnotic treatment should be supplemented with behavioral and cognitive therapies when possible.
	• When pharmacotherapy is utilized, the choice of a specific pharmacological agent should be directed by: symptom pattern, treatment goals, past treatment responses, patient preference, availability of other treatments, comorbid conditions, contraindications, concurrent medication interactions, and side effects.
	• For patients with primary insomnia, when pharmacologic treatment is utilized alone or in combination therapy, the recommended general sequence of medication trials is:
	  o Short-intermediate acting benzodiazepine receptor agonists or ramelteon.
	  o Alternate short-intermediate acting benzodiazepine receptor agonists or ramelteon if the initial agent has been unsuccessful.
	  o Sedating antidepressants, especially when used in conjunction with treating comorbid depression/anxiety. Examples of these include trazodone, amitriptyline, doxepin, and mirtazapine.
	  o Combined benzodiazepine receptor agonists or ramelteon and sedating antidepressant.
	  o Other sedating agents. Examples include anti-epilepsy medications (gabapentin, tiagabine) and atypical antipsychotics (quetiapine and olanzapine). These medications may only be suitable for patients with comorbid insomnia who may benefit from the primary action of

Clinical Guideline	Recommendation(s)
	these drugs as well as from the sedating effect. • Over-the-counter antihistamine or antihistamine/analgesic type drugs (over-the-counter "sleep aids"), as well as herbal and nutritional substances (e.g., valerian and melatonin), are not recommended in the treatment of chronic insomnia due to the relative lack of efficacy and safety data. • Older approved drugs for insomnia including barbiturates, barbiturate-type drugs and chloral hydrate are not recommended for the treatment of insomnia. • Pharmacological treatment should be accompanied by patient education regarding treatment goals, safety concerns, potential side effects and drug interactions, other treatment modalities (cognitive and behavioral treatments), potential for dosage escalation, and rebound insomnia. • Patients should be followed on a regular basis, every few weeks in the initial period of treatment when possible, to assess for effectiveness, possible side effects, and the need for ongoing medication. • Efforts should be made to employ the lowest effective maintenance dosage of medication and to taper medication when conditions allow. Medication tapering and discontinuation are facilitated by cognitive behavioral therapy for insomnia. • Chronic hypnotic medication may be indicated for long-term use in those with severe or refractory insomnia or chronic comorbid illness. Whenever possible, patients should receive an adequate trial of cognitive behavioral treatment during long-term pharmacotherapy. • Long-term prescribing should be accompanied by consistent follow-up, ongoing assessment of effectiveness, monitoring for adverse effects, and evaluation for new onset or exacerbation of existing comorbid disorders. • Long-term administration may be nightly, intermittent (e.g., three nights per week), or as needed.
National Institutes of Health: **Manifestations and Management of Chronic Insomnia in Adults (2005)**[27]	<u>Behavioral and cognitive therapies</u> • Behavioral methods include relaxation training, stimulus control, and sleep restriction. • Cognitive therapy methods have been added to behavioral methods and include cognitive restructuring, in which anxiety-producing beliefs and erroneous beliefs about sleep and sleep loss are specifically targeted. • The combination of cognitive methods and behavioral methods has been found to be as effective as prescription medications for short-term treatment of chronic insomnia. The beneficial effects of cognitive-behavioral therapy may last well beyond the termination of active treatment. <u>Benzodiazepine receptor agonists</u> • Benzodiazepine receptor agonists include benzodiazepines (e.g., flurazepam, temazepam, and triazolam) as well as nonbenzodiazepine-structured anxiolytic agents acting at benzodiazepine receptors (e.g., eszopiclone, zaleplon, and zolpidem). • Benzodiazepine receptor agonists have been shown to be effective in the short-term management of insomnia. • The frequency and severity of the adverse effects are much lower for the newer benzodiazepine receptor agonists, most likely because these agents have shorter half-lives. • In the short term, abuse of the benzodiazepine receptor agonists is not a major problem, but problems associated with their long-term use require further study. • Barbiturates (e.g., phenobarbital) have been used in the treatment of insomnia, however, short-term and long-term studies are lacking; such drugs bear significant risks and are not recommended in the treatment of chronic insomnia.

Clinical Guideline	Recommendation(s)
	Other prescription medications • Other sedating medications have been used in the treatment of insomnia. These include barbiturates and antipsychotics. • Studies demonstrating the usefulness of these medications for either short- or long-term management of insomnia are lacking. • All of these agents have significant risks. Thus, their use in the treatment of chronic insomnia cannot be recommended. Antidepressants • Antidepressants (especially trazodone) are often prescribed for insomnia, although they are not FDA-approved for this purpose. • In short-term use, trazodone and doxepin have been shown to have some beneficial effects, but there are no studies on long-term use. • Data on other antidepressants (e.g., amitriptyline and mirtazapine) in individuals with chronic insomnia are lacking. • These guidelines were published prior to the FDA approval of ramelteon. Nonprescription medications • Antihistamines are the most commonly used over-the-counter treatments for chronic insomnia, but there is no systematic evidence for efficacy and there are significant concerns about risks of these medications. • Adverse effects include residual daytime sedation, diminished cognitive function, and delirium, the latter being of particular concern in the elderly. Other adverse effects include dry mouth, blurred vision, urinary retention, constipation, and risk of increased intraocular pressure in individuals with narrow angle glaucoma.

American Society for Gastrointestinal Endoscopy:
Sedation and Anesthesia in Gastrointestinal Endoscopy (2008)[28]
	• Adequate and safe sedation can be achieved in most patients undergoing routine esophagogastroduodenoscopy and colonoscopy by using an intravenous benzodiazepine and opioid combination.
	• In patients who are not adequately sedated with an intravenous benzodiazepine and opioid combination, the addition of other intravenous agents such as droperidol, promethazine, or diphenhydramine may allow adequate and safe sedation to be achieved. These medications potentiate the action of the benzodiazepine/narcotic regimen; thus, a deeper level of sedation may result.
	• Droperidol is a neuroleptic agent in the same class as haloperidol with sedative effects. Randomized trials have demonstrated the efficacy of droperidol in patients undergoing therapeutic endoscopy, particularly those who are difficult to sedate.
	• Use droperidol only in select patients with the inability to achieve an acceptable response or intolerance to standard sedatives, or for an anticipated long procedure.
	  o Obtain 12-lead electrocardiogram before procedure.
	  o Droperidol is contraindicated if the QTc is prolonged (>440 milliseconds in males, >450 milliseconds in females).
	  o Patients should remain on a cardiac monitor during the procedure and for two to three hours afterward.
	  o Use with caution in patients at high risk for development of prolonged QT syndrome such as congestive heart failure, bradycardia, cardiac hypertrophy, hypokalemia/magnesemia, or other drugs known to prolong the QTc interval.
	• Propofol has the advantages of more rapid onset of action and shorter recovery time compared to traditional sedative regimens. However, clinically important benefits in average-risk patients undergoing upper endoscopy and

Clinical Guideline	Recommendation(s)
	colonoscopy have not been consistently demonstrated with regard to patient satisfaction and safety. Therefore, the routine use of propofol in average- risk patients cannot be endorsed.
International Anesthesia Research Society: **Consensus Guidelines for Managing Postoperative Nausea and Vomiting (2003)**[29]	• There is no evidence of any difference in the efficacy and safety profiles of the serotonin (5-HT3) receptor antagonists in the prophylaxis of post operative nausea and vomiting. • Because the 5-HT3 antagonists as a group have greater efficacy in the prevention of vomiting than nausea, they are the drugs of first choice for prophylaxis in children. • If a patient has received no prophylaxis, therapy with small-dose 5-HT3 receptor antagonists should be initiated on the first signs of post operative nausea and vomiting. • Dexamethasone effectively prevents nausea and vomiting. It appears to be most effective when administered before the induction of anesthesia rather than at the end. • Prophylactic doses of droperidol are effective for the prevention of post operative nausea and vomiting. The efficacy of droperidol is equivalent to that of ondansetron for post operative nausea and vomiting prophylaxis. It is most effective when administered at the end of surgery. It is also effective when given concomitantly with patient-controlled analgesia devices that deliver morphine. • When prophylaxis with dexamethasone fails to prevent post operative nausea and vomiting, treatment with a small-dose 5-HT3 receptor antagonist has been recommended. • When prophylaxis with a 5-HT3 antagonist is inadequate to prevent post operative nausea and vomiting, a 5-HT3 antagonist should not be initiated as rescue therapy within the first six hours after surgery because it confers no additional benefit. • When post operative nausea and vomiting occurs more than six hours after surgery, repeat dosing of 5-HT3 antagonists and droperidol can be considered. • Dimenhydrinate seems to be similar in efficacy to that of the 5-HT_3 receptor antagonists and droperidol. • The role of prochlorperazine in the treatment of post operative nausea and vomiting is still poorly understood. • Prochlorperazine 5 to 10 mg intravenous, administered at the end of surgery, has been shown to be effective. However, use of phenothiazines is limited in the ambulatory setting because of the resulting sedation.
American Gastroenterological Association: **Technical Review: Nausea and Vomiting (2001)**[30]	• For the prevention of acute post chemotherapy- and radiation-related nausea and vomiting, the combination of a 5-HT_3 receptor antagonist and dexamethasone is the preferred option. • For post operative nausea and vomiting, the use of 5-HT_3 receptor antagonists and droperidol have proven most effective in comparisons both with placebo and with other agents in large randomized trials. Comparisons between the various 5-HT_3 antagonists or between members of this class of compounds and droperidol have generally found similar efficacies for all. • Droperidol has been shown to be useful in the treatment of anticipatory and acute chemotherapy-related nausea and vomiting, and also in the therapy of post operative nausea and vomiting.
National Institute for Health and Clinical Excellence: **Alcohol-Use Disorders. Diagnosis, Assessment and Management of**	<u>Treatment for acute alcohol withdrawal</u> • Offer pharmacotherapy to treat the symptoms of acute alcohol withdrawal. • Consider offering a benzodiazepine or carbamazepine. • Clomethiazole may be offered as an alternative to a benzodiazepine or carbamazepine.

Clinical Guideline	Recommendation(s)
Harmful Drinking and Alcohol Dependence (2011)[31]	Management of delirium tremens • Lorazepam is considered a first-line treatment option. • If symptoms persist or oral medication is declined, give parenteral lorazepam, haloperidol or olanzapine. Management of alcohol withdrawal seizures • In people with alcohol withdrawal seizures, consider offering a quick-acting benzodiazepine (e.g., lorazepam) to reduce the likelihood of further seizures. • Do not offer phenytoin to treat alcohol withdrawal seizures.
American Psychiatric Association: **Treatment of Patients with Substance Use Disorders, Second Edition (2007)**[32]	Alcohol use disorders: treatment principles and alternatives • The treatment of patients in moderate to severe withdrawal includes efforts to reduce central nervous system irritability and restore physiological homeostasis. • Management of alcohol withdrawal generally requires the use of thiamine and fluids, benzodiazepines, and occasionally other medications such as anticonvulsants, clonidine, or antipsychotic agents. • Once clinical stability is achieved, the tapering of benzodiazepines and other medications should be carried out as necessary. • Naltrexone may attenuate some of the reinforcing effects of alcohol; however, long-term data regarding efficacy are limited. • Acamprosate may also be an effective adjunctive medication in motivated patients who are receiving psychosocial treatment. • Disulfiram is an effective adjunct to a comprehensive treatment program for reliable, motivated patients whose drinking may be triggered by events that suddenly increase alcohol craving.

III. Indications

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

Table 3. FDA-Approved Indications for the Miscellaneous Anxiolytics, Sedatives, and Hypnotics (Drugs B-E)[2-5,7,15]

Indication	Buspirone	Dexmedetomidine	Droperidol	Eszopiclone
Anxiety Disorders				
Management of anxiety disorders	✔			
Short-term relief of symptoms of anxiety	✔			
Sedative-Hypnotic				
Sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting; administer by continuous infusion not to exceed 24 hours		✔		
Sedation of non-intubated patients prior to and/or during surgical and other procedures		✔		
Treatment of insomnia (shown to decrease sleep latency and improve sleep maintenance)				✔
Miscellaneous				
To reduce the incidence of nausea and vomiting associated with surgical and diagnostic procedures			✔	

Table 4. FDA-Approved Indications for the Miscellaneous Anxiolytics, Sedatives, and Hypnotics (Drugs H-Z)[2-58-14]

Indication	Hydroxyzine	Meprobamate	Ramelteon	Zaleplon	Zolpidem
Anxiety Disorders					
Management of anxiety disorders		✔			
Short-term relief of symptoms of anxiety		✔			
Symptomatic relief of anxiety and tension associated with psychoneurosis and as an adjunct in organic disease states in which anxiety is manifested	✔				
Sedative-Hypnotic					
Sedation when used as premedication and following general anesthesia	✔				
Short-term treatment of insomnia (shown to decrease the time to sleep onset for up to 30 days in controlled clinical studies; it has not been shown to increase total sleep time or decrease the number of awakenings; the clinical trials performed in support of efficacy ranged from a single night to five weeks in duration; the final formal assessments of sleep latency were performed at the end of treatment)				✔	
Short-term treatment of insomnia characterized by difficulties with sleep initiation (shown to decrease sleep latency for up to 35 days in controlled clinical studies)					✔ *
Insomnia when a middle-of-the-night awakening is followed by difficulty returning					✔ †

Indication	Hydroxyzine	Meprobamate	Ramelteon	Zaleplon	Zolpidem
to sleep (not indicated for the treatment of middle-of-the night awakening when the patient has fewer than four hours of bedtime remaining before the planned time of waking)					
Treatment of insomnia characterized by difficulty with sleep onset			✔		
Insomnia characterized by difficulties with sleep onset and/or sleep maintenance					✔ ‡
Miscellaneous					
Management of pruritus caused by allergic conditions such as chronic urticaria and atopic or contact dermatoses and in histamine-mediated pruritus	✔				

*Immediate-release formulations (oral spray, sublingual tablet [Edluar®], and tablet).
†Immediate-release formulations (sublingual tablet [Intermezzo®].
‡Extended-release formulation.

IV. Pharmacokinetics

The pharmacokinetic parameters of the miscellaneous anxiolytics, sedatives, and hypnotics are listed in Table 5.

Table 5. Pharmacokinetic Parameters of the Miscellaneous Anxiolytics, Sedatives, and Hypnotics[2-5,7-15]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Buspirone	Variable	92.5	Liver	Primarily renal	2.6 to 3.0
Dexmedetomidine	Not reported	94	Liver	Renal (95) Feces (4)	2
Droperidol	Complete	Extensive	Liver	Renal (75) Feces (22)	134 minutes
Eszopiclone	Rapidly absorbed	52 to 59	Liver	Renal	6
Hydroxyzine	Rapidly absorbed orally	Not reported	Liver	Not reported	Not reported
Meprobamate	Well absorbed	Not reported	Liver	Renal (8 to 19)	10
Ramelteon	1.8	82	Liver	Renal (84) Feces (4)	1.0 to 2.6
Zaleplon	30	60	Liver	Renal (71) Feces (17)	1
Zolpidem	70	93	Liver	Renal (<1)	2.5 to 3.0

V. Drug Interactions

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

Table 6. Significant Drug Interactions with the Miscellaneous Anxiolytics, Sedatives, and Hypnotics[2]

Generic Name(s)	Significance Level	Interaction	Mechanism
Buspirone	1	Linezolid	Serotonin syndrome (e.g., agitation, altered consciousness, ataxia, myoclonus, overactive, reflexes, shivering) may occur in some patients. Unless patients are carefully observed for signs and symptoms of serotonin syndrome, do not coadminister.
Droperidol	1	Ziprasidone	The combination of ziprasidone and droperidol may have cause additive prolongation of the QT interval.
Ramelteon	1	Fluvoxamine	Plasma concentrations of ramelteon/zolpidem may be increased by coadministration of fluvoxamine. Inhibition of CYP1A2 by fluvoxamine may decrease the metabolic elimination of ramelteon/zolpidem.
Buspirone, zolpidem	2	Azole antifungals	Inhibition of CYP3A4 by azole antifungals may decrease the metabolic elimination and increase plasma concentrations of eszopiclone.
Buspirone	2	Class IA, IC, III antiarrhythmics	Droperidol in combination with Class IA, Class IC or Class III antiarrhythmics may cause additive QT interval prolongation and arrhythmias.
Buspirone	2	Macrolides and ketolides	Inhibition of CYP3A4 by macrolides and ketolides may decrease the metabolic

Generic Name(s)	Significance Level	Interaction	Mechanism
			elimination and increase plasma concentrations of buspirone or eszopiclone.
Buspirone	2	Rifamycins	Induction of CYP3A4 isoenzymes by rifampin may increase the metabolic elimination of eszopiclone, ramelteon, zaleplon or zolpidem.
Meprobamate	2	Ethanol	Coadministration may enhance central nervous system depressant effects affecting coordination and judgment.
Zolpidem	2	Human immunodeficiency virus protease inhibitors	Inhibition of CYP3A4 by protease inhibitors may decrease the metabolic elimination and increase plasma concentrations of eszopiclone and zolpidem.

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

VI. Adverse Drug Events

The most common adverse drug events reported with the miscellaneous anxiolytics, sedatives, and hypnotics are listed in Table 7. The boxed warning for droperidol is listed in Table 8. Chloral hydrate, meprobamate, eszopiclone, zaleplon and zolpidem are classified as Schedule IV controlled substances by federal regulation because of their abuse potential. The risk of abuse and dependence increases with the dose, duration of treatment and concomitant use of other psychoactive drugs. The risk is also greater for patients who have a history of alcohol/drug abuse or psychiatric disorders.

Table 7. Adverse Drug Events (%) Reported with the Miscellaneous Anxiolytics, Sedatives, and Hypnotics[2-5,7-15]

Adverse Events	Buspirone	Dexmedetomidine	Droperidol	Eszopiclone	Hydroxyzine	Meprobamate	Ramelteon	Zaleplon	Zolpidem
Cardiovascular									
Angina	-	-	-	-	-	-	-	<1	-
Arrhythmia	-	✔	-	-	-	✔	-	-	-
Atrial fibrillation	-	4 to 5	-	-	-	-	-	-	-
Atrioventricular block	-	✔	-	-	-	-	-	-	-
Bigeminy	-	-	-	-	-	-	-	<1	-
Bradycardia	<1	5 to 14	-	-	-	-	-	-	-
Bundle branch block	-	-	-	-	-	-	-	<1	-
Cardiac arrest	-	✔	✔	-	-	-	-	-	-
Cardiomyopathy	<1	-	-	-	-	-	-	-	-
Cardiospasm	-	-	-	-	-	-	-	<1	-
Chest pain	≥1	-	-	1 to 10	-	-	-	≥1	1 to 10
Electrocardiogram changes	-	-	-	-	-	✔	-	-	-
Extrasystoles	-	✔	-	-	-	-	-	-	-
Heart block	-	✔	-	-	-	-	-	-	-
Heart failure	<1	-	-	-	-	-	-	-	-
Hypertension	<1	✔	✔	<1	-	-	-	<1	<1
Hypotension	<1	24 to 54	✔	-	-	-	-	<1	<1
Hypotensive crisis	-	-	-	-	-	✔	-	-	-
Hypovolemia	-	3	-	-	-	-	-	-	-
Myocardial infarction	<1	✔	-	-	-	-	-	-	-
Palpitation	-	-	-	-	-	✔	-	<1	1 to 10
Pericardial effusion	-	-	-	-	-	-	-	<1	-
Peripheral edema	-	-	-	1 to 10	-	✔	-	≤1	-
QTc prolongation	-	-	✔	-	-	-	-	-	-
Supraventricular tachycardia	-	✔	-	-	-	-	-	-	-
Syncope	<1	-	-	-	-	✔	-	<1	<1
T-wave inversion	-	✔	-	-	-	-	-	-	-
Tachycardia	-	-	✔	-	-	✔	-	-	<1
Torsades de pointes	-	-	✔	-	-	-	-	-	-
Vasodilation	-	-	-	-	-	-	-	<1	-
Ventricular arrhythmia	-	✔	-	-	-	-	-	-	-
Ventricular extrasystoles	-	-	-	-	-	-	-	<1	-
Ventricular tachycardia	-	✔	✔	-	-	-	-	<1	-
Central Nervous System									
Abnormal gait	-	-	-	<1	-	-	-	-	-

Adverse Events	Buspirone	Dexmedetomidine	Droperidol	Eszopiclone	Hydroxyzine	Meprobamate	Ramelteon	Zaleplon	Zolpidem
Abnormal thinking	-	-	-	-	-	-	-	≥1	-
Agitation	-	✔	-	<1	-	-	-	-	<1
Amnesia	-	-	-	-	-	-	-	2 to 4	1 to 10
Anger	2	-	-	-	-	-	-	-	-
Anxiety	-	-	✔	1 to 3	-	-	-	≤1	1 to 10
Apathy	-	-	-	-	-	-	-	-	1 to 10
Ataxia	<1	-	-	<1	-	✔	-	<1	1 to 10
Attention disturbance	-	-	-	-	-	-	-	-	1 to 10
Burning sensation	-	-	-	-	-	-	-	-	1 to 10
Cerebrovascular attack	<1	-	-	-	-	-	-	<1	<1
Chills	-	-	✔	-	-	✔	-	-	-
Central nervous system stimulation	-	-	-	-	-	-	-	<1	-
Cognition decreased	-	-	-	-	-	-	-	-	<1
Complex sleep-related activities	-	-	-	<1	-	-	✔	<1	<1
Concentration decreased	-	-	-	-	-	-	-	-	<1
Confusion	2	✔	-	≤3	-	-	-	≤1	1 to 10
Delirium	-	✔	-	-	-	-	-	-	-
Delusions	-	-	-	-	-	-	-	<1	-
Depersonalization	-	-	-	-	-	-	-	<1 to 2	1 to 10
Depression	-	-	✔	1 to 4	-	-	2	≥1	1 to 10
Disinhibition	-	-	-	-	-	-	-	-	1 to 10
Disorientation	-	-	-	-	-	-	-	-	1 to 10
Dizziness	12	✔	✔	5 to 7	✔	✔	4 to 5	7 to 9	1 to 12
Dream disturbances	≥1	-	-	1 to 3	-	-	-	-	1 to 10
Drowsiness	10	-	✔	-	✔	✔	-	-	1 to 10
Drugged feeling	-	-	-	-	-	-	-	-	1 to 10
Dysphoria	-	-	✔	-	-	-	-	-	-
Emotional lability	-	-	-	<1	-	-	-	-	<1
Euphoria	-	-	-	<1	-	✔	-	-	1 to 10
Excitement	2	-	-	-	-	✔	-	-	-
Extrapyramidal symptoms	<1	-	✔	-	-	-	-	-	-
Fatigue	-	-	-	-	✔	-	3 to 4	-	1 to 10
Fever	-	✔	-	<1	-	✔	-	≥1	1 to 10
Hallucinations	<1	✔	✔	1 to 3	✔	-	-	≤1	1 to 10
Hangover effect	-	-	-	-	-	-	-	-	-
Headache	6	✔	-	15 to 21	✔	✔	-	30 to 42	3 to 19
Hostility	-	-	-	<1	-	-	-	-	-
Hyperactivity	-	-	✔	-	-	-	-	-	-
Hypoesthesia	-	-	-	-	-	-	-	<1 to 2	1 to 10
Illusion	-	✔	-	-	-	-	-	-	<1
Incoordination	1	-	-	-	-	-	-	-	-
Insomnia	-	-	-	-	-	-	3	-	1 to 10
Involuntary movements	-	-	-	-	✔	-	-	-	-
Lethargy	-	-	-	-	-	-	-	-	1 to 10
Lightheadedness	3	-	-	-	-	-	-	-	1 to 10
Memory impairment	-	-	-	<1	-	-	-	-	1 to 10

Adverse Events	Buspirone	Dexmedetomidine	Droperidol	Eszopiclone	Hydroxyzine	Meprobamate	Ramelteon	Zaleplon	Zolpidem
Malaise	-	-	-	<1	-	-	-	<1 to 2	-
Migraine	-	-	-	1 to 10	-	-	-	≥1	<1
Mood disorder	-	-	-	-	-	-	-	-	1 to 10
Nervousness	5	-	-	≤5	✔	-	-	≥1	-
Neuralgia	-	✔	-	≤3	-	-	-	-	-
Neuritis	-	✔	-	<1	-	-	-	-	-
Neuroleptic malignant syndrome	-	-	✔	-	-	-	-	-	-
Neuropathy	-	-	-	<1	-	-	-	-	-
Neurosis	-	-	-	<1	-	-	-	-	-
Nightmares	-	-	-	-	-	-	-	-	-
Numbness	2	-	-	-	-	-	-	-	-
Overstimulation	-	-	-	-	-	✔	-	-	-
Paresthesia	1	-	-	<1	✔	✔	-	3	<1 to 10
Parkinsonism	<1	-	-	-	-	-	-	-	-
Personality disorders	<1	-	-	-	-	-	-	-	-
Psychosis	<1	-	-	-	-	-	-	-	-
Restlessness	-	-	✔	-	-	-	-	-	-
Sedation	-	-	-	-	-	-	-	-	-
Seizure	<1	✔	-	-	✔	-	-	-	-
Sleep disorder	-	-	-	-	-	-	-	-	1 to 10
Somnolence	-	-	-	8 to 10	-	-	3 to 5	5 to 6	6 to 15
Speech disorder	-	✔	-	-	-	✔	-	-	<1
Stress	-	-	-	-	-	-	-	-	1 to 10
Stupor	-	-	-	-	-	-	-	-	<1
Suicidal ideation	<1	-	-	-	-	-	-	-	-
Temperature regulation altered	-	-	-	-	-	-	-	-	1 to 10
Tremor	1	-	-	<1	✔	-	-	2	1 to 10
Vertigo	-	-	-	<1	-	✔	-	≤1	1 to 10
Dermatological									
Alopecia	-	-	-	<1	-	-	-	<1	-
Contact dermatitis	-	-	-	<1	-	✔	-	-	-
Ecchymosis	<1	-	-	-	-	✔	-	<1	-
Eczema	-	-	-	<1	-	-	-	-	-
Erythema multiforme	-	-	-	<1	-	✔	-	-	-
Maculopapular rash	-	-	-	<1	-	-	-	-	-
Petechiae	-	-	-	-	-	✔	-	-	-
Photosensitivity reaction	-	-	-	<1	-	-	-	≤1	-
Pruritus	-	-	-	1-4	✔	-	-	≥1	<1
Purpura	-	-	-	-	-	✔	-	<1	-
Rash	1	-	-	3-4	✔	✔	-	≥1	1 to 10
Stevens-Johnson syndrome	-	-	-	-	-	✔	-	-	-
Urticaria	-	-	-	<1	✔	-	-	-	1 to 10
Vesiculobullous rash	-	-	-	<1	-	-	-	-	-
Wrinkling	-	-	-	-	-	-	-	-	1 to 10
Endocrine and Metabolic									
Acidosis	-	✔	-	-	-	-	-	-	-

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

Adverse Events	Buspirone	Dexmedetomidine	Droperidol	Eszopiclone	Hydroxyzine	Meprobamate	Ramelteon	Zaleplon	Zolpidem
Dysmenorrhea	-	-	-	≤3	-	-	-	3 to 4	-
Dysuria	-	-	-	<1	-	-	-	<1	1 to 10
Enuresis	<1	-	-	-	-	-	-	-	-
Hematuria	-	-	-	<1	-	-	-	<1	-
Impotence	-	-	-	-	-	-	-	<1	-
Incontinence	-	-	-	-	-	-	-	<1	<1
Kidney calculus	-	-	-	<1	-	-	-	-	-
Kidney pain	-	-	-	<1	-	-	-	-	-
Libido decreased	-	-	-	≤3	-	-	-	-	-
Menorrhagia	-	-	-	<1	-	-	-	-	1 to 10
Menstrual irregularities	<1	-	-	-	-	-	-	-	-
Oliguria	-	✔	-	<1	-	✔	-	-	-
Pelvic inflammatory disease	<1	-	-	-	-	-	-	-	-
Pyelonephritis	-	-	-	<1	-	-	-	-	-
Renal failure	-	-	-	-	-	-	-	-	<1
Urethritis	-	-	-	<1	-	-	-	-	-
Urinary frequency	-	-	-	<1	-	-	-	-	-
Urinary incontinence	-	-	-	<1	-	-	-	-	-
Urinary retention	-	1	-	-	-	-	-	<1	-
Urinary tract infection	-	-	-	≤3	-	-	-	-	1 to 10
Vaginal hemorrhage	-	-	-	<1	-	-	-	-	-
Vaginitis	-	-	-	<1	-	-	-	-	<1
Vulvovaginal dryness	-	-	-	-	-	-	-	-	1 to 10
Hematologic									
Acute intermittent porphyria	-	-	-	-	-	-	-	-	-
Agranulocytosis	-	-	-	-	-	✔	-	-	-
Anemia	-	✔	-	-	-	-	-	<1	<1
Aplastic anemia	-	-	-	-	-	✔	-	-	-
Eosinophilia	<1	-	-	-	-	✔	-	<1	-
Leukocytosis	-	-	-	-	-	-	-	<1	-
Leukopenia	<1	-	-	-	-	✔	-	-	<1
Lymphadenopathy	-	-	-	-	-	-	-	<1	<1
Lymphocytosis	-	-	-	-	-	-	-	<1	-
Porphyria exacerbation	-	-	-	-	-	✔	-	-	-
Thrombocytopenia	<1	-	-	-	-	-	-	-	-
Thrombocytopenic purpura	-	-	-	-	-	✔	-	-	-
Thrombophlebitis	-	-	-	<1	-	-	-	<1	-
Hepatic									
Abnormal hepatic function	-	-	-	-	-	-	-	-	<1
Alkaline phosphatase increased	-	✔	-	-	-	-	-	-	-
Alanine transaminase increased	-	✔	-	-	-	-	-	<1	-
Aspartate aminotransferase increased	-	✔	-	-	-	-	-	<1	-
Gamma-glutamyl transpeptidase increased	-	✔	-	-	-	-	-	-	-
Hepatic impairment	-	✔	-	-	-	-	-	-	-
Hepatitis	-	-	-	<1	-	-	-	-	-
Hepatomegaly	-	-	-	<1	-	-	-	-	-

Adverse Events	Buspirone	Dexmedetomidine	Droperidol	Eszopiclone	Hydroxyzine	Meprobamate	Ramelteon	Zaleplon	Zolpidem
Hyperbilirubinemia	-	✔	-	-	-	-	-	<1	-
Liver damage	-	-	-	<1	-	-	-	-	-
Liver function tests abnormal	-	-	-	-	-	-	-	<1	-
Transaminases increased	<1	-	-	-	-	-	-	-	-
Laboratory Test Abnormalities									
Blood urea nitrogen increased	-	✔	-	-	-	-	-	-	-
Cortisol decreased	-	-	-	-	-	-	1	-	-
Hypercholesterolemia	-	-	-	<1	-	-	-	-	-
Hyperglycemia	-	-	-	-	-	-	-	<1	<1
Hyperkalemia	-	✔	-	-	-	-	-	-	-
Hyperuricemia	-	-	-	-	-	-	-	<1	-
Hypocalcemia	-	1	-	-	-	-	-	-	-
Hypoglycemia	-	✔	-	-	-	-	-	<1	-
Hypokalemia	-	-	-	<1	-	-	-	-	-
Hypothyroidism	-	-	-	-	-	-	-	<1	-
Prolactin increased	-	-	-	-	-	-	✔	-	-
Testosterone decreased	-	-	-	-	-	-	✔	-	-
Musculoskeletal									
Arthralgia	-	-	-	-	-	-	2	≥1	1 to 10
Arthritis	-	-	-	-	-	-	-	≥1	-
Back pain	-	-	-	-	-	-	-	≥1	1 to 10
Balance disorder	-	-	-	-	-	-	-	-	1 to 10
Cogwheel rigidity	<1	-	-	-	-	-	-	-	-
Dysarthria	-	-	-	-	-	-	-	<1	-
Dyskinesia	<1	-	-	-	-	-	-	-	-
Dystonia	<1	-	-	-	-	-	-	<1	-
Hypertonia	-	-	-	-	-	-	-	1	-
Involuntary muscle contractions	-	-	-	-	-	-	-	-	1 to 10
Muscle spasms	<1	-	-	-	-	-	-	-	-
Myalgia	-	-	-	-	-	-	2	≥1	1 to 10
Myasthenia	-	-	-	<1	-	-	-	<1	-
Myopathy	-	-	-	<1	-	-	-	-	-
Myositis	-	-	-	-	-	-	-	<1	-
Neck pain	-	-	-	-	-	-	-	-	1 to 10
Neck rigidity	-	-	-	<1	-	-	-	-	-
Osteoporosis	-	-	-	-	-	-	-	<1	-
Psychomotor retardation	-	-	-	-	-	-	-	-	1 to 10
Restless leg syndrome	<1	-	-	-	-	-	-	-	-
Rigors	-	✔	-	-	-	-	-	-	-
Weakness	2	-	-	-	-	✔	-	5 to 7	1 to 10
Respiratory									
Apnea	-	✔	-	-	-	-	-	-	-
Asthma	-	-	-	<1	-	-	-	-	-
Bronchitis	-	-	-	<1	-	-	-	≥1	-
Bronchospasm	-	✔	✔	-	-	✔	-	-	-
Dyspnea	<1	✔	-	<1	-	-	-	-	<1

Adverse Events	Buspirone	Dexmedetomidine	Droperidol	Eszopiclone	Hydroxyzine	Meprobamate	Ramelteon	Zaleplon	Zolpidem
Epistaxis	<1	-	-	<1	-	-	-	≤1	-
Hypercapnia	-	✔	-	-	-	-	-	-	-
Hyperventilation	<1	-	-	-	-	-	-	-	-
Hypoventilation	-	✔	-	-	-	-	-	-	-
Hypoxia	-	✔	-	-	-	-	-	-	-
Laryngospasm	-	-	✔	-	-	-	-	-	-
Nasal congestion	≥1	-	-	-	-	-	-	-	-
Pharyngitis	-	-	-	-	-	-	-	-	1 to 10
Pleural effusion	-	2	-	-	-	-	-	-	-
Pulmonary congestion	-	✔	-	-	-	-	-	-	-
Pulmonary embolus	-	-	-	-	-	-	-	<1	-
Respiratory acidosis	-	✔	-	-	-	-	-	-	-
Respiratory depression	-	37	-	-	✔	-	-	-	-
Sinusitis	-	-	-	-	-	-	-	-	1 to 10
Throat irritation	≥1	-	-	-	-	-	-	-	1 to 10
Upper respiratory tract infection	-	-	-	-	-	-	3	-	1 to 10
Wheezing	-	≤1	-	-	-	-	-	-	-
Special Senses									
Accommodation impaired	-	-	-	-	-	✔	-	-	-
Asthenopia	-	-	-	-	-	-	-	-	1 to 10
Blurred vision	2	-	-	-	✔	-	-	-	1 to 10
Conjunctivitis	<1	-	-	<1	-	-	-	≥1	-
Depth perception altered	-	-	-	-	-	-	-	-	1 to 10
Diplopia	-	-	-	-	-	-	-	-	1 to 10
Dry eyes	-	-	-	<1	-	-	-	-	-
Ear pain	-	-	-	-	-	-	-	≤1	-
Eye pain	-	-	-	-	-	-	-	3 to 4	-
Eye redness	-	-	-	-	-	-	-	-	1 to 10
Glaucoma	-	-	-	-	-	-	-	<1	-
Hyperacusis	-	-	-	-	-	-	-	1 to 2	-
Mydriasis	-	-	-	<1	-	-	-	-	-
Nystagmus	-	-	-	<1	-	-	-	-	-
Parosmia	-	-	-	-	-	-	-	1 to 2	-
Photophobia	-	-	-	<1	-	-	-	<1	-
Photopsia	-	✔	-	-	-	-	-	-	-
Ptosis	-	-	-	-	-	-	-	<1	-
Scleritis	-	-	-	-	-	-	-	-	<1
Tinnitus	≥1	-	-	<1	-	-	-	-	1 to 10
Vestibular disorder	-	-	-	<1	-	-	-	-	-
Visual disturbance	<1	✔	-	-	-	-	-	<1 to 2	1 to 10
Other									
Accidental injury	-	-	-	≤3	-	-	-	-	-
Allergic reaction	<1	-	-	<1	✔	-	-	-	1 to 10
Anaphylaxis	-	-	✔	<1	-	✔	✔	<1	<1
Angioedema	<1	-	-	<1	-	-	✔	<1	<1
Angioneurotic edema	-	-	-	-	-	✔	-	-	-

Adverse Events	Buspirone	Dexmedetomidine	Droperidol	Eszopiclone	Hydroxyzine	Meprobamate	Ramelteon	Zaleplon	Zolpidem
Binge eating	-	-	-	-	-	-	-	-	1 to 10
Diaphoresis	1	✔	-	<1	-	-	-	-	<1
Drug dependence	-	-	-	-	-	-	-	-	-
Edema	<1	-	-	<1	-	-	-	-	<1
Facial edema	-	-	-	<1	-	-	-	-	-
Facial paralysis	-	-	-	-	-	-	-	<1	-
Falling	-	-	-	-	-	-	-	-	<1
Flu-like syndrome	-	-	-	-	-	-	-	-	1 to 10
Heat stroke	-	-	-	<1	-	-	-	-	-
Hemorrhage	-	✔	-	-	-	-	-	-	-
Herpes zoster	-	-	-	<1	-	-	-	-	-
Hypersensitivity	-	-	-	-	-	✔	-	-	-
Infection	-	-	-	5 to 10	-	-	-	-	-
Influenza	-	-	-	-	-	-	1	-	-
Lactose intolerance	-	-	-	-	-	-	-	<1	-
Pain	1	✔	-	4 to 5	-	-	-	-	-
Serotonin syndrome	<1	-	-	-	-	-	-	-	-
Shivering	-	-	✔	-	-	-	-	-	-
Somnambulism	-	-	-	-	-	-	-	-	<1
Thrombosis	-	-	-	-	-	-	-	-	<1
Twitching	-	-	-	<1	-	-	-	-	-
Viral infection	-	-	-	3	-	-	-	-	-

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

Table 8. Boxed Warning for Droperidol[2]

WARNING
Cases of QT prolongation and/or torsade de pointes have been reported in patients receiving droperidol at doses at or below recommended doses. Some cases have occurred in patients with no known risk factors for QT prolongation, and some cases have been fatal. Due to its potential for serious proarrhythmic effects and death, reserve droperidol for use in the treatment of patients who fail to show an acceptable response to other adequate treatments, either because of insufficient effectiveness or the inability to achieve an effective dose due to intolerable adverse effects from those drugs. Cases of QT prolongation and serious arrhythmias (e.g., torsade de pointes) have been reported in patients treated with droperidol. Based on these reports, all patients should undergo a 12-lead electrocardiogram prior to administration of droperidol to determine if a prolonged QT interval (i.e., QTc greater than 440 msec for males or 450 msec for females) is present. If there is a prolonged QT interval, do not administer droperidol. For patients in whom the potential benefit of droperidol treatment is felt to outweigh the risks of potentially serious arrhythmias, perform electrocardiogram monitoring prior to treatment and continue for two to three hours after completing treatment to monitor for arrhythmias. Droperidol is contraindicated in patients with known or suspected QT prolongation, including patients with congenital long QT syndrome. Administer droperidol with extreme caution to patients who may be at risk for development of prolonged QT syndrome (e.g., congestive heart failure, bradycardia, use of a diuretic, cardiac hypertrophy, hypokalemia, hypomagnesemia, or administration of other drugs known to increase the QT interval). Other risk factors may include age greater than 65 years, alcohol abuse, and use of agents such as benzodiazepines, volatile anesthetics, and intravenous opiates. Initiate droperidol at a low dose and adjust upward, with caution, as needed to achieve the desired effect.

VII. Dosing and Administration

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

Table 9. Usual Dosing Regimens for the Miscellaneous Anxiolytics, Sedatives, and Hypnotics[2-5,7-15]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Buspirone	Management of anxiety disorders; short-term relief of symptoms of anxiety: Tablet: 7.5 mg twice daily; increase by 5 mg/day every two to three days as needed; maximum, 60 mg/day	Safety and efficacy in children have not been established.	Tablet: 5 mg 7.5 mg 10 mg 15 mg 30 mg
Dexmedetomidine	Sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting; administer by continuous infusion not to exceed 24 hours: Injection: 1 µg/kg intravenous over 10 minutes, then 0.2 to 0.7 µg/kg/hour Sedation of non-intubated patients prior to and/or during surgical and other procedures: Injection: 1 µg/kg intravenous over 10 minutes, then 0.2 to 1.0 µg/kg/hour	Safety and efficacy in children have not been established.	Injection: 200 µg/2 mL 200 µg/50 mL 400 µg/100 mL

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Droperidol	To reduce the incidence of nausea and vomiting associated with surgical and diagnostic procedures: Injection: 2.5 mg; additional 1.25 mg doses may be given to achieve desired effect	To reduce the incidence of nausea and vomiting associated with surgical and diagnostic procedures in patients two to 12 years of age: Injection: 0.1 mg/kg To reduce the incidence of nausea and vomiting associated with surgical and diagnostic procedures in patients ≥12 years of age: Injection: 2.5 mg	Injection: 2.5 mg/mL
Eszopiclone	Treatment of insomnia: Tablet: 2 mg immediately before bedtime; maximum, 3 mg	Safety and efficacy in children have not been established.	Tablet: 1 mg 2 mg 3 mg
Hydroxyzine	Symptomatic relief of anxiety and tension associated with psychoneurosis and as an adjunct in organic disease states in which anxiety is manifested: Injection: 50 to 100 mg intramuscular stat, then every four to six hours as needed Capsule, syrup, tablet: 50 to 100 mg four times daily Management of pruritus caused by allergic conditions such as chronic urticaria and atopic or contact dermatoses and in histamine-mediated pruritus: Capsule, syrup, tablet: 25 mg three to four times per day Sedation when used as premedication and following general anesthesia: Injection: 25 to 100 mg intramuscular Capsule, syrup, tablet: 50 to 100 mg	Symptomatic relief of anxiety and tension associated with psychoneurosis and as an adjunct in organic disease states in which anxiety is manifested in patients ≥6 years of age: Capsule, syrup, tablet: 50 to 100 mg daily in divided doses Symptomatic relief of anxiety and tension associated with psychoneurosis and as an adjunct in organic disease states in which anxiety is manifested in patients <6 years of age: Capsule, syrup, tablet: 50 mg daily in divided doses Management of pruritus caused by allergic conditions such as chronic urticaria and atopic or contact dermatoses and in histamine-mediated pruritus in patients ≥6 years of age: Capsule, syrup, tablet: 50 to 100 mg daily in divided doses	Capsule: 25 mg 50 mg 100 mg Injection: 25 mg/mL 50 mg/mL Syrup: 10 mg/5 mL Tablet: 10 mg 25 mg 50 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
		Management of pruritus caused by allergic conditions such as chronic urticaria and atopic or contact dermatoses and in histamine-mediated pruritus in patients <6 years of age: Capsule, syrup, tablet: 50 mg daily in divided doses Sedation when used as premedication and following general anesthesia: Injection: 0.5 mg/lb Capsule, syrup, tablet: 0.6 mg/kg	
Meprobamate	Management of anxiety disorders, short-term relief of symptoms of anxiety: Tablet: 1,200 to 1,600 mg/day in three to four doses; maximum, 2,400 mg	Management of anxiety disorders, short-term relief of symptoms of anxiety in patients six to 12 years of age: Tablet: 200 to 600 mg/day in two to three divided doses	Tablet: 200 mg 400 mg
Ramelteon	Treatment of insomnia characterized by difficulty with sleep onset: Tablet: 8 mg within 30 minutes of going to bed; maximum, 8 mg	Safety and efficacy in children have not been established.	Tablet: 8 mg
Zaleplon	Short-term treatment of insomnia: Capsule: 10 mg immediately before bedtime; maximum, 20 mg	Safety and efficacy in children have not been established.	Capsule: 5 mg 10 mg
Zolpidem	Short-term treatment of insomnia characterized by difficulties with sleep initiation: Immediate release sublingual tablet (Edluar®), tablet: 5 mg for women and 5 or 10 mg for men, immediately before bedtime with at least seven to eight hours remaining before the planned time of awakening Immediate release oral spray : 10 mg once daily immediately before bedtime Insomnia when a middle-of-the-night awakening is followed by difficulty returning to sleep: Immediate release sublingual tablet	Safety and efficacy in children have not been established.	Extended release tablet (Ambien CR®): 6.25 mg 12.5 mg Immediate release oral spray (Zolpimist®): 5 mg/0.1 mL Immediate release tablet (Ambien®): 5 mg 10 mg Sublingual tablet: 1.75 mg (Intermezzo®) 3.5 mg (Intermezzo®) 5 mg (Edluar®) 10 mg (Edluar®)

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	(Intermezzo®): 1.75 mg for women and 3.5 mg for men, taken only once per night if needed; take only if four hours of bedtime remain before the planned time of waking Insomnia characterized by difficulties with sleep onset and/or sleep maintenance: Extended release tablet: 6.25 mg for women, and 6.25 or 12.5 mg for men, immediately before bedtime with at least seven to eight hours remaining before the planned time of awakening		

VIII. Effectiveness

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

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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Anxiety				
Gammans et al.[33] (1992) Buspirone 10 to 60 mg/day vs placebo	MA Adult outpatients with generalized anxiety disorder	N=509 (8 trials) 4 weeks	Primary: HAM-A score, HAM-D score, CGI score to determine responders Secondary: Not reported	Primary: Overall, patients treated with buspirone demonstrated significant (P<0.001) improvement over baseline in total HAM-A scores compared to placebo. Significantly more buspirone-treated patients (54%) were classified as responders than placebo-treated patients (28%) (P<0.001). Patients with GAD and concurrent depressive symptoms exhibited significantly greater improvement with buspirone compared to placebo (P<0.01 to P<0.03 depending upon the parameter measured and severity of depressive symptoms). Weekly ratings indicated that buspirone produced a progressively increasing anxiolytic response relative to placebo throughout the four-week DB treatment period in patients with GAD and coexisting depressive symptoms (P<0.05 at week one for HAM-D and P<0.05 at week two for HAM-A). Secondary: Not reported
Lader et al.[34] (1998) Buspirone 20 mg/day vs hydroxyzine 50 mg/day	DB, MC, PC, RCT Adult outpatients with GAD	N=244 6 weeks	Primary: HAM-A scores Secondary: CGI, MADRS, HAD Scale, FARD, Tyrer Withdrawal Symptom Scale	Primary: Hydroxyzine (P<0.02), but not buspirone (P=NS), significantly improved HAM-A scores over placebo after 28 days of treatment. HAM-A scores were not significantly different between hydroxyzine and buspirone. Secondary: Significantly (P<0.02) more patients on hydroxyzine improved CGI scores than placebo. There was no significant difference between buspirone and placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				With respect to the MADRS, both buspirone and hydroxyzine patients were significantly better than placebo (P<0.001). HAD scores for both depression (P<0.01 for buspirone, P<0.02 for hydroxyzine) and anxiety (P<0.001 for both buspirone and hydroxyzine) were significantly better with the active drugs compared to placebo. The FARD total scores (P<0.001 for both buspirone and hydroxyzine) were also significantly better than placebo. There was no rebound with respect to HAM-A or other efficacy variables following placebo substitution at day 28. Both the buspirone and hydroxyzine patients continued to improve. No significant withdrawal symptoms for either active drug were detected on the Tyrer Scale. Both active treatments were well tolerated. The only side effects affecting more than 5% of the exposed patients were headache and migraine (6.1%) in the buspirone-treated patients (0% in hydroxyzine and 2.5% in placebo patients) and somnolence in the hydroxyzine group (9.9%) as compared to 4.9% in the buspirone and none in the placebo group.
Llorca et al.[35] (2002) Hydroxyzine 50 mg/day or bromazepam* 6 mg/day vs placebo	DB, MC, PG, RCT Adult outpatients with GAD	N=334 18 weeks	Primary: HAM-A scores Secondary: Responder and remission rates, change in CGI-S scale score and HAD scale score, maintenance of treatment efficacy, evaluation of rebound and withdrawal symptoms, safety	Primary: Mean change in HAM-A scores from baseline was significantly greater for hydroxyzine (-12.16) compared to placebo (-9.64; P=0.019). Bromazepam was also significantly more effective than placebo in decreasing HAM-A scores (P<0.03). Secondary: Results at endpoint for percentage of responders (P=0.003), remission rates (P=0.028), change in CGI-S scale score (P=0.001), HAD scale score (P=0.008), and maintenance of efficacy (P=0.022) on day 84 also confirmed the efficacy of hydroxyzine over placebo. The study showed no statistically significant difference between hydroxyzine and bromazepam; however, the study was not designed or powered to detect differences between these two active treatments. Efficacy was significantly maintained vs placebo in 86.5% of patients in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				the hydroxyzine group (P=0.022) and in 88.1% of patients in the bromazepam group (P=0.010) until day 84. In the placebo, hydroxyzine, and bromazepam groups, only 10.1%, 14.7% and 14.0% of patients, respectively, experienced at least one adverse event considered to be related to treatment. Safety results were comparable in the 3 groups with the exception of drowsiness, which was reported most frequently in the bromazepam group (7.9%), followed by hydroxyzine (3.9%) and then placebo (1.8%). There were no statistically significant differences between each treatment group with regards to rebound effect. Differences in withdrawal symptoms that reached statistical significance were the following: hydroxyzine induced more sweating than placebo (P=0.048) and bromazepam induced more sleep disturbances than placebo (P=0.002).
Blanco et al.[36] (2003) Benzodiazepines, SSRIs, MAOIs, RIMAs, β-blockers, gabapentin, buspirone vs placebo	MA Patients with social anxiety disorder	N=2,954 (23 trials) 6 to 20 weeks	Primary: Outcome data on the LSAS or a categorical measure of status Secondary: CGI score	Primary: In terms of LSAS, no statistical difference was detected between medications or medication groups. Secondary: In terms of responders, effect sizes of each medication group were: benzodiazepines (16.61), brofaromine (6.96), phenelzine (4.10), gabapentin (3.78), SSRIs (3.22), atenolol (1.36), and moclobemide (1.27). No statistical differences were detected between these medications or medication groups.
Insomnia				
Zammit et al.[37] (2004) Eszopiclone 2 to 3 mg vs	DB, MC, PC, RCT Adults 21 to 64 years of age with chronic primary insomnia	N=308 6 weeks	Primary: Efficacy (PSG and patient reports), next day residual effects (DSST), tolerance, rebound insomnia, safety	Primary: Eszopiclone 2 and 3 mg had significantly less time to sleep onset (P≤0.001 and P≤0.0001, respectively), more TST (P≤0.01 and P≤0.0001), better SE (P≤0.001 and P≤0.0001), and enhanced quality and depth of sleep (both P<0.05) across the DB period compared to placebo. Eszopiclone 3 mg (P≤0.01) but not 2 mg significantly improved sleep maintenance compared to placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo			Secondary: Not reported	Median DSST scores showed no decrement in psychomotor performance relative to baseline and did not differ from placebo in either eszopiclone group. There was no evidence of tolerance or rebound insomnia after therapy discontinuation. Treatment was well tolerated; unpleasant taste was the most common adverse event reported with eszopiclone. Secondary: Not reported
Krystal et al.[38] (2003) Eszopiclone 3 mg vs placebo	DB, MC, PC, RCT Adults with chronic insomnia	N=788 6 months	Primary: SL, WASO, NAW, TST, quality of sleep, next-day ratings of ability to function, daytime alertness, sense of physical well-being, safety Secondary: Not reported	Primary: At the first week and each month for the study duration, eszopiclone produced significant and sustained improvements in SL, WASO, NAW, number of nights awakened per week, TST, and quality of sleep compared to placebo (all $P \leq 0.003$). Monthly ratings of next-day function, alertness, and sense of physical well-being were also significantly better with the use of eszopiclone than with placebo (all $P \leq 0.002$). There was no evidence of tolerance and the most common adverse events were unpleasant taste and headache. Secondary: Not reported
Walsh et al.[39] (2007) Eszopiclone 3 mg vs placebo	DB, MC, PC, RCT Adults 21 to 64 years of age with primary insomnia	N=830 26 weeks	Primary: Patient-reported sleep measures (SL, WASO, TST, NAW, sleep quality, daytime alertness, ability to concentrate, physical well-	Primary: Patient-reported sleep and daytime function improved more with eszopiclone than with placebo at all months ($P<0.001$). Eszopiclone reduced ISI scores to below clinically meaningful levels for 50% of patients (vs 19% of patients with placebo; $P<0.05$) at six months. Lower mean scores on the FSS and the ESS were observed in the eszopiclone group relative to placebo for each month and the month one to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			being, and ability to function), ISI, FSS, ESS, Medical Outcomes Study SF-36, Work Limitations Questionnaire, safety (assessments performed at baseline, treatment months one to six, and two weeks after discontinuation of treatment) Secondary: Not reported	six average (P<0.05). SF-36 domains of Physical Functioning, Vitality, and Social Functioning were improved with eszopiclone vs placebo for the month one to six average (P<0.05). Similarly, improvements were observed for all domains of the Work Limitations Questionnaire with eszopiclone vs placebo for the month one to six average (P<0.05). There was no evidence of rebound insomnia after discontinuation of eszopiclone as SL, WASO and TST remained significantly improved from baseline (all P<0.001). There were no between-treatment differences observed during the discontinuation period except for a significantly greater SL on the first night after discontinuation with eszopiclone vs placebo (45 vs 30 minutes; P=0.015). No significant group differences were observed in mean Benzodiazepine Withdrawal Symptom Questionnaire scores (3.0 with eszopiclone and 2.3 with placebo; P=0.12), or overall adverse event rates (15.2% for eszopiclone and 11.1% for placebo; P value not reported). Unpleasant taste (19.7 vs 1.1%; P<0.001), somnolence (8.8 vs 3.2%; P=0.0029), and myalgia (6.0 vs 2.9; P=0.047) were reported in significantly more patients receiving eszopiclone than those receiving placebo. Secondary: Not reported
Joffe et al.[40] (2009) Eszopiclone 3 mg for 4 weeks vs placebo for 4 weeks Each treatment	DB, PC, RCT, XO Perimenopausal and postmenopausal women 40 to 65 years of age with sleep-onset and/or sleep-maintenance insomnia co-occurring with hot flashes and depressive and/or	N=59 11 weeks Each treatment period was separated by a 2-week washout period	Primary: Changes in the ISI scale Secondary: Diary-based sleep parameters (WASO, SE, sleep-onset latency, TST, NAW); number of hot flashes/night sweats, depressive	Primary: The ISI score was reduced by 8.7 more points with eszopiclone than with placebo (P<0.0001). The ISI score was 7 or less after four weeks of treatment in 87% of women on eszopiclone and in 34% of women on placebo. Secondary: SL was reduced by 17.8 more minutes with eszopiclone than with placebo (P=0.04). For both treatment periods together, WASO was reduced by 37.7 minutes more with eszopiclone than placebo (P=0.05), SE improved by 14.6% more with eszopiclone than with placebo (P=0.01), and TST increased by 66.5 minutes more with eszopiclone than with placebo

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
period was separated by a 2-week washout period.	anxiety symptoms		symptoms (via MADRS), anxiety symptoms (assessed via BAI), MENQOL, and functional impairment, safety	(P=0.01). Among patients with anxiety symptoms at baseline, BAI scores were reduced by a mean of 1.5 more with eszopiclone than with placebo (P=0.03). Quality of life (P=0.0002) and functional disability (P=0.09) improved more on eszopiclone than on placebo. Among those with depressive symptoms at baseline, MADRS scores were reduced by a mean of 7.4 more points with eszopiclone than with placebo (P=0.0004). Compared to placebo, eszopiclone had a significant effect on depressive symptoms during the second (P=0.003), but not first, treatment period. There was a significant reduction in nighttime hot flashes with eszopiclone compared to placebo (reduction by 1.5 nighttime hot flashes; P=0.047), but the effect on daytime symptoms was not different. Compared to placebo, eszopiclone had a significant effect on nighttime hot flashes during the second (P=0.0006), but not first, treatment period. Overall, the treatment was well tolerated. The only adverse event occurring in >5% of the population was metallic taste on eszopiclone (25%).
Scharf et al.[41] (2005) Eszopiclone 1 to 2 mg vs placebo	DB, MC, PC, RCT Community-dwelling elderly patients (mean age 72.3 years) with primary insomnia	N=231 2 weeks	Primary: Patient-reported efficacy (SL, TST) Secondary: WASO, NAW, number and length of naps, quality of sleep, depth of sleep, ratings of daytime alertness, sense of physical well-being, morning sleepiness, ability	Primary: Patients treated with eszopiclone 1 and 2 mg had a significantly shorter SL compared to placebo (P<0.05 and P=0.0034, respectively). The eszopiclone 2-mg group (P=0.0003) but not the 1-mg group (P>0.1) had significantly longer TST compared to placebo. Secondary: Compared to placebo, patients receiving eszopiclone 2 mg had significantly less WASO but similar NAW per night (P>0.1). Patients receiving eszopiclone 2 mg had significantly fewer (P=0.028) and shorter in duration (P=0.011) daytime naps, higher ratings of sleep quality (P=0.0006) and depth (P=0.0015), better daytime alertness (P=0.022) and sense of physical well-being (P=0.047) compared to patients receiving

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			to function, quality of life (Q-LES-Q), safety	placebo. The differences between eszopiclone 2 mg and placebo were marginally significant for morning sleepiness (P=0.055) and ability to function (P=0.058). Duration of nap was significantly shorter in the eszopiclone 1-mg group compared to the placebo group (P<0.05); however, there were no other significant differences in any other secondary efficacy endpoints. Compared to placebo, the eszopiclone 2-mg group had significantly higher quality of life scores on five of the 16 Q-LES-Q domains (physical health, mood, household activities, leisure time activities and medications; P<0.05). The differences between eszopiclone 2 mg and placebo were marginally significant for the Q-LES-Q global score (P=0.064). There were no significant differences between eszopiclone 1 mg and placebo for any of the Q-LES-Q dimensions. Eszopiclone was well tolerated with unpleasant taste reported as the most frequent treatment-related adverse event.
Ancoli-Israel et al.[42] (2010) Eszopiclone 2 mg vs placebo	DB, MC, PC, RCT Patients 65 to 85 years of age with primary insomnia	N=388 12 weeks Treatment was followed by a two week, SB run out period	Primary: Change from baseline sTST Secondary: Change from baseline in sSL and WASO	Primary: After 12 weeks, the mean sTST was 360.08 minutes with eszopiclone compared to 297.86 minutes at baseline (mean change of 63.24 minutes). This was significantly greater than placebo (P<0.0001). Secondary: There was a greater improvement in sSL with eszopiclone compared to placebo (mean decrease of 24.62 vs 19.92 minutes; respectively; P=0.0014). Patients receiving eszopiclone experienced a greater decrease in WASO compared to those receiving placebo (mean decrease of 36.4 vs 14.8 minutes; P<0.0001). The reported NAW per night was reduced (P≤0.01), and the quality (P<0.001) and depth of sleep (P≤0.001) was improved at all time points with eszopiclone compared to placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There was a significantly greater decrease in naps per week over the first three weeks of treatment with eszopiclone (1.2 naps per week decrease) vs placebo (0.4 naps per week; P=0.006), but not at subsequent time points. Similar results were obtained for total nap time per week. Patients receiving eszopiclone had significantly greater improvements in ISI total scores than those receiving placebo at all time points (all P<0.001). The percentage of patients with ISI total scores categorized as "no insomnia" and "sub-threshold insomnia" was greater in the eszopiclone group (78.0% at week 12) than in the placebo group (61.1%; P<0.05). Changes in self-reported daytime alertness, ability to function, ability to concentrate, and sense of physical well-being were significantly increased with eszopiclone compared to placebo at all times points (all P≤0.001). Patients receiving eszopiclone had significant improvements in the vitality scale of the SF-36 at week six (P=0.04) and week 12 (P=0.008), and in the general health scale at week 12 (P=0.009) compared to placebo. There were no significant differences on the other SF-36 individual scale scores, or on the mental or physical component summary scores among the treatment groups. On the SDS, there were significant improvements observed in the eszopiclone group compared to the placebo group for the social life and family life/home responsibilities items (both P≤0.03) at week six, but not at week 12. There was no significant difference on the work/school item at either time point. The overall incidence of adverse events was 59.3% for eszopiclone and 50.5% for placebo. The most common adverse events reported in the eszopiclone group were headache (13.9 vs 12.4% for placebo), unpleasant taste (12.4 vs 1.5% for placebo), and nasopharyngitis (5.7 vs 6.2% for placebo).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Lettieri et al.[43] (2009) Eszopiclone 3 mg 30 minutes prior to PSG (premedication) vs placebo30 minutes prior to PSG (premedication)	DB, PC, RCT Patients 18 to 64 years of age with newly diagnosed obstructive sleep apnea who were initiating CPAP	N=117 4-6 weeks	Primary: CPAP compliance during the initial four to six weeks of therapy Secondary: CPAP titration quality as assessed by WASO), TST, total arousal index, SL, SE, AHI	Primary: CPAP was used on a higher percentage of nights in the eszopiclone group than in the placebo group (75.9 vs 60.1%, respectively; P=0.005). Eszopiclone was associated with more hours of use per night during nights used (4.8 vs 3.9 hours, respectively; P=0.03) and for more hours per night for all nights of the study period (4.0 vs 2.9 hours, respectively; P=0.03). The percentage of days with >4 hours of use also was greater among the eszopiclone group (59.2 vs 37.0%, respectively; P=0.007). Good compliance (>4 hours of use per night on >70% of nights) was observed in more patients pretreated with eszopiclone than with placebo (53.1 vs 27.1%, respectively; P=0.009). Secondary: Premedication with eszopiclone improved the quality of CPAP titration PSG compared to placebo as evidenced by shortened SL (19.4 vs 31.8 minutes, respectively; P=0.08), improved SE (87.8 vs 80.1%, respectively; P=0.002), expanded TST (350.9 vs 319.7 minutes, respectively; P=0.007), and decreased WASO (39.3 vs 59.9 minutes, respectively; P=0.009). The residual AHI tended to be lower following eszopiclone premedication (6.4 vs 12.8 events/hour, respectively; P=0.08).
Lettieri et al.[44] (2009) Eszopiclone 3 mg for 2 weeks vs placebo for 2 weeks To promote adherence with CPAP, OL use of	DB, PC, RCT Patients 18 to 64 years of age with newly diagnosed obstructive sleep apnea who were initiating CPAP	N=160 24 weeks	Primary: Adherence to CPAP at week 24 Secondary: Rate of CPAP discontinuation and OL use of sedative-hypnotic agents	Primary: Patients receiving eszopiclone used CPAP for 64.4% of nights compared to 45.2% of nights in those receiving placebo (P=0.003). In the eszopiclone and placebo groups, CPAP was used for 3.57 vs 2.42 hours per night, respectively for all study nights (P=0.005) and for 4.05 vs 3.02 hours per night, respectively for nights when CPAP was used (P=0.019). Secondary: The mean duration of regular use of CPAP was 13.3 weeks for the placebo group and 17.6 weeks for the eszopiclone group (P=0.005). The mean time to discontinuation of CPAP for the placebo and eszopiclone groups was 17.2 and 19.7 weeks, respectively (P=0.033).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
sedative-hypnotic agents was allowed after the first 4 weeks of treatment.				A total of 24.7% of patients requested OL non-benzodiazepines. This request was more frequent among those receiving placebo than eszopiclone (31% vs 19%; P=0.084). The mean duration of hypnotic use (9.7 days) was similar for both groups. Adverse events were reported in 7.1% of patients and did not differ between the groups.
Menza et al.[45] (2010) Eszopiclone 2 to 3 mg vs placebo	DB, MC, PC, PG, RCT Patients 35 to 85 years of age with Parkinson's disease and sleep maintenance insomnia or SL insomnia, as well as clinically significant daytime distress or impairment secondary to insomnia	N=30 6 weeks	Primary: Patient-reported TST Secondary: WASO, NAW and SII, quality of sleep, quality of life (assessed via PDQ-8), motor function (assessed via UPDRS), severity and change (assessed via CGI), ability to function, daytime alertness, fatigue severity (assessed via FSS), caregiver quality of life and depression (assessed via MCBI and CES-D)	Primary: There was no significant difference in the improvement seen in TST among the groups (66.5 minutes with eszopiclone vs 47.0 minutes with placebo; P=0.1099). Secondary: There were significant differences in NAW (P=0.035), quality of sleep (P=0.018), and CGI-improvement in sleep (P=0.035) among the groups. There was no significant difference in WASO (P=0.071). There were no differences in the UPDRS motor, activities of daily living, therapeutic complications, mood or Schwab subscales. There were no significant differences in SL, FSS, SII, PDQ-8, Ability to Function Scale, the MCBI caregiver burden, the CES-D, or the Daytime Alertness Scale. Overall, 30% of patients reported adverse events; 33% of patients receiving eszopiclone and 27% of patients receiving placebo.
Pollack et al.[46] (2011) Eszopiclone 3 mg for 3 weeks	DB, PC, RCT, XO Patients 18 to 64 years of age with PTSD with associated sleep	N=24 7 weeks	Primary: Changes in scores on the SPRINT and PSQI scales Secondary:	Primary: Eszopiclone was associated with significant improvement in PTSD symptomatology as measured by the SPRINT compared to placebo (P=0.032). Eszopiclone was associated with a significantly greater reduction in PSQI

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo for 3 weeks Each treatment period was separated by a 1-week washout period.	disturbance		CAPS, SL and TST	score compared to placebo (P=0.011). Secondary: In phase 1, the CAPS was also significantly reduced with eszopiclone compared to placebo (P=0.003). SL was significantly reduced with eszopiclone compared to placebo (P=0.044). There was no significant difference in TST among the treatment groups (P=0.061). Adverse events with eszopiclone were of mild to moderate severity, with the most common comprising unpleasant taste (32%), sedation (16%), and headaches (12%).
McCall et al.[47] (2010) Eszopiclone 3 mg vs placebo All patients started with one week of OL fluoxetine; patients experiencing insomnia after this period were randomized to 8 weeks of eszopiclone or placebo in addition to the OL fluoxetine.	DB, PC, RCT Patients 18 to 70 years of age with depression and insomnia	N=60 8 weeks	Primary: DLRF subscale of the Basis-32 Secondary: Safety	Primary: Final DLRF scores were better (lower) in the eszopiclone group than in the placebo group (0.81±0.64 vs 1.2±0.72). Secondary: The only meaningful adverse event reported, was unpleasant taste, and it occurred in 46% of patients treated with eszopiclone.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Rosenberg et al.[48] (2005) Eszopiclone 1, 2, 3 or 3.5 mg vs placebo	DB, PC, RCT Healthy adult volunteers with transient insomnia	N=436 1 night	Primary: Efficacy and next-morning effects evaluated by PSG, DSST and self report Secondary: Not reported	Primary: Patients treated with eszopiclone had significantly less PSG LPS (all doses except 1 mg; P≤0.0001), WASO (all doses; P≤0.05) and NAW (3 and 3.5 mg doses; P<0.005), and greater SE (all doses; P≤0.02) compared to placebo. Self-reported efficacy results were similar to PSG. Self-reported morning sleepiness scores were significantly better for eszopiclone 3 and 3.5 mg compared to placebo (P<0.05). Treatment was well tolerated by patients, and the most common treatment-related adverse event was unpleasant taste. Secondary: Not reported
Krystal et al.[49] (2012) Eszopiclone 3 mg vs placebo	Post hoc analysis of a 6-month PC, RCT Patients diagnosed with chronic primary insomnia	N=195 6 months	Primary: Determination of the distribution of baseline WASO; continuous analysis of the relationship between baseline WASO severity and drug-placebo difference at month one and six; and categorical efficacy analyses of subgroups delimited by the following WASO thresholds: 0, 30, 45, 60, and 90 minutes Secondary:	Primary: The baseline WASO distribution was: <30 minutes, 32.2%; >0 to <45 minutes, 41.5%; >30 to <90 minutes, 33.0%; >45 to <90 minutes, 23.7%; >90 minutes, 22.6%. A relationship between greater baseline WASO severity and a significantly greater drug-placebo difference in efficacy for WASO was evident. Eszopiclone was found to have significant sleep maintenance efficacy at each time point across the entire range of WASO severity studied. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Not reported	
Uchimura et al (abstract).[50] (2011) Ramelteon 4 and 8 mg vs placebo	DB, PC, RCT Japanese adults with chronic insomnia	N=1,130 Duration not reported	Primary: Not reported Secondary: Not reported	Primary: Not reported Secondary: Not reported There was no statistically significant difference between ramelteon and placebo in the change in subjective SL (P value not reported). Significant improvement was observed in the change in subjective TST with ramelteon 8 mg at week one (P value not reported). Post hoc analyses indicated that treatment with ramelteon 8 mg resulted in a reduction in subjective SL in individuals with smaller fluctuations (within ±30 minutes) of subjective SL at baseline, in those with a shorter (<1 year) history of insomnia, and in individuals who had not used benzodiazepines (P value not reported). Ramelteon was safe and well tolerated up to 16 mg nightly.
Kohsaka et al (abstract).[51] (2011) Ramelteon 4, 8, 16, or 32 mg vs placebo	DB, PC, XO Japanese patients with chronic insomnia	N=65 Each dose was given for two nights over five study periods	Primary: Not reported Secondary: Not reported	Primary: Not reported Secondary: Not reported Ramelteon 8 and 32 mg significantly shortened the mean LPS when compared to placebo (P value not reported). Overall changes in sleep architecture were modest (<3% changes vs placebo; P value not reported), with increases in stage 1 and decreases in stage 3/4. When compared to SL data from a similarly designed United States study, there was no evidence of any ethnic differences in the efficacy of ramelteon between Japanese and United States patients. Overall, ramelteon 8 mg showed the most favorable balance between sleep-promoting effects and tolerability (P value not reported). Ramelteon was well tolerated, the most common adverse effect was somnolence, which was similar to placebo at doses up to 8 mg, but

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				increased with higher doses (P value not reported). Next-day residual effects occurred no more frequently with ramelteon at any dose than with placebo (P value not reported).
Wang-Weigand et al.[52] (2011) Ramelteon 8 mg vs placebo	PC, RCT Adults 18 to 64 years of age with chronic insomnia	N=552 Nightly treatment for 3 weeks with a one week, placebo run-out period to assess rebound insomnia	Primary: Patient reported SL at week three Secondary: Patient reported SL at week one and two, patient reported TST, patient reported WASO, patient reported NAW, and sleep quality (all assessed each week), safety	Primary and secondary: There was a reduction in the average patient reported SL (as measured by the PSQ-IVRS) at weeks one, two, and three, when compared to placebo; however, none of these reductions reached statistical significance (P value not reported). There were no significant differences seen between ramelteon and placebo at any time point regarding the following patient-reported parameters: TST, WASO, NAW, or sleep quality (P value not reported). There was no evidence of rebound insomnia detected during the placebo run-out period for the groups that had received placebo or ramelteon. Headache and somnolence occurred in more than 3% of subjects in either group. Overall, the proportion of subjects with any treatment-related adverse events was similar between the ramelteon and placebo-groups (16.5 vs 15.4%, respectively; P-value not reported).
Wang-Weigand et al.[53] (2009) Ramelteon 8 mg vs placebo	DB, PC, RCT (pooled analysis of 4 trials) Patients 18 to 83 years of age with chronic insomnia	N=1,122 Duration varied among included trials	Primary: LS mean LPS for nights one and two for each included trial Secondary: Safety	Primary: At nights one and two, mean LPS was 43.3 minutes for the placebo group and 30.2 minutes, resulting in a between-group difference of 13.1 minutes (P<0.001). Secondary: The total number of adverse events was similar for ramelteon 8 mg (209 [36.5%]) and placebo (192 [34.3%]) (P value not reported). The most common adverse events were headache and somnolence.
Zammit et al.[54] (2009) Ramelteon 8 or 16 mg vs placebo	DB, MC, PC, RCT, SD Healthy patients 18 to 64 years of age	N=289 1 night	Primary: LPS assessed by PSG Secondary: PSG assessed endpoints include TST, WASO, and NAW after persistent sleep	Primary: Treatment with ramelteon 8 mg resulted in a significant decrease in LS mean LPS when compared to placebo (12.2 vs 19.7 minutes; P=0.004). Treatment with ramelteon 16 mg resulted in a numeric decrease in LS mean LPS when compared to placebo; however, this decrease did not reach statistical significance (14.8 vs 19.7 minutes; P=0.065). Secondary: Treatment with ramelteon 8 and 16 mg resulted in significant increases in the LS mean TST when compared to placebo (8 mg: 436.8 vs 419.7

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			onset; subjective measures include SL, TST, WASO, NAW after persistent sleep onset, and overall sleep quality, safety	minutes; P=0.009 and 16 mg: 433.1 vs 419.7 minutes; P=0.043). There were no significant changes in any other objective or subjective measures of sleep. A total of 31 subjects (10.7%) reported at least one adverse event during the study. The incidence rates were 12.4, 13.3, and 6.4% for the placebo, ramelteon 8 and 16 mg groups, respectively. Most adverse events were mild or moderate in severity and the most commonly reported adverse event was somnolence.
Erman et al.[55] (2006) Ramelteon 4 to 32 mg vs placebo	DB, MC, PC, RCT, 5-period XO Men and non-pregnant, non-lactating women 18 to 64 years of age with chronic insomnia	N=107 2 nights per treatment	Primary: Mean LPS Secondary: TST, WASO, percentage of sleep time in each sleep stage, subjective sleep quality, next-day performance and alertness, safety	Primary: All tested doses of ramelteon resulted in statistically significant reductions in LPS compared to placebo (P<0.001). Secondary: All tested doses of ramelteon resulted in statistically significant increases in TST compared to placebo (P=0.001). No significant differences in WASO (P=0.470), percentage of time spent in the different sleep stages and subjective sleep quality (P=0.525) were reported between the ramelteon groups and the placebo group. There were no differences between the placebo group and any ramelteon dose group on next-day performance and alertness (P values not reported). The safety of ramelteon at each dose was similar to that of placebo and the most commonly reported adverse events were headache, somnolence, and sore throat.
Mayer et al.[56] (2009) Ramelteon 8 mg vs placebo	DB, PC, RCT Patients ≥18 years of age with chronic primary insomnia	N=451 6 months	Primary: LPS (measured by PSG) Secondary: TST (measured by PSG), total time spent in each sleep stage, latency to REM, self-reported	Primary: Greater reductions in LPS occurred with ramelteon compared to placebo (P<0.05 for each time point). A greater change from baseline occurred with ramelteon (54 to 56%) compared to placebo (30 to 47%). Secondary A greater increase in TST occurred with ramelteon (381.1 minutes) compared to placebo (365.7 minutes) at week one (P<0.001), but not at any other time points.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			efficacy	There were no significant changes in percent of time spent in Stage 1 or REM sleep with ramelteon vs placebo. There was a significant increase in percent of time spent in Stage 2 sleep and a significant decrease in time spent in Stage 3/4 with ramelteon compared to placebo (P values not reported). There was a greater reduction in subjective SL with ramelteon compared to placebo at week one, as well as months one and five (P<0.05). There were no significant reductions at other time points between the treatment groups. There were no significant differences between ramelteon and placebo at any time point on the following measures: subjective TST, subjective NAW and sleep quality. No significant differences in sWASO was observed between ramelteon (90.89 minutes) and placebo (79.54 minutes) at any time point except month six (P=0.036). There were no significant differences on measures of morning level of alertness and ability to concentrate, or immediate/delayed morning recall between the treatment groups. No rebound insomnia was observed during the placebo run-out period. There were no differences between the treatment groups with regards to measures of withdrawal during the placebo run-out period.
Uchiyama et al.[57] (2011) Ramelteon 8 mg vs placebo	DB, MC, PC, RCT Japanese patients 20 to 85 years of age with primary insomnia	N=1,605 2 weeks	Primary: Mean patient-reported SL during week one of treatment Secondary: Mean SL during week two of treatment, mean patient-reported	Primary: The mean SL was reduced in week one in both the ramelteon and placebo groups (-15.98 and -11.73 minutes, respectively; P=0.0010). Secondary: The mean SL decreased further in week two in both groups; however, the difference between the groups of -2.36 minutes in favor of ramelteon did not achieve statistical significance (P=0.1093). Ramelteon increased TST significantly more than placebo at week one (difference in LS mean, 4.2 minutes; P=0.0484), but not at week two (2.4

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			TST for week one and for week two, patient's global impression of treatment, rebound insomnia, and safety	minutes; P=0.2378). The mean NAW reported by patients in the ramelteon group was significantly less than that in the placebo group at week two (difference in LS mean of -0.07; P=0.0469) but not for week 1 (-0.04; P=0.2592). The mean sleep quality score with ramelteon was significantly smaller than that with placebo for week one (difference in LS mean, -0.12; P=0.0174), but not week two (-0.06; P=0.2059). There was no evidence of rebound insomnia with ramelteon during the run-out period. The mean total score for patients' global impression of treatment improved significantly with ramelteon compared to placebo at the end of week one (1.52 vs 1.59; P=0.0041) and week two (1.45 vs 1.53; P=0.0028). The proportion of patients scoring individual items as ''improved'' was significantly higher for ramelteon than placebo at weeks one and two for time to fall asleep (week one, 53.1 vs 44.3%; P=0.0100, week two, 58.3 vs 52.5%; P=0.0434), TST (week one, 42.0 vs 34.0%; P=0.0121, week two, 47.6 vs 38.8%; P=0.0031), sleep quality (week one, 56.4 vs 48.2%; P=0.0115, week two, 62.5 vs 56.1%; P=0.0463), and usefulness of treatment (week one, 58.2 vs 47.6%; P=0.0008, week two, 64.6 vs 56.8%; P=0.0123), but not for daytime distress (week one, 33.4 vs 31.9%; P=0.9116, week two, 42.7 vs 37.7%; P=0.0881). A total of 26.4% of patients in the ramelteon group and 20.5% of patients in the placebo group reported at least one treatment-emergent adverse event. All events were mild or moderate in severity. The most common adverse event leading to discontinuation was nasopharyngitis.
Uchiyama et al.[58] (2011) Ramelteon 4 to 16 mg	MC, SB Japanese patients 20 to 85 years of age with primary insomnia	N=222 24 weeks	Primary: Adverse events, residual effects, rebound insomnia, withdrawal symptoms, and dependence	Primary: During the study, 77.4% of patients reported adverse events. The most frequent reported adverse events were nasopharyngitis, inflammation of upper respiratory tract, eczema, elevated γ-glutamyltransferase, laryngopharyngitis, and headache. Endocrine adverse events that were considered drug-related included metrorrhagia, dysmenorrhea, polymenorrhea, increased estradiol, increased cortisol, and decreased

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			Secondary: Subjective SL and TST	cortisol. The mean change in next-morning residual scores significantly improved from baseline with ramelteon (P<0.05). The mean change from baseline in SL at week 24 and the placebo run-out period using the full analysis set with 8 mg were -30.4 and -28.6 minutes in the group continuously treated with ramelteon, which confirms the lack of rebound insomnia. Ramelteon was not associated with withdrawal symptoms and there was no evidence of dependence. Secondary: Mean subjective SL decreased significantly during the study. In the group that continuously received ramelteon 8 mg, it decreased from a baseline of 70.5 to 54.4 minutes after one week (P<0.0001) and 33.8 minutes after 20 weeks (P<0.0001), then plateaued until the end of the study. The mean subjective TST was 5.52 hours at baseline, increasing to 5.78 hours at week one (P<0.0001) and 6.30 hours at week 20 (P<0.0001), and remained stable until the end of the study.
Gooneratne et al.[59] (2010) Ramelteon 8 mg vs placebo	DB, PC, RCT Patients ≥60 years of age with obstructive sleep apnea and insomnia symptoms	N=21 4 weeks	Primary: Objective change in SOL using PSG Secondary: PSQI, (ISI, FOSQ, quality of life (SF-36)	Primary: Using PSG, there was a 10.7 minute decrease in SOL in the ramelteon arm compared to a 17.8 minute increase in the placebo arm (difference, 28.5 minutes; P=0.008). For self-reported SOL, there was no significant difference among the two study arms (−1.3 minutes; P=0.9). Neither objective nor subjective SE differed significantly between study arms. Secondary: There were no significant differences in the PSQI, ISI, FOSQ, or SF-36 among the treatment groups. The adverse events reported with ramelteon were diarrhea, skin ulcer, sinusitis, and fracture after being hit by a bicyclist. For placebo, the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				adverse events were abdominal pain and nausea. All adverse events were thought to be unrelated to study drug treatments, and none were serious adverse events.
Liu et al.[60] (2012) Ramelteon vs placebo	MA Patients with chronic insomnia	N=8 trials Duration varied	Primary: Subjective and polysomnographic SL, TST and latency to REM Secondary: Not reported	Primary: There were significant improvements in all outcomes (subjective and polysomnographic SL, TST and latency to REM), except for the percentage of REM. By subgroup analysis, subjective SL was reduced only in the patients 18 to 64 years of age. For the safety, ramelteon was not associated with higher risk ratio of any frequent adverse events comparing with control. Secondary: Not reported
Dobkin et al.[61] (2009) Ramelteon 8 mg	OL, PRO Patient population not specified	N=20 6 weeks	Primary: Patient reported LPS Secondary: Patient reported endpoints include TST, WASO, total number of nighttime awakenings, SE, and number of hot flashes/ night sweats; other secondary endpoints include sleep impairment (assessed via the SII), daytime functioning, daytime alertness,	Primary: Treatment with ramelteon resulted in improvements in LPS at week six when compared to baseline (24.0±15.0 vs 46.2±19.8 minutes; P<0.001). The average improvement across all participants was 22 minutes. Secondary: Treatment with ramelteon 8 mg resulted in improvements at week six when compared to baseline in the following parameters: TST (420±38 vs 336±62 minutes; P<0.001), SE (0.91±0.06 vs 0.80±0.10; P<0.001), night time awakenings (1.86±1.53 vs 2.32±1.36; P<0.05), and hot flashes (1.52±1.32 vs 2.31±1.95; P<0.05). There were no significant improvements in WASO at any time period throughout the study when compared to baseline. Significant improvements were observed in patient reported sleep quality (P<0.001), daytime dysfunction (P<0.01), daytime alertness (P<0.001), SII scores (P<0.001), MENQOL scores (P<0.01), BDI scores (P<0.001), and anxiety (P<0.001). At the end of this trial, 55% of women were considered “responders” according to the CGI-I scale. Insomnia severity, assessed by the CGI-S,

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			quality of life (assessed via the MENQOL), mood (assessed via the BDI), CGI-S, and CGI-I, safety	also improved over baseline (3.14 vs 4.65; P<0.001). Of the subjects treated with ramelteon in this trial, 40% reported side effects. The most frequently reported side effects included headaches, daytime fatigue/fogginess, dry mouth, lightheadedness, and dizziness. Most side effects were mild and transient.
Richardson et al.[62] (2009) Ramelteon 8 or 16 mg Subjects >65 years of age received 8 mg/day, subjects 18 to 64 years of age received 16 mg/day.	OL, PRO Adults with primary insomnia	N=1,213 48 weeks	Primary: Adverse events, changes in vital signs, laboratory values, 12-ECG, and results of physical examination Secondary: Safety	Primary: There were no noteworthy changes in vital signs, physical examinations, clinical chemistry, hematology, or urinalysis values. There were also no ECG changes to suggest adverse cardiac effects. Consistent statistically significant (P≤0.05) decreases in free thyroxine and free testosterone (in older men) were detected. Duration of menses increased by approximately one day. In both groups, those older and younger than 65, subjective SL and TST improved by month one and was sustained during the one-year period. At six months and one year, CGI indices were improved. During the placebo run-out period, SL did increase but did not return to baseline. Secondary: A total of 69.8% of patients reported at least one adverse event. There was no difference in adverse event incidence between those older and younger than 65 (P value not reported). The overall incidence of adverse events was similar at six months and one year.
Gross et al.[63] (2009) Ramelteon 8 mg All patients continued to take their antidepressant; dose reductions were permitted at any time but no	OL, PRO Patients 18 to 80 years of age with GAD and related insomnia	N=27 10 weeks	Primary: CGI-I, CGI-S, daytime sleepiness (assessed via ESS), HAMA, and patient reported sleep diaries Secondary: Safety	Primary: The addition of ramelteon 8 mg resulted in significant improvement over baseline in the following study parameters: time to fall asleep (34.67±29.26 vs 77.52±47.73 minutes; P<0.001), TST (7.52±1.22 vs 5.02±0.96 hours; P<0.001), CGI-S Insomnia (1.67±0.73 vs 4.30±0.47; P<0.001), CGI-I Insomnia (1.59±0.64 vs 3.85±0.36; P<0.001), HAMA (3.96±2.97 vs 8.26±2.94; P<0.001), ESS (5.48±3.27 vs 11.56±2.14; P<0.001), CGI-S Anxiety (1.25±0.64 vs 2.85±0.66; P<0.001), CGI-I Anxiety (1.41±0.50 vs 2.33±0.78; P<0.001). Secondary: The most common adverse events regarding ramelteon use were headache

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
dose increases were permitted during the study period.				upon stopping ramelteon (7.4%), daytime tiredness (3.7%), and depression (3.7%). All side effects were reported as transient.
Roth et al.[64] (2006) Ramelteon 4 mg vs ramelteon 8 mg vs placebo	DB, PC, RCT Patients 64 to 93 years of age with chronic primary insomnia	N=829 5 weeks	Primary: SL at week one Secondary: TST at weeks one, three and five; reductions in SL at weeks three and five; sleep diaries; rebound insomnia and withdrawal effects during the seven-day placebo run out	Primary: Significant reductions in SL at week one were reported with both ramelteon 4 mg (70.2 vs 78.5 minutes; P=0.008) and 8 mg (70.2 vs 78.5 minutes; P=0.008) compared to placebo. Secondary: Patients continued to report reduced SL at week three with ramelteon 8 mg (P=0.003) and at week five with ramelteon 4 and 8 mg (P=0.028 and P<0.001, respectively) compared to placebo. Patient-reported TST at weeks one and three was significantly longer compared to placebo for ramelteon 4 mg (324.6 vs 313.9 minutes; P=0.004 and 336.0 vs 324.3 minutes; P=0.007, respectively). TST for ramelteon 4 mg at five weeks and for ramelteon 8 mg at weeks one, three and five were longer than placebo but did not reach statistical significance (P values >0.05). Analyses of other sleep parameters obtained via sleep diaries (e.g., NAW, ease of falling back asleep after an awakening and sleep quality) yielded no statistically significant differences among groups at weeks one, three and five. There was no evidence of significant rebound insomnia or withdrawal effects following treatment discontinuation. Incidence of adverse events was 51.5, 54.8 and 58.0% of patients in the placebo, 4 and 8 mg ramelteon groups, respectively.
Roth et al.[65] (2005) Ramelteon 16 mg vs	DB, PC, MC, RCT Healthy adult volunteers with transient insomnia (35 to 60 years of	N =375 1 night	Primary: Mean LPS as measured by PSG Secondary: TST, WASO,	Primary: Participants who had received either ramelteon dosage had significantly shorter LPS relative to placebo (both P<0.001). Secondary: Participants who had received ramelteon 16 or 64 mg had significantly

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ramelteon 64 mg vs placebo Doses were given 30 minutes before bedtime.	age with total sleep duration 6.5 to 8.5 hours, a usual SL of 30 minutes or less, a habitual bedtime between 8:30 PM and midnight)		percentage of sleep time in each sleep stage, NAW, residual effects assessed by DSST and postsleep questionnaire, safety	longer TST compared to participants who had received placebo (P=0.007 and P=0.033, respectively). There were no significant differences between the ramelteon groups and placebo with regard to WASO, percentage of sleep time in each sleep stage, and NAW. No significant differences in DSST scores were reported among the groups, but ramelteon 64 mg was associated with statistically significant declines in subjective levels of alertness (P=0.020) and ability to concentrate (P=0.043) compared to placebo. No serious adverse events were reported.
Scharf et al.[66] (1994) Zolpidem 10 to 15 mg vs placebo	DB, MC, PC, PG, RCT Adults with chronic insomnia	N=75 5 weeks	Primary: LPS, SE, sleep maintenance, sleep quality, effects on sleep stages, residual drug effects, safety Secondary: Not reported	Primary: Zolpidem had a significant (P<0.05) effect on LPS and SE from weeks two through five in the 10-mg group and at weeks two through six in the 15-mg group. Polysomnographic measures of sleep maintenance were not significantly different among the three treatment groups (P>0.05). Patients receiving zolpidem 15 mg reported significantly better quality of sleep than those receiving the 10 mg dose at week two and placebo at week five. Stages 1, 2, and 3 to 4 sleep were not significantly affected by either the 10- or 15-mg doses of zolpidem compared to placebo. However, there were significant (P<0.05) decreases in REM sleep at weeks three and four with zolpidem 15 mg compared to placebo. There was no evidence of residual effect with zolpidem 10 or 15 mg. There was no evidence of tolerance at either dose. The only significant treatment difference was in the percent of time in Stage 3 to 4 sleep (P<0.05 for both zolpidem doses compared to placebo). There were no significant treatment differences between the 10-mg

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				zolpidem group and the placebo group in LPS, SE, WTDS or sleep quality during the post treatment period when zolpidem was discontinued. The 15-mg zolpidem group did not differ significantly from the placebo group on LPS or SE on the first night post treatment, but did result in a significantly greater WTDS and poorer quality of sleep (P<0.05 compared to placebo) during the first night post treatment. Comparison of the subsequent two nights post treatment showed no significant differences between zolpidem 15 mg and placebo on any of these variables. Overall, the incidence of treatment emergent adverse events in the zolpidem groups was similar to those in the placebo group. While none of the adverse events were severe, two patients in the 15-mg zolpidem group withdrew from the study: one patient experienced drowsiness, dizziness, and nausea; and one patient experienced visual disturbance and over sedation. The 15-mg zolpidem dosage provided no clinical advantage over the 10 mg zolpidem dosage. Secondary: Not reported
Roehrs et al.[67] (2011) Zolpidem 10 mg vs placebo	DB, PC, RCT Patients 21 to 70 years of age with primary insomnia	N=33 12 months	Primary: Number of zolpidem or placebo choices made, total number of zolpidem or placebo capsules chosen, and given a placebo or zolpidem choice on a given night, the nightly number of capsules taken Secondary: Not reported	Primary: On weekly telephone interviews, patients reported taking 73 to 89% of the single nightly capsules each month while at home. The groups did not differ in the average percentage of capsules used over the 12 months (placebo, 81% vs zolpidem, 84%). Over the three one-week laboratory self-administration assessments, the zolpidem group selected zolpidem (80.3%) more often than placebo (P<0.020). The placebo group showed no color preference, choosing the red capsule 51% of opportunities and the blue capsule 49% of opportunities. Overall, the zolpidem group self-administered more zolpidem capsules than placebo capsules (P<0.001). In the zolpidem group, the total number of capsules chosen, whether placebo or zolpidem, did not differ over months one, four, and 12. The total number of placebo capsules self-

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				administered by the placebo group increased significantly during month four and month 12 compared to month one (P<0.02). Within the zolpidem group, the nightly number of placebo vs zolpidem capsules self-administered each month did not differ. On average, the zolpidem group self-administered a 9.1 mg dose nightly in month one, a 9.4 mg dose in month four, and a 9.4 mg dose in month 12. In the placebo group, the nightly number of capsules increased over time (P<0.02). The percent of patients increasing the dose did not differ between the zolpidem and placebo groups and did not change from month four to month 12. A significantly greater percent of patients receiving zolpidem compared to placebo decreased the dose they self-administered in month four and month 12 compared to month one (P<0.001). The self-administration rates did not differ when at the laboratory vs at home for patients receiving zolpidem. These rates also did not differ over the three assessments. Secondary: Not reported
Roth et al.[68] (1995) Zolpidem 5, 7.5, 10, 15, 20 mg vs placebo Statistical analyses were primarily performed between zolpidem 7.5 and 10 mg and placebo.	DB, PC, PG, RCT Healthy adult volunteers with transient insomnia	N=462 SD	Primary: SL, sleep duration, SE (TST divided by time in bed) NAW (sleep maintenance), effect on sleep stages, next day psychomotor performance and alertness (DSST, Symbol Copying Tests, Visual Analog Scales on the Morning Questionnaire)	Primary: Compared to placebo, zolpidem 7.5 and 10 mg significantly decreased SL, increased sleep duration and efficiency, and reduced the NAW (all P<0.05). Subjective quality of sleep was also rated significantly better with both doses of zolpidem compared to placebo (both P<0.001). Increasing the dose above 10 mg did not result in a corresponding increase in hypnotic efficacy. Treatment with zolpidem had no effect on stage 1, stage 2 and stages 3 to 4 sleep. Significantly less REM sleep was reported in the zolpidem groups compared to the placebo group (both P<0.001). Zolpidem 7.5 or 10 mg had no significant effect on next day psychomotor performance and alertness. No statistically significant differences in the overall side effects were

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			Secondary: Not reported	found between zolpidem doses of 7.5 mg (4.9%) or 10 mg (6.7%) and placebo (7.8%). Higher doses of zolpidem were associated with more side effects (17.6% with 15 mg [P=0.069 vs placebo] and 31.4% with 20 mg [P<0.001 vs placebo]). Secondary: Not reported
Randall et al.[69] (2012) Zolpidem 5 or 10 mg vs placebo	DB, PC, RCT Adults 23 to 70 years of age with chronic primary insomnia	N=91 8 months	Primary: Polysomnographic sleep parameters and morning subject assessments of sleep on two nights in months one and eight Secondary: Not reported	Primary: Relative to placebo, zolpidem significantly increased overall TST and SE, reduced SL and wake after sleep onset when assessed at months one and eight. Overall, subjective evaluations of efficacy were not shown among treatment groups. Secondary: Not reported
Krystal et al.[70] (2008) Zolpidem ER 12.5 mg vs placebo Treatments were taken 3 to 7 nights per week.	DB, MC, PC, RCT Patients 18 to 64 years of age with chronic primary insomnia	N=1,025 26 weeks	Primary: Score on the PGI, Item 1, (aid to sleep) at week 12 of the treatment period in the ITT population Secondary: Scores on CGI-I, PGI, PMQ, TST, WASO, SOL, quality of sleep, and NAW in the ITT population	Primary: At week 12, PGI, Item 1 (aid to sleep) was scored as favorable (i.e., "helped me sleep") by 89.8% of zolpidem patients vs 51.4% of placebo patients (P<0.0001). Secondary: The percentage of patients who reported a treatment benefit on the PGI (Items 1 to 4) was higher in the zolpidem ER group compared to placebo at each four-week interval during the 24-week treatment period (all P<0.0001). The percentage of patients who obtained a positive evaluation on the CGI-I scale was greater in the zolpidem ER group compared to the placebo group at all four-week intervals during the 24-week treatment period (all P<0.0001). At every time point, results on the PMQ were greater for patients in the zolpidem ER group compared to the placebo group for the TST

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				(P<0.0001), WASO (P<0.0001), SOL (P≤0.0014), quality of sleep (P<0.0001), and NAW (month one; P=0.0515, months two to six; P<0.0001). Patients in the zolpidem ER group demonstrated improvements in their ability to concentrate in the morning at each month throughout the treatment period, as compared to those in the placebo group (months one to five; P<0.0001, month six; P=0.0014). Patients in the zolpidem ER group had sustained reductions in their level of sleepiness in the morning compared to placebo at each month throughout the treatment period (P<0.0001). The most common adverse events occurring at a higher frequency in the zolpidem extended-release group than in the placebo group were headache, anxiety, somnolence, dizziness, fatigue, disturbance inattention, irritability, nausea, and sinusitis.
Fava et al.[71] (2011) Zolpidem ER 12.5 mg vs placebo Patients were also receiving OL escitalopram 10 mg daily.	DB, MC, PC, PG, RCT Patients 21 to 64 years of age with major depressive disorder and associated insomnia	N=358 24 weeks Two phases were included Phase 1 was 8 weeks; responders (≥50% in 17-item $HDRS_{17}$) at week 8 continued to receive an additional 16 weeks of therapy in phase 2	Primary: Change from baseline in subjective TST Secondary: Subjective LSO, NAW, WASO, sleep quality, sleep-related next-day functioning, $HDRS_{17}$ SIS score, PGI-IT, CGI-I, CGI-S, MGH-CPFQ, Q-LES-Q, safety	Primary: Phase 1 During phase 1, treatment with zolpidem ER led to significantly greater improvements in TST when compared to treatment with placebo (P<0.0001). Phase 2 During phase 2, treatment with zolpidem ER led to improvements in TST that were significant at weeks 12 and 16 (P<0.05 for both), but not at weeks 20 and 24 (P value not reported). Secondary: Phase 1 Treatment with zolpidem ER led to significantly greater improvement in TST at each assessment. The LSM difference between the treatment groups in the change from baseline TST ranged from 37.9 to 45.5 minutes (P<0.0001 for all comparisons). The group receiving zolpidem ER had a TST of approximately seven hours at week eight, compared to approximately five hours at baseline (P<0.0001 vs placebo for improvement over baseline).

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				Treatment with zolpidem ER led to significantly greater improvements in WASO, LSO, NAW, and sleep quality when compared to treatment with placebo (P<0.001 for all comparisons at all time points). Total improvement in insomnia-only $HDRS_{17}$ was also significantly greater in the group receiving zolpidem ER compared to those receiving placebo (P<0.001 for all time points). Treatment with zolpidem ER also produced favorable results on all domains of the SIS, except mental fatigue, when compared to treatment with placebo at week eight (P<0.05). There were no significant differences at week eight between the two groups on the improvement in functioning and quality of life on the Q-LES-Q; however, at week eight, there were greater improvements seen in the MGH-CPFQ total score, wakefulness/alertness, energy, memory/recall, and mental acuity in those patients receiving zolpidem ER compared to those receiving placebo (P<0.05). There were no significant improvements found with zolpidem ER compared to placebo on motivation/enthusiasm, attention focus/sustain, or ability to find words, at week eight. Treatment with zolpidem ER was also associated with greater improvements than placebo in some aspects of sleep-related next-day functioning, including morning energy, sleep impact on daily activities, and morning concentration ability. Decreases seen in the $HDRS_{17}$ scores at week eight were comparable between the two treatment groups; at the end of phase 1 58.4 and 63.7% of patients in the placebo and zolpidem ER groups, respectively, met the criteria for depression treatment response. PGI-IT scores were superior in the group receiving zolpidem ER compared to those in the placebo group (P<0.001) and both CGI-S and CGI-I scores were comparable between the groups throughout phase 1. Phase 2 During phase 2, treatment with zolpidem ER continued to show significantly greater improvement at each visit in the NAW and sleep quality, when compared to treatment with placebo (P value not reported). For WASO, treatment with zolpidem ER resulted in significant

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				improvements over treatment with placebo at weeks 16 and 20 and there were no significant differences between the treatment groups in LSO during phase 2 (P value not reported). The $HDRS_{17}$ total score of insomnia-only items demonstrated significantly greater improvement in the zolpidem ER group throughout phase 2 (P<0.05 for all time points). Treatment with zolpidem ER was associated with significant differences on all of the SIS domain scores at week 24, except mental fatigue (P<0.05). There were no differences between the groups in any of the MGH-CPFQ subscales at week 24 (P-value not reported). Treatment with zolpidem ER resulted in improvements over placebo on the physical health/activities and medication satisfaction subscales of Q-LES-Q (P<0.05); however, treatment with placebo resulted in improvements over zolpidem ER on the school/course work subscale (P<0.05). Both groups experienced improvements in depression treatment remission and depression symptoms; however, these improvements were not significantly different between groups (P value not reported). PGI-IT scores indicated insomnia treatment was rated higher with zolpidem ER compared to placebo (P<0.001). Ratings of severity and mental illness by clinicians were comparable between the two groups throughout phase 2. A greater percentage of patients treated with zolpidem ER experienced at least one adverse event during phase 1 when compared to patients treated with placebo (72.9 vs 66.3%; P value not reported). The most common adverse events that occurred more frequently in the group receiving zolpidem ER, compared to the placebo group, include nausea, somnolence, dry mouth, dizziness, fatigue, upper respiratory tract infection, and decreased libido. During phase 2, 57.3% of zolpidem ER-treated patients and 60% of placebo-treated patients experienced an adverse event (P value not reported). The most frequently reported events among both treatment groups include headache, diarrhea, and nasopharyngitis.

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Fava et al.[72] (2009) Zolpidem ER 12.5 mg vs placebo All patients received OL escitalopram 10 mg/day.	DB, MC, PC, PG, RCT Patients 21 to 64 years of age with insomnia and comorbid GAD	N=383 8 weeks	Primary: Change from baseline to week eight in subjective TST Secondary: Subjective SOL, NAW, WASO, sleep quality, HAMA, BAI, SIS, MGH-CPFQ, SDS, safety	Primary: At week eight, the mean TST increased from baseline by 106 minutes in the group receiving zolpidem ER and by 68.2 minutes in the placebo group (LSM in the change from baseline between groups 39.4 minutes, 90% CI, 24.81 to 53.99; P<0.0001). Secondary: From week one through week eight, mean TST was significantly greater in the group receiving zolpidem ER when compared to those receiving placebo (P<0.0001). Significant improvements in SOL, WASO, NAW, and quality of sleep were observed throughout the treatment period with zolpidem ER vs placebo based on the difference in LSM change from baseline (P<0.0001 for all comparisons). Significant improvements were also seen with MSQ measures of sleep-related next-day symptoms, including morning energy, morning concentration, and impact of sleep on daily activities (P<0.0001 for all comparisons). The change from baseline in PGI-IT for the zolpidem ER-treated group was significantly greater when compared to the placebo-treated group (P<0.0001 for all comparisons). At week two, there was a significant difference in favor of treatment with zolpidem ER on all seven items of the SIS (P<0.0001 for six comparisons; P<0.01 for one comparison). This improvement was sustained to week eight on four of the seven items: daily activities (P=0.107), emotional impact (P<0.0001), energy/fatigue (P<0.001), and satisfaction with sleep (P<0.0001). Between group differences in the total MGH-CPFQ score were significant at week four but not at week eight (P=0.0586). There were statistically significant differences between groups at one or both of the time points for three of seven items. There was statistically significantly greater improvement in the zolpidem ER group on three items (motivation, wakefulness/alertness, and energy) at week four (P<0.05) and on two items (wakefulness/alertness and energy) at week eight (P<0.01). The mean HAMA total scores decreased for both groups throughout the study. At week eight, HAMA total scores for both the group receiving zolpidem ER and the group receiving placebo showed comparable

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				reductions (-13.3 vs -12.5, respectively; P=0.4095). Rates of treatment response in the group receiving zolpidem ER and the group receiving placebo were similar at week eight (63.4 vs 64.2%, respectively; P=0.8564). Both treatment groups demonstrated at least a 40% reduction in the BAI at week one and continued to improve throughout the study. By week six, there was a difference in favor of the placebo group that as also present at week eight. There were no significant differences in Q-LES-Q between groups at week eight and there were no significant differences between groups in SDS scores at any time point measured. Treatment-emergent adverse events that occurred in at least 10% of patients and either group but with a higher incidence in the group receiving zolpidem ER included dizziness, nausea, and fatigue. Six patients receiving zolpidem ER experienced seven events of non-global amnesia between two and 59 days of taking the study medication. One patient in each group experienced one serious adverse event. Laboratory values, vital signs, and physical examination findings revealed no meaningful changes or clinically relevant differences between groups.
Erman et al.[73] (2008) zolpidem ER 12.5 mg vs placebo Zolpidem ER or placebo was to be taken nightly or at least 3 times per week.	DB, PC, RCT (subset analysis) Adults under 65 years of age with chronic insomnia	N=1,012 24 weeks	Primary: Change from baseline to week 12 in the Time Management and Output scales of the WLQ Secondary: Change from baseline to week four and to week 24 in the Time Management and Output scales of	Primary: At week 12, treatment with zolpidem ER 12.5 resulted in a 4.86 point reduction in the Output Scale (95% CI, -8.37 to -1.36; P=0.0066) and a 7.29 point reduction in the Time Management Scale (95% CI, -10.77 to -3.81; P<0.0001) vs placebo. Secondary: At week four, scores for the Output Scale and the Time Management Scale were significantly lower than at baseline (P value not reported). The decrease was significantly greater with zolpidem ER than for placebo for both the Output Scale (-9.59 vs -2.16; P<0.0001) and the Time Management Scale (-12.22 vs -3.85; P<0.0001).

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			the WLQ, or premature discontinuation	
Roth et al.[74] (2013) Zolpidem SL tablets 3.5 mg vs placebo	DB, MC, PC, PG, RCT Adults with primary insomnia and difficulty returning to sleep after MOTN	N=295 28 nights	Primary: LSO after MOTN, adverse events Secondary: Not reported	Primary: Zolpidem SL tablets significantly (P<0.0001) decreased LSO over four weeks (baseline, 68.1 minutes; zolpidem SL tablets, 38.2 minutes) compared to placebo (baseline, 69.4 minutes; placebo, 56.4 minutes). Ratings of morning sleepiness/alertness significantly (P=0.0041) favored the zolpidem SL tablets group on nights medication was taken but not on other nights. Participants in the zolpidem SL tablets group took the study drug on 62% of nights during the four weeks; members of the placebo group took study medication on 64% of nights. Adverse events were generally mild and at the same rate (19.3% of participants) in both groups. There were no treatment-related serious adverse events, and one adverse event-related study discontinuation from the placebo group. Dosing/week did not increase across the study. Secondary: Not reported
Roth et al.[75] (2008) Zolpidem 1.75 or 3.5 mg SL vs placebo Subjects were awakened 4 hours after lights out, dosed with zolpidem SL or placebo, kept	DB, PC, XO Adults with insomnia characterized by difficulty returning to sleep following MOTN awakenings	N=82 3 2-night treatment periods Each treatment period consisted of 2 consecutive nights of dosing separated by a washout of 5 to 12 days.	Primary: LPS following MOTN comparing zolpidem SL 3.5 mg to placebo Secondary: TST, SE, sleep quality, subjective SOL, subjective TST, and mean LPS for zolpidem SL 1.75 compared to placebo (all assessed after MOTN); according	Primary: Treatment with zolpidem SL 3.5 mg resulted in a significant improvement in LPS after MOTN compared to treatment with placebo (9.69 vs 28.12 minutes; P<0.001 vs placebo, P<0.001 vs zolpidem SL 1.75 mg). Secondary: Treatment with zolpidem SL 1.75 mg resulted in a significant improvement in LPS after MOTN compared to treatment with placebo (16.89 vs 28.12 minutes; P<0.001). Treatment with zolpidem SL 1.75 mg resulted in improvements in the following parameters: TST after MOTN (197.80 vs 183.12 minutes; P<0.001), subjective SOL after MOTN (28.58 vs 40.43 minutes; P<0.001), and subjective TST after MOTN (162.36 vs 148.61 minutes; P<0.011). Treatment with zolpidem SL 3.5 mg resulted in improvements in the following parameters: TST after MOTN (208.99 vs 183.12 minutes; P<0.001 vs placebo, P=0.005 vs zolpidem SL 1.75 mg), subjective SOL after MOTN (25.23 vs 40.43 minutes; P<0.001), and

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awake for 30 minutes, and then returned to bed for 30 minutes.			to the statistical analysis plan, if any test of a secondary endpoint did not attain statistical significance, then inferential analyses of secondary endpoints would cease and no further inferential assessment of remaining secondary endpoints would be made, safety	subjective TST after MOTN (172.51 vs 148.61 minutes; P<0.011). The endpoints of WASO after MOTN and NAW after MOTN failed to reach significance for either dose of zolpidem SL compared to placebo. Treatment with zolpidem SL 3.5 mg resulted in the greater improvement in sleep quality compared to treatment with placebo (P<0.001) and compared to treatment with zolpidem SL 1.75 mg (P=0.018). Sleep quality ratings in the group receiving zolpidem SL 1.75 mg were not significantly different than the group receiving placebo. No serious adverse events occurred and no subject discontinued the study due to an adverse event. Out of the 82 included subjects, 14 reported an adverse event. All adverse events were mild in severity and transient.
Staner et al.[76] (2010) Zolpidem 10 mg SL tablet vs zolpidem 10 mg tablet	DB, MC, RCT, XO Patients 18 to 65 years of age with primary insomnia	N=70 SD	Primary: LPS, SOL, time spent in sleep stage 1 Secondary: TST, WASO, SE index, total time spent awake, time spent in stage 2, time spent in slow wave sleep; time spent in REM sleep; REM SL, LSEQ, DSST, CFF Test	Primary: Zolpidem SL shortened the LPS by about 34% or 10.3 minutes (P=0.001), SOL with about 8.6 minutes (P<0.01) and time spent in sleep stage 1with about 7.4 minutes (P<0.01) compared to zolpidem. Secondary: There were no significant differences on in TST and WASO among the treatment groups. The TST was 432 minutes for zolpidem SL and 425 minutes for zolpidem. WASO was 31 and 30 minutes for zolpidem SL and zolpidem, respectively. There was a significant difference in SE index (P<0.05) and total time spent awake (P<0.05), favoring zolpidem SL. No differences were found between the treatments for the sleep architecture parameters time spent in sleep stage 1, slow wave sleep, REM and REM SL. The difference found for time spent in stage 2 reached statistical significance (P<0.05), favoring zolpidem SL. There were no significant differences in LSEQ scores among the treatment groups.

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				There were no significant differences in the way patients rated their subjective feelings of alertness, contentedness and calmness on the visual analog scale. There were no significant differences in DSST between the two treatments. CFF Test results indicated that, during the descending runs, patients had a lower flicker fusion threshold after zolpidem SL than after zolpidem (P<0.05). There were no between-treatment differences for the ascending runs. Both routes of administration were well tolerated with a similar overall incidence of adverse events. The most common adverse events with zolpidem SL were somnolence and dysgeusia. Nausea, dysgeusia, somnolence and dizziness were the most common adverse events with zolpidem.
Valente et al.[77] Zolpidem 5 and 10 mg SL vs zolpidem 10 mg oral	DB, DD, OL, RCT Healthy volunteers	N=58 Duration not specified	Primary: PSG and post-sleep questionnaires Secondary: Not reported	Primary: A significant main treatment effect was evident considering the SOL and persistent SL. An earlier sleep onset was induced by SL zolpidem 10 mg (SOL; P<0.004 and persistent SL; P<0.006) and SL zolpidem 5 mg (SOL; P<0.025 and persistent SL; P<0.046) compared to oral zolpidem 10 mg. Subjects that received SL zolpidem 10 mg reported an earlier sleep onset (latency to sleep and latency until persistent sleep) when compared to subjects from other groups (P<0.005). Secondary: Not reported
Staner et al.[78] (2009) Zolpidem 5 mg SL tablet vs zolpidem 10 mg SL tablet vs	OL, RCT, XO Healthy volunteers in a post-nap model of insomnia	N=21 SD	Primary: LPS, SOL, latency to stage 1, TST, SE, awakening after sleep onset, REM SL, stage 4 duration Secondary: Not reported	Primary: For zolpidem 10 mg SL tablets, LPS was significantly decreased by 6.11 minutes as compared to zolpidem 10 mg tablets (P<0.05). Zolpidem 10 mg SL tablets decreased SOL by 5.81 minutes as compared to zolpidem 10 mg tablets (P<0.05). Zolpidem 10 mg SL tablets decreased latency to stage 1 by 6.17 minutes as compared to zolpidem 10 mg tablets (P<0.05). Similar differences were demonstrated for sleep initiation parameters between zolpidem 5 and 10 mg SL tablets (7.28 minute difference for

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zolpidem 10 mg tablet				LPS, 6.69 minute difference for SOL and 6.06 minute difference for latency to stage 1; all P<0.05). There were no significant differences in the three sleep initiation parameters between zolpidem 5 and 10 mg SL tablets. There were no significant differences between the three treatments for sleep maintenance parameters, including TST, SE or awakening after sleep onset. There were no differences in sleep maintenance between zolpidem 5 and 10 mg SL tablets. Significant treatment effects were evidenced for REM SL and stage 4 duration. Both REM SL and stage 4 duration were similar with zolpidem 5 and 10 mg SL tablets. Both parameters were significantly shorter in patients receiving zolpidem 5 mg SL tablets compared to zolpidem 10 mg tablets (REM SL, -19.22 minutes; P<0.01, stage 4 duration, -11.89 minutes; P<0.01). There were no differences in sleep architecture between zolpidem 5 and 10 mg SL tablets. No differences were detected in subjective sleep parameters as indicated by a lack of significant treatment effect on any of the LSEQ variables. Next-day residual effects were comparable between treatments. Vigilance, psychomotor performances, attention and concentration were comparable between treatments. The most frequent adverse events were somnolence, headache and fatigue. All were of moderate or mild intensity and resolved spontaneously. Secondary: Not reported
Elie et al.[79] (1999) Zaleplon 5 to 20 mg or zolpidem 10 mg vs	DB, MC, PC, RCT Adults with primary insomnia or insomnia associated with mild nonpsychotic psychiatric	N=615 4 weeks	Primary: Patient's assessment of SL Secondary: Patient's assessment of sleep duration, sleep	Primary: Median SL was significantly lower with zaleplon 10 and 20 mg than with placebo during all four weeks of treatment, and with zaleplon 5 mg and zolpidem 10 mg for the first three weeks. Secondary: Zaleplon 20 mg significantly (P<0.05) increased sleep duration compared to placebo in all but week three of the study, while zolpidem 10 mg

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placebo	disorders		quality, NAW, rebound insomnia, withdrawal effects, safety	significantly (P<0.05) increased sleep duration at all time points. Mean scores for sleep quality were significantly (P<0.05) better than with placebo during week one with zaleplon 10 mg and 20 mg, and for all weeks with zolpidem 10 mg. No significant differences were observed in NAW between the placebo and active treatment groups. The number of patients treated with zaleplon showing rebound insomnia was not significantly different from placebo on the first night after discontinuation of four weeks of treatment. Significant differences in SL (P<0.05) and NAW (P<0.01) were noted in patients treated with zolpidem 10 mg. On the second night after discontinuation of treatment, there were significantly more patients (P<0.05) showing rebound insomnia for the NAW with zaleplon 10 and 20 mg than with placebo, and on the third night there were significantly fewer patients (P<0.05) showing rebound for the NAW with zaleplon 20 mg. There was no evidence of withdrawal symptoms after discontinuation of four weeks of zaleplon treatment. Significantly more patients who had received zolpidem than placebo reported withdrawal effects on the first night after treatment was discontinued; however, there was no statistically significant difference on the second or third night between the two groups. The frequency of adverse events in the active treatment groups did not differ significantly from that in the placebo group. The study did not report any direct comparisons between the zaleplon.
Huedo et al.[80] (2012) Eszopiclone, zaleplon, or zolpidem	MA DB, PG, PC, RCTs of eszopiclone, zaleplon, or zolpidem	N=4,378 Duration varied	Primary: Polysomnographic and subjective SL Secondary: Waking after sleep	Primary: Significant improvements (reductions) in primary outcomes were documented: polysomnographic SL (weighted standardized mean difference; 95% CI, -0.57 to -0.16) and subjective SL (-0.33, -0.62 to -0.04) compared to placebo. Analyses of weighted mean raw differences showed that the active agents decreased polysomnographic SL by 22

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo			onset, NAW, TST, SE, and subjective sleep quality	minutes (-33 to -11 minutes) compared to placebo. Secondary: No significant results were identified in the secondary outcomes.
Uchimura et al.[81] (2012) Eszopiclone 1, 2, and 3 mg vs zolpidem 10 mg vs placebo	DB, PC, RCT, XO Japanese patients with primary insomnia	N=72 10 nights	Primary: Sleep measures from PSG and subjective patient reports Secondary: Not reported	Primary: All active treatments produced significant improvement in objective and subjective SL compared to placebo (P<0.05 for all comparisons); linear dose-response relationships were observed for eszopiclone. PSG-determined WASO, SE, and NAW, and patient-reported measures of WASO, NAW, sleep quality, sleep depth, and daytime functioning significantly improved following treatment with eszopiclone 2 mg and 3 mg and zolpidem 10 mg vs placebo (P<0.05). Eszopiclone at all doses increased TST and stage 2 sleep time (P<0.001 for both comparisons), but did not alter REM or slow-wave sleep. Eszopiclone was generally well tolerated; the most frequently reported adverse event was mild dysgeusia. Secondary: Not reported
Erman et al.[82] (2008) Eszopiclone 1 mg for 2 nights vs eszopiclone 2 mg for 2 nights vs eszopiclone 2.5 mg for 2 nights	MC, RCT, XO Patients 21 to 64 years of age with primary insomnia; with a 3 to 7 day washout between XO treatments	N=65 2 nights for each treatment	Primary: LPS Secondary: SE, WASO, WTDS, NAW, and patient-reported variables	Primary: All active treatments reduced median LPS by 42 to 55% compared to placebo (P<0.05). The median LPS was 13.1 minutes for eszopiclone 3 mg and zolpidem 10 mg. The median LPS was 29.0, 16.8, 15.5, and 13.8 minutes for the placebo, eszopiclone 1, 2, and 2.5 mg dose groups, respectively. The two highest doses of eszopiclone (2.5 and 3 mg) and zolpidem demonstrated significantly lower LPS when compared to eszopiclone 1 mg (P<0.05). Secondary: Significant differences were found between all active treatments in SE compared to placebo (P<0.05). Eszopiclone 2, 2.5, and 3 mg, and zolpidem 10 mg demonstrated significantly higher SE when compared to eszopiclone 1 mg (P<0.05). Treatment with eszopiclone 3 mg resulted in significant differences

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs eszopiclone 3 mg for 2 nights vs zolpidem 10 mg for 2 nights vs placebo for 2 nights There was a 3 to 7 day washout between XO treatments				compared to treatment with placebo for WASO, WTDS, and NAW. Eszopiclone 2.5 mg demonstrated significant differences compared to placebo for WASO and WTDS. Neither of the lower doses of eszopiclone nor zolpidem 10 mg was different from placebo for WASO or WTDS. Comparisons of eszopiclone 3 mg and zolpidem 10 mg were not significantly different for WASO (P=0.12), for WTDS (P=0.07), or for NAW (P=0.10). Treatment with eszopiclone 2 and 3 mg and zolpidem 10 mg showed improvements in patient-reported measures of sleep relative to placebo. Both doses of eszopiclone and zolpidem 10 mg significantly improved sSL, sTST, quality of sleep, and depth of sleep relative to placebo (P<0.05). Eszopiclone 2 and 3 mg and zolpidem 10 mg were significantly different from placebo for subject reported NAW and sWASO (P<0.05). Morning sleepiness was significantly less with eszopiclone 3 mg compared to placebo (P<0.05). Evening ratings of daytime alertness were significantly increased with eszopiclone 2 mg and with zolpidem 10 mg compared to placebo (P<0.05), and daytime ability to function was significantly improved for eszopiclone 2 and 3 mg and zolpidem 10 mg compared to placebo (P<0.05). The most common adverse events were headache, unpleasant taste, somnolence, dizziness, and nausea. The overall rate of central nervous system adverse events was 7.9% for placebo, 6.2 to 12.5% for the eszopiclone groups, and 23.4% for zolpidem 10 mg.
Zammit et al.[83] (2009) Ramelteon 8 mg vs zolpidem 10 mg vs	DB, MC, PC, XO Adults over the age of 65 with self-reported chronic insomnia	N=33 Each study drug was taken for one night each with a 4 to 10 day washout period between treatments.	Primary: SOT composite score Secondary: Equilibrium scores on the SOT, SOT ratios, SQTT scores, and memory tests, safety	Primary: There were no differences between placebo and ramelteon on the SOT (P=0.837). Secondary: There were no significant differences between placebo and ramelteon on turn time (P=0.776) or turn sway (P=0.982). Treatment with zolpidem, the positive control, did result in significant impairments on the SOT, turn time, and turn sway (P<0.001 for all). Immediate and delayed memory recall were not significantly different with ramelteon (P=0.683 and P=0.650, respectively); however, immediate recall declined significantly

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo Subjects were administered the study drug 30 minutes prior to bedtime and were awakened 2 hours after dosing to evaluate balance.				with zolpidem (P=0.002). Adverse events were infrequent and none were serious. The same proportion of subjects in the ramelteon and placebo groups reported adverse events (21.2%) compared to 39.4% of subjects in the zolpidem group. Adverse events that occurred in at least two subjects in any group include dizziness, headache, nausea, and somnolence.
Huang et al.[84] (2011) Zaleplon 10 mg vs zolpidem 10 mg	AC, DB, RCT Patients 20 to 65 years of age with primary insomnia	N=48 2 weeks	Primary: Change in subjective SL from baseline to week two Secondary: Sleep duration, NAW, sleep quality and incidence of rebound insomnia	Primary: There was a significant reduction in subjective SL in the zaleplon group (reduced from 63.0 minutes to 31.6 minutes; P<0.05) and zolpidem group (reduced from 61.9 minutes to 30.0 minutes; P<0.05). There was no significant difference between the zaleplon group and zolpidem group in SL (P=0.084). Secondary: There was no significant difference in sleep duration, NAW, or sleep quality among the groups. None of the patients experienced rebound insomnia. The most frequently reported adverse effects were headache, dizziness, anxiety and urinary tract infection. There was no significant difference in the frequency of each adverse effect between the zaleplon and zolpidem groups.
Dunbar et al.[85] (2004) Zaleplon 5 to 20 mg vs zolpidem 5 to 10 mg	MA Patients 16 to 85 years of age with insomnia	N=1,539 (6 trials) 2 nights to 4 weeks	Primary: SOL, TST, quality of sleep, adverse events, rebound insomnia Secondary: Not reported	Primary: Of the two studies that directly compared SOL, one study reported a significantly shorter SL with zaleplon (P<0.001), whereas the other study reported results in favor of zolpidem (P=0.03). Of the two studies that directly compared TST, one study reported that sleep duration was significantly less in the zaleplon group (290.7 vs 308.6 minutes for zolpidem; P=0.05) but another study found no difference (eight hours for zaleplon vs 8.3 hours on zolpidem). Patients on zaleplon were less likely to experience an improvement in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				sleep quality than those on zolpidem (OR, 0.66; 95% CI, 0.51 to 0.87). There was no statistically significant difference in the frequency of treatment-emergent adverse events (OR, 0.86; 95% CI, 0.62 to 1.20). One study reported that patients taking zaleplon were less likely to suffer withdrawal symptoms on the first night of the placebo run-out phase than those on zolpidem (1.5 and 7.1% respectively; P=0.01). Combined results from two trials noted that patients receiving zaleplon were less likely to experience rebound insomnia compared to those on zolpidem (SL OR, 0.27; 95% CI, 0.17 to 0.44, sleep duration OR, 0.25; 95% CI, 0.15 to 0.41, and NAW OR, 0.34; 95% CI, 0.18 to 0.61). In a XO study, 62.3% of patients favored zolpidem compared to 37.7% of patients who favored zaleplon (P=0.08). Secondary: Not reported
Zammit et al.[86] (2006) Zaleplon 10 mg for 2 nights vs zolpidem 10 mg for 2 nights vs placebo for 2 nights Each treatment period was	DB, PC, RCT, XO Patients 18 to 65 years of age with primary sleep-maintenance insomnia	N=37 2 nights	Primary: LPS and TST, daytime SL Secondary: Not reported	Primary: LPS after the administration of zaleplon 10 mg, zolpidem 10 mg, and placebo was 14.9, 11.7, and 42.2 minutes, respectively (overall P<0.001), which made the LPS with active agents shorter by approximately 27 and 31 minutes (P<0.001 for both comparisons). TST was significantly longer with zaleplon 10 mg and zolpidem 10 mg than placebo by approximately 22 and 30 minutes, respectively (overall P<0.001). Daytime SL was not significantly different between the zaleplon 10 mg and placebo groups (P>0.136); however, it was shorter with zolpidem 10 mg compared to placebo (overall P<0.001) when tested at four (P<0.001), five (P<0.001), and seven (P<0.05) hours, respectively, after dose administration. There was no significant difference between the zaleplon 10 mg and placebo in patients' subjective level of alertness or ability to concentrate.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
separated by a 5- or 12-day washout period.				Patients reported significantly less alertness after the SLT performed at four hours after dosing with zolpidem 10 mg compared to placebo (overall P=0.005). Daytime subjective reports of ability to concentrate following zolpidem 10 mg were significantly worse than following placebo when tested after the SLT at four, five, and six hours after treatment (overall P<0.05). Secondary: Not reported
Danjou et al.[87] (1999) 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 five, four, three, or two hours before morning awakening, tests included DSST, CFF threshold, CRT, Memory Test, Sternberg Memory Scanning Task, LARS, LSEQ, adverse events Secondary: Not reported	Primary: No residual effects were demonstrated after zaleplon 10 mg, when administered as little as two hours before waking, on either subjective or objective assessments. Zolpidem 10 mg showed significant residual effects on DSST and memory after administration up to five hours before waking and CRT, CFF threshold and Sternberg Memory Scanning Task after administration up to four hours before waking. Residual effects of zolpidem were apparent in all objective and subjective measurements when the drug was administered later in the night. There were no serious adverse experiences during the study; all adverse events were mild-to-moderate. Overall, the number of subjects who reported any adverse experience after administration of study drug was similar for zaleplon and placebo (11 and 33% regardless of the time of drug administration) but was significantly higher following zolpidem (56 to 72%) when zolpidem was administered two, three, four, and five hours before awakening (P values not reported). Secondary: Not reported
Verster et al.[88] (2002) Zaleplon 10 mg	DB, XO Healthy volunteers with mean age 24.0 years	N=30 SD with at least a 5-day washout	Primary: Driving ability (standard deviation of the lateral position, standard	Primary: Zaleplon 10 and 20 mg did not significantly impair driving ability four hours after middle-of-the-night administration (significant difference defined as P<0.0125).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
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.		period	deviation of speed, memory, psychomotor performance) (subjects given study medication five hours after going to bed and awakened three hours after dose, driving test performed four hours after awakened, memory and psychomotor tests performed six hours after awakened) Secondary: Not reported	Relative to placebo, after zolpidem 10 mg, standard deviation of the lateral position (amount of weaving of the car) was significantly elevated but the magnitude of the difference was small and not likely to be of clinical importance (difference, 2.87 cm; P<0.005). Standard deviation of speed (speed variability) was not significantly different for zolpidem 10 mg than placebo (P=0.256). Zolpidem 20 mg significantly increased SDLP and speed variability (both P<0.001). Memory and psychomotor test performances were unaffected after both doses of zaleplon and zolpidem 10 mg. Zolpidem 20 mg significantly impaired performance on psychomotor and memory tests. (Note: the recommended dose for zolpidem is 10 mg immediately before bedtime.) Secondary: Not reported
Piccione et al.[89] (1980) Triazolam 0.25 mg vs triazolam 0.50 mg	DB, XO Elderly patients >60 years of age with insomnia	N=27 5 days	Primary: Efficacy (questionnaire with subjective estimates of SL, TST, NAW, overall quality of sleep), side effects	Primary: The patients' global evaluation of effectiveness indicated that triazolam 0.25 and 0.50 mg improved sleep more than placebo (both P<0.05), while chloral hydrate 250 and 500 mg were not better than placebo. Triazolam 0.50 mg, but not 0.25 mg, was significantly better than chloral hydrate 250 mg (P<0.01) and 500 mg (P<0.05) in the global evaluation of effectiveness.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs chloral hydrate 250 mg vs chloral hydrate 500 mg vs placebo			Secondary: Not reported	There was no significant difference in SL, TST and NAW between placebo and either dose of chloral hydrate. Triazolam 0.25 mg significantly decreased SL and increased TST compared to placebo (both P<0.05). Triazolam 0.50 mg significantly decreased the NAW compared to placebo (P<0.01). Patients estimated their TST to be longer following the use of triazolam 0.25 mg as compared to chloral hydrate 250 or 500 mg (both P<0.05). There were no significant differences in reported side effects between the active treatments and placebo. Secondary: Not reported
Johnson et al.[90] (2006) Triazolam 0.25, 0.5 or 0.75 mg vs ramelteon 16, 80 or 160 mg vs placebo	DB, XO Adults with a history of sedative abuse	N=14 18 days	Primary: Subject-rated measures (drug liking, street value, pharmacological classification), observer-rated measures (sedation, impairment), motor and cognitive performance (balance task, DSST, word recall) Secondary: Not reported	Primary: Triazolam showed dose-related effects on subject-rated, observer-rated, and motor and cognitive performance measures. Compared to placebo, all doses of ramelteon showed no significant effect on any of the subjective effect measures, including those related to potential for abuse (all P>0.05). In the pharmacological classification, 79% of patients identified the highest dose of ramelteon as placebo. Compared to placebo, ramelteon had no effect at any dose on any observer-rated or motor and cognitive performance measure (all P>0.05). Secondary: Not reported
Hindmarch et al.[91] (2006) Flurazepam 30 mg	DB, RCT, XO Healthy volunteers ≥65 years of age	N=24 SD treatment	Primary: Psychometric tests performed 8 hours after study medication (CFF,	Primary: There were no significant differences in psychometric tests between the zolpidem modified release treatment groups and placebo (P>0.05). Psychometric performance was significantly impaired with flurazepam compared to placebo for all tests with the exception of the DSST

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs zolpidem modified release 6.25 mg vs zolpidem modified release 12.5 mg vs placebo			CRT, word recall, CTT, DSST), subjective evaluation of sleep (LSEQ), safety, pharmacokinetics (zolpidem modified release only) Secondary: Not reported	(P=0.0526). Ease of falling asleep and sleep quality were significantly improved with both doses of zolpidem modified release and with flurazepam (all P<0.05). Neither zolpidem modified release, nor flurazepam, modified perception of well-being on awakening. The frequency of adverse events was similar in all four treatment conditions. None of the adverse events was serious or led to withdrawal from the study. The plasma concentration ratio was 1.96 between the two doses of zolpidem modified release, which is consistent with dose linearity. Secondary: Not reported
Holbrook et al.[92] (2000) Benzodiazepines vs zopiclone, diphenhydramine, glutethimide, promethazine, cognitive behavioral therapy, placebo	MA Patients with insomnia	N=2,672 (45 trials) 1 day to 6 weeks	Primary: SL, total sleep duration, adverse effects, dropout rates, cognitive function decline Secondary: Not reported	Primary: Using sleep records, benzodiazepines demonstrated a decrease in SL by 4.2 minutes compared to placebo (95% CI, -0.7 to 9.2). Benzodiazepines demonstrated a significant increase in sleep duration compared to placebo by 61.8 minutes (95% CI, 37.4 to 86.2). Benzodiazepines were more likely to be associated with complaints of daytime drowsiness (OR, 2.4; 95% CI, 1.8 to 3.4) and dizziness/ lightheadedness (OR, 2.6; 95% CI, 0.7 to 10.3) compared to placebo. No difference was observed in dropout rates between the two groups. Pooled results from three trials indicated there was no significant difference between benzodiazepines and zopiclone in SL, but benzodiazepine therapy may lead to a longer sleep by 23.1 minutes (95% CI, 5.6 to 40.6). There was no significant difference in adverse events among the treatment groups (OR, 1.5; 95% CI, 0.8 to 2.9).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Comparisons between benzodiazepines and antihistamines did not detect any significant differences on sleep outcomes. Triazolam was found to be more effective in reducing SL early in one trial, but efficacy decreased by the second week of treatment. Behavioral therapy efficacy was maintained throughout the nine-week follow-up. Secondary: Not reported
Buscemi et al.[93] (2007) Benzodiazepines, non-benzodiazepines, antidepressants vs placebo	MA Adults with chronic insomnia	105 trials 1 night to 6 months	Primary: SL, WASO, SE, sleep quality, TST, adverse events Secondary: Not reported	Primary: SL assessed by PSG was significantly decreased for benzodiazepines (WMD, -10.0 minutes; 95% CI, -16.6 to -3.4), non-benzodiazepines (WMD, -12.8 minutes; 95% CI, -16.9 to -8.8) and antidepressants (WMD, -7.0 minutes; 95% CI, -10.7 to -3.3). SL assessed by sleep diaries was also significantly improved for benzodiazepines (WMD, -19.6 minutes; 95% CI, -23.9 to -15.3), non-benzodiazepines (WMD, -17.0 minutes; 95% CI, -20.0 to -14.0) and antidepressants (WMD, -12.2 minutes; 95% CI, -22.3 to -2.2). MA for WASO, SE, sleep quality and TST measured by PSG and sleep diary were statistically significant and favored benzodiazepines and non-benzodiazepines vs placebo with the exception of PSG studies measuring WASO and TST, which were marginally nonsignificant. In contrast, PSG results significantly favored antidepressants vs placebo, but sleep diary results were fewer and non-significantly favored antidepressants for WASO and non-significantly favored placebo for TST. Indirect comparisons between benzodiazepines and non-benzodiazepines resulted in no significant difference in SL; however, benzodiazepines were associated with more adverse events. Indirect comparisons between benzodiazepines and antidepressants resulted in no significant difference in SL or adverse events. Indirect comparisons between non-benzodiazepines and antidepressants resulted in a significantly greater SL assessed by PSG but not by sleep

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				diary for non-benzodiazepines. There was no significant difference in adverse events. All drug groups had a statistically significant higher risk of harm compared to placebo, although the most commonly reported adverse events were minor. The adverse events most commonly reported in these studies were headache, drowsiness, dizziness and nausea. Secondary: Not reported
Smith et al.[94] (2002) Benzodiazepines or benzodiazepine receptor agonists vs behavioral treatment vs placebo	MA Patients with primary insomnia for ≥1 month	N=470 (21 trials) 1 to 10 weeks	Primary: SL, TST, NAW, WASO, and sleep quality before and after treatment Secondary: Not reported	Primary: SL was reduced by 30% with pharmacological treatment compared to 43% with behavioral interventions. Pharmacotherapy increased TST by 12% compared to 6% with behavior therapy. Both pharmacotherapy and behavior therapy reduced NAW per night by one. WASO was reduced by 46% with pharmacotherapy and by 56% with behavior therapy. Pharmacotherapy improved sleep quality by 20% compared to 28% with behavior therapy. Overall, there were no differences in TST, NAW, WASO, and sleep quality between benzodiazepine receptor agonists and behavioral therapy. The behavioral therapy group had a greater reduction in LSO than the group that took the benzodiazepine receptor agonists (95% CI, 0.17 to 1.04). Secondary: Not reported
Nowell et al.[95] (1997)	MA Adults <65 years of	N=1,894 (22 trials)	Primary: SL, TST, NAW, sleep quality	Primary: Zolpidem and benzodiazepines were significantly more effective than placebo with regards to SL, TST, NAW and sleep quality (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Benzodiazepines or benzodiazepine receptor agonists vs placebo	age with chronic insomnia	4 to 35 days	Secondary: Not reported	Secondary: Not reported
Post Operative Nausea and Vomiting				
Schauen et al.[96] (2012) Droperidol vs placebo (or no treatment)	MA RCTs testing prophylactic droperidol in adults undergoing general anaesthesia and reporting on post operative nausea and vomiting	N=25 trails Duration varied	Primary: Prevention of nausea and vomiting; adverse events Secondary: Not reported	Primary: For the prevention of early nausea (within six hours postoperatively), the RR was 0.45 (95% CI, 0.35 to 0.58) and the number needed to treat was 7, 4, and 2 for low, medium and high baseline risk. For the prevention of early vomiting the RR was 0.65 (95% CI, 0.57 to 0.74), and the number needed to treat was 11, 6, and 4 respectively. For the prevention of late nausea (within 24 hours) the RR was 0.74 (95% CI, 0.62 to 0.87) and the number needed to treat was 15, 8, and 5 respectively. For the prevention of late vomiting the RR was 0.61 (95% CI, 0.47 to 0.80) and the number needed to treat was 10, 5, and 3 respectively. Droperidol decreased the risk of headache but increased the risk of restlessness. There were no differences in the incidences of sedation or dizziness. Two patients receiving droperidol 0.625 mg had extrapyramidal symptoms. Cardiac toxicity data were not reported. Secondary: Not reported
Sedation				
Fraser et al.[97] (2013) Dexmedetomidine or propofol	MA RCTs consisting of critically ill, mechanically ventilated adults	N=1,235 Duration varied	Primary: Duration of intensive care unit length of stay, duration of mechanical	Primary: Compared to a benzodiazepine sedative strategy, a nonbenzodiazepine sedative strategy was associated with a shorter intensive care unit length of stay (difference, 1.62 days; 95% CI, 0.68 to 2.55; P=0.0007) and duration of mechanical ventilation (difference, 1.9 days; 95% CI, 1.70 to 2.09; P<0.00001) but a similar prevalence of delirium (risk ratio, 0.83; 95% CI,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs benzodiazepine	requiring sedation regimen		ventilation, delirium prevalence, and/or short-term mortality Secondary: Not reported	0.61 to 1.11; P=0.19) and short-term mortality rate (risk ratio, 0.98; 95% CI, 0.76 to 1.27; P=0.88). Secondary: Not reported

Drug regimen abbreviations: ER=extended release, SL=sublingual
Study abbreviations: AC=active control, CI=confidence interval, DB=double-blind, DD=double dummy, ITT=intent to treat, LS=least square, LSM=least squares mean, MA=meta-analysis, MC=multicenter, NS=not significant, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RR=relative risk, SB=single-blind, SD=single dose, XO=crossover, WMD=weighted mean difference
Miscellaneous abbreviations: AHI=apnea hypopnea index, BAI=Beck Anxiety Inventory, CAPS=Clinician Administered PTSD Scale, CES-D=Center for Epidemiologic Studies Depression Scale, CFF=Critical Flicker Fusion, CGI=Clinical Global Impression, CGI-I=Clinical Global Impression-Improvement, CGI-S=Clinical Global Impressions-Severity, CPAP=Continuous positive airway pressure, CRT=Choice Reaction Time, CTT=Continuous Tracking Test, DLRF=Daily Living and Role Functioning, DSST=Digit-Symbol Substitution Test, ECG=electrocardiogram, ESS=Epworth Sleepiness Scale, FARD=Ferreri Anxiety Rating Diagram, FOSQ=Functional Outcomes of Sleepiness Questionnaire, FSS=Fatigue Severity Scale, HAD=Hospital Anxiety and Depression, HAMA=Hamilton Rating Scale for Anxiety, HAM-D=Hamilton Rating Scale for Depression, $HDRS_{17}$=Hamilton Depression Rating Scale 17-item, ISI=Insomnia Severity Index, LPS=latency to persistent sleep, LSAS=Liebowitz Social Anxiety Scale, LSEQ=Leeds Sleep Evaluation Questionnaire, LSO=latency to sleep onset, MADRS=Montgomery-Åsberg Depression Rating Scale, MAOI=monoamine oxidase inhibitors, MCBI=Multidimensional Caregiver Burden Inventory, MENQOL=Menopause-Related Quality of Life, MGH-CFPQ=Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire, MOTN=middle-of-the-night awakening, NAW=number of awakenings, PDQ-8=Parkinson Disease Questionnaire Short Form, PGI=Patient Global Impression, PGI-IT= Patient Global Impression of Insomnia Treatment, PMQ=Patient Morning Questionnaire, PSG=polysomnography, PSQI=Pittsburg Sleep Quality Index, PSQ-IVRS=Post-Sleep Questionnaire Interactive Voice Response System, PTSD=posttraumatic stress disorder, Q-LES-Q=Quality of Life Enjoyment and Satisfaction Questionnaire, REM=rapid eye movement, RIMA=reversible inhibitors of monoamine oxidase-A, SDS=Sheehan Disability Scale, SE=sleep efficiency, SF-36=Short Form-36, SII=Sleep Impairment Index, SIS=Sleep Impact Scale, SL=sleep latency, SOL=sleep onset latency, SOT=Sensory Organization Test, SPRINT=Short PTSD Rating Interview, SQTT=Step Quick Turn Test, SSRI=selective serotonin-reuptake inhibitor, sTST=subject reported total sleep time, sWASO=subjective wake time after sleep onset, TST=total sleep time, WASO=wake time after sleep onset, WLQ=Work Life Questionnaire, WTDS=wake time during sleep

Additional Evidence

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

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

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

IX. Cost

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

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

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

Rx=prescription

Table 11. Relative Cost of the Miscellaneous Anxiolytics, Sedatives, and Hypnotics

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

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

X. Conclusions

The miscellaneous anxiolytics, sedatives, and hypnotics are used primarily for the treatment of anxiety disorders and insomnia. In addition, some agents are approved for the treatment of acute alcohol withdrawal, management

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

The agents that are approved for the treatment of anxiety disorders include buspirone, hydroxyzine and meprobamate.[1-3] The American Psychiatric Association recommends the initial use of either a serotonin-norepinephrine reuptake inhibitor (SNRI) or a selective serotonin reuptake inhibitor (SSRI) for the treatment of panic disorder due to their favorable safety and tolerability profiles.[19] Buspirone and sedating antihistamines are not effective as monotherapy for the treatment of panic disorder.[18-19] For the long-term treatment of generalized anxiety disorder, the National Institute for Health and Clinical Excellence recommends the use of an SSRI as first-line therapy.[18] Sedating antihistamines are one of several options for the short-term, immediate treatment of generalized anxiety disorder.[18] Buspirone is not recommended for the initial treatment of obsessive-compulsive disorder or posttraumatic stress disorder.[21-22] The available guidelines do not provide any recommendations regarding the use of meprobamate for the treatment of anxiety disorders.[18-25]

Chloral hydrate, eszopiclone, ramelteon, zaleplon and zolpidem are approved for the treatment of insomnia.[1-15] The American Academy of Sleep Medicine recommends the use of a short/intermediate-acting benzodiazepine, benzodiazepine receptor agonist, or ramelteon for the initial treatment of insomnia.[26] They do not give preference to one agent over another. Chloral hydrate is not recommended for the treatment of insomnia.[26] Symptom pattern, treatment goals, past treatment responses, patient preference, comorbid conditions, contraindications, drug interactions and adverse events should be considered when selecting a specific agent.[26] The frequency and severity of adverse events may be lower with benzodiazepine receptor agonists (e.g., eszopiclone, zaleplon and zolpidem) and ramelteon than benzodiazepines due to their shorter half-lives.[26-27] Hypnotic treatments should be combined with behavioral and cognitive therapies.[26] Patients should be followed every few weeks during the initial treatment period to assess for effectiveness, adverse events and the need for ongoing medication. Chronic use of hypnotic medications may be necessary in those individuals with severe/refractory insomnia or for those with chronic comorbid illnesses.[26] Results from clinical trials demonstrate that these agents are effective for the treatment of insomnia. Relatively few studies were found in the medical literature directly comparing the efficacy and safety of these agents.

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

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

XI. Recommendations

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

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Genitourinary Smooth Muscle Relaxants
AHFS Class 861200
May 14, 2014

I. Overview

Urinary incontinence is the involuntary leakage of urine, which may be classified as urge, stress, overflow or mixed incontinence.[1] Urge incontinence is accompanied by a sense of urgency, while stress incontinence generally occurs with effort, exertion, sneezing or coughing. Overflow incontinence is associated with dribbling and/or continuous leakage due to incomplete bladder emptying. Overactive bladder is a functional disorder characterized by urinary urgency, daytime frequency (>8 voids during the daytime), nocturia (>1 void at night), with or without incontinence.[2,3] Urinary incontinence and overactive bladder may be due to lower urinary tract dysfunction or secondary to non-genitourinary disorders. The most common cause of overactive bladder is overactivity of the bladder's detrusor muscle. Symptoms may be assessed by patient history, the use of validated questionnaires, and/or bladder diaries. Clinical testing (e.g., bladder stress test, postvoid residual volume testing, urine flow rate and urodynamic testing) may help identify the pathology, but are not always necessary for diagnosis or initiation of therapy.[1,2] Urinary incontinence and overactive bladder cause both physical and psychological morbidity, as well as adversely impact quality of life.[1] Initial treatment options include lifestyle modifications (weight loss and dietary changes), behavioral therapy (bladder training, physical therapy and toileting assistance) and pharmacologic therapy.[2,4] Neurogenic lower urinary tract disorder is caused by a lesion at any level of the nervous system.[5,6] The lesion interferes with the normal nerve pathways associated with urination. Early diagnosis and treatment of neurogenic lower urinary tract disorder is essential for both congenital and acquired disorders as irreversible changes may occur.[6]

Normal voiding is dependent on acetylcholine-induced stimulation of muscarinic receptors on bladder smooth muscle. There are five muscarinic receptor subtypes, of which M1, M2 and M3 mediate bladder contractility. Muscarinic receptors are also found in the gastrointestinal tract, salivary glands and tear ducts. Antimuscarinic drugs increase bladder capacity, decrease urgency and are useful for the treatment of urge incontinence.[4,7-20] Darifenacin, fesoterodine, solifenacin, tolterodine and trospium are muscarinic receptor antagonists. Flavoxate is an antispasmodic which exerts its effects directly on muscle and counteracts the smooth muscle spasm of the urinary tract. Oxybutynin has a direct antispasmodic effect on smooth muscle and inhibits the muscarinic action of acetylcholine on smooth muscle. Some antimuscarinic agents claim to have greater affinity for specific receptor subtypes that mediate bladder contractility, but the clinical significance of this is unclear. The most common adverse effects associated with the use of antimuscarinic agents include dry mouth, blurred vision, abdominal discomfort, drowsiness, nausea and dizziness. These agents may also cause confusion or cognitive impairment in the elderly.[4]

Mirabegron is the first beta-3 adrenergic receptor agonist to be approved for the treatment of overactive bladder. Mirabegron relaxes the detrusor smooth muscle during the storage phase of the urinary bladder fill-void cycle which increases bladder capacity. Because it acts via the beta-3 adrenergic receptor rather than through muscarinic cholinergic receptors, mirabegron may have a better tolerability profile compared to other urinary antispasmodics.[21]

The genitourinary smooth muscle relaxants that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Flavoxate, oxybutynin, tolterodine and trospium are available in a generic formulation. This class was last reviewed in August 2012.

Table 1. Genitourinary Smooth Muscle Relaxants Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Darifenacin	extended-release tablet	Enablex®	none
Fesoterodine	extended-release tablet	Toviaz®	none
Flavoxate	tablet	N/A	flavoxate
Mirabegron	extended-release tablet	Myrbetriq®	none
Oxybutynin	extended-release tablet, syrup,	Ditropan XL®*, Gelnique®,	oxybutynin, Oxytrol®

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
	tablet, transdermal gel, transdermal patch	Oxytrol®	
Solifenacin	tablet	VESIcare®	none
Tolterodine	extended-release capsule, tablet	Detrol®*, Detrol LA®	tolterodine
Trospium	extended-release capsule, tablet	Sanctura®*, Sanctura XR®*	trospium

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

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the genitourinary smooth muscle relaxants are summarized in Table 2.

Table 2. Treatment Guidelines Using the Genitourinary Smooth Muscle Relaxants

Clinical Guideline	Recommendation(s)

National Institute for Health and Clinical Excellence: **Urinary Incontinence: The Management of Urinary Incontinence in Women (2013)**[22]	Behavioral therapy
	• Bladder training should be offered as first-line treatment to women with urge or mixed urinary incontinence.
	• If women do not achieve satisfactory benefit from bladder training, the combination of an antimuscarinic agent and bladder training should be considered if frequency is a troublesome symptom.
	• In women with urinary incontinence who also have cognitive impairment, prompted and timed voiding toileting programs are recommended as strategies for reducing leakage episodes.
	• Do not offer transcutaneous sacral nerve stimulation, transcutaneous posterior tibial nerve stimulation, or percutaneous posterior tibial nerve stimulation to women with urinary incontinence.
	
	Pharmacologic therapy
	• Prescribe the lowest recommended dose when starting a new overactive bladder drug treatment and if treatment is effective do not change the drug or dose.
	• Immediate-release oxybutynin, immediate-release tolterodine or once-daily darifenacin should be offered to women with overactive bladder or mixed urinary incontinence as first-line drug treatment if bladder training has been ineffective.
	  o Do not offer oxybutynin (immediate release) to frail older women.
	• If initial therapy is not well tolerated, another alternative should be considered.
	  o Transdermal oxybutynin may be considered for patients who cannot tolerate oral medication.
	• Flavoxate, propantheline and imipramine should not be used for the treatment of urinary incontinence or overactive bladder in women.
	• The use of desmopressin may be considered to reduce nocturia in women with urinary incontinence or overactive bladder who find it a troublesome symptom.
	• Duloxetine is not recommended as a first-line treatment for women with predominant stress urinary incontinence. Duloxetine should not routinely be used as a second-line treatment for women with stress urinary incontinence, although it may be offered as second-line therapy if women prefer pharmacological to surgical treatment or are not suitable for surgical treatment.
	• Systemic hormone replacement therapy is not recommended for the treatment of urinary incontinence.
	• Intravaginal estrogens are recommended for the treatment of overactive bladder symptoms in postmenopausal women with vaginal atrophy.

Clinical Guideline	Recommendation(s)
	Complementary therapy Complementary therapies are not recommended for the treatment of urinary incontinence or overactive bladder.
European Association of Urology: **Guidelines on Urinary Incontinence (2013)**[23]	Lifestyle intervention • Weight loss (>5% in women), fluid restriction, reduction of caffeine or alcohol intake, limiting heavy activity, and smoking cessation may improve urinary incontinence. Behavioral therapy • Examples of behavioral therapy include pelvic floor muscle training, bladder training, electrical or magnetic stimulation, and posterior tibial nerve stimulation. • Pelvic floor muscle training is better than no treatment for reducing incontinence episodes and improving quality of life in women with stress or mixed incontinence. There is no evidence that pelvic floor muscle training is better than no treatment in providing a cure. Additionally, there is no consistent evidence to show superiority of drug therapy over behavioral therapy. • Pelvic floor muscle training, lasting at least three months, should be offered as a first-line therapy to women with stress or mixed urinary incontinence. In patients with mixed incontinence, pelvic floor muscle training is less satisfactory than for stress incontinence alone. Biofeedback should be considered as an adjunct in women with stress incontinence. • Pelvic floor exercises should be taught to men undergoing radical prostatectomy to speed recovery or urinary incontinence. • Bladder training is a first-line therapy to adults with urgency or mixed urinary incontinence. Antimuscarinic drugs • Antimuscarinic drugs are the mainstay of treatment for urgency urinary incontinence. They act by blocking muscarinic receptors in the bladder wall, which reduces detrusor contractility and alters sensation. There is no consistent evidence that one antimuscarinic drug is more efficacious to an alternative antimuscarinic drug for cure or improvement of urgency urinary incontinence. Dry mouth is the most common adverse effect, but others include constipation, blurred vision, fatigue, and cognitive dysfunction. • It is recommended to offer immediate-release or extended-release formulations of antimuscarinic drugs as initial drug therapy for adults with urgency urinary incontinence. If immediate-release formulations of antimuscarinic drugs are unsuccessful for adults with urgency urinary incontinence, offer extended-release formulations or longer-acting antimuscarinic agents. • Consider using transdermal oxybutynin if oral antimuscarinic agents cannot be tolerated due to dry mouth. • Offer mirabegron extended release to people with urge urinary incontinence depending on local licensing arrangements. • Due to the high rate of medication nonadherence, offer and encourage early review (of efficacy and side effects) of patients on antimuscarinic medication for urgency urinary incontinence (<30 days). If oral antimuscarinic agents cannot be tolerated due to dry mouth, consider using transdermal oxybutynin. • When prescribing antimuscarinic drugs to elderly patients, be aware of the risk of cognitive side effects, especially in those receiving cholinesterase inhibitors. Solifenacin, darifenacin, and tolterodine should be used with caution in patients at risk of cognitive dysfunction, whereas oxybutynin immediate-release should be avoided. Consider use of trospium chloride in patients known to have cognitive dysfunction. An objective assessment of mental

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	function should be assessed before and during treatment in patients whose cognitive function may be at risk.
	
	Duloxetine
	• Duloxetine inhibits the presynaptic reuptake of the neurotransmitters serotonin and norepinephrine leading to an increase in levels of these neurotransmitters. This increase ultimately increases the resting tone and contraction strength of the urethral striated sphincter.
	• Duloxetine has not been shown to cure incontinence and should not be offered to women or men who are seeking a cure for their incontinence.
	• Duloxetine, 80 mg daily, can modestly improve symptoms of stress incontinences and urgency incontinence in women and men. But, it causes significant gastrointestinal and central nervous system side effects leading to a high rate of treatment discontinuation. Due to these adverse effects, duloxetine should be initiated using dose titration.
	
	Intravaginal estrogen
	• Women using systemic estrogen should be counseled that they have an increased risk for developing urinary incontinence or worsening their existing incontinence.
	• Post-menopausal women with urinary incontinence should be offered local estrogen therapy, despite the ideal duration and best delivery method being unknown.
	
	Desmopressin
	• Desmopressin is a synthetic analogue of vasopressin that is most commonly used to treat diabetes insipidus and, when used at night, to treat nocturnal enuresis.
	• The risk of urinary incontinence is reduced within four hours of taking oral desmopressin, but not after four hours. Desmopressin should be offered to patients requiring occasional short-term relief from urinary incontinence. It should not be used for long-term control of urinary incontinence and it is not licensed for this indication.
	
	Botulinum toxin
	• Botulinum toxin A injections into the bladder wall are being increasingly used to treat persistent or refractory urgency urinary incontinence in adult women, as well as in men despite the lack of high-quality data in males.
	• A single treatment session with botulinum toxin is more effective than placebo at curing and improving urgency urinary incontinence for up to 12 months. There is no evidence that repeated injections have reduced efficacy.
	• It is recommended to offer botulinum toxin A intravesical injections to patients with urgency urinary incontinence refractory to antimuscarinic therapy.
	• There is no evidence that repeated injections have reduced efficacy, but there is a high risk of increased post-voiding residual volume, which is dose dependent and may require intermittent self-catheterization. Those who require intermittent self-catheterization have a high risk of a urinary tract infection.
	
	Incontinence in men
	• For men with stress, urgency or mixed urgency/stress incontinence, initial treatment should include:
	  o Lifestyle and behavioral interventions.
	  o Pelvic floor muscle training±biofeedback.
	  o Scheduled voiding (bladder training).
	  o Antimuscarinics (mixed or urgency incontinence).

Clinical Guideline	Recommendation(s)
	Incontinence in women • For women with stress, urgency or mixed urgency/stress incontinence, initial treatment should include: o Lifestyle and behavioral interventions. o Supervised, intensive pelvic floor muscle training±biofeedback±bladder training (stress or mixed incontinence). o Bladder training (mixed or urgency incontinence). o Antimuscarinics (mixed or urgency incontinence).
American Urological Association: **Diagnosis and Treatment of Overactive Bladder (Non-Neurogenic) in Adults: American Urological Association/ Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction Guideline (2012)**[24]	Diagnosis • Overactive bladder is a symptom complex that is not generally life threatening. • The clinician should engage in a diagnostic process to document symptoms and signs that characterize overactive bladder and exclude other disorders that could be the cause of the patient's symptoms. • After assessment has been performed to exclude conditions requiring treatment and counseling, no treatment is an acceptable choice. First line treatment • Behavioral therapies (e.g. bladder training, bladder control strategies, pelvic floor muscle training, fluid management) should be offered as first line therapy. • Behavioral therapies can also be combined with antimuscarinic therapies. Second line treatment • Clinicians should offer oral antimuscarinics as second line therapy. Agents include: o Darifenacin. o Fesoterodine. o Oxybutynin. o Solifenacin. o Tolterodine. o Trospium. • No agent in the group is indicated as a preferred. • If extended-release and immediate-release formulations are available the extended-release should be preferred over the immediate-release given formulation due to lower adverse events. Transdermal oxybutynin is also an option. • If a patient experiences inadequate symptom control and/or unacceptable adverse drug events with one agent then a dose modification or a different antimuscarinic medication may be tried. • Anti-muscarinics should be avoided in patients with narrow-angle glaucoma unless approved by the treating ophthalmologist and should also be used with extreme caution in patients with impaired gastric emptying or a history of urinary retention. Third line treatment • Clinicians may offer sacral neuromodulation as third line treatment in a carefully selected patient population characterized by server refractory overactive bladder symptoms or patients who are not candidates for second-line therapy and are willing to undergo a surgical procedure. • Clinicians can also offer peripheral tibial nerve stimulation as third-line treatment. • Clinicians may also offer intradetrusor onabotulinumtoxinA as a third-line option in the carefully selected patients who has been refractory to first and second line overactive bladder treatments.

Clinical Guideline	Recommendation(s)
National Institute for Health and Clinical Excellence: **Management of Lower Urinary Tract Dysfunction in Neurological Disease (2012)**[25]	Behavioral treatment • For patients with neurogenic lower urinary tract dysfunction, behavioral management programs should be considered (e.g., timed voiding, bladder retraining or habit retraining). • When choosing a behavioral management program, take into account that prompted voiding and habit retraining are particularly suitable for people with cognitive impairment. Antimuscarinics • Antimuscarinic drugs should be offered to patients with spinal cord disease (e.g., spinal cord injury or multiple sclerosis) who have symptoms of overactive bladder such as increased frequency, urgency and incontinence. • In patients with conditions affecting the brain (e.g., cerebral palsy, head injury or stroke) with symptoms of an overactive bladder, antimuscarinic drugs should be considered. • Antimuscarinic drug treatment should be considered in patients with urodynamic investigations showing impaired bladder storage. • Residual urine volume should be monitored in patients not using intermittent or indwelling catheterization after beginning treatment. • Antimuscarinic treatment can reduce bladder emptying, which may increase the risk of urinary tract infections and may precipitate or exacerbate constipation. Botulinum toxin A • Bladder wall injection with botulinum toxin A should be offered to adult patients with spinal cord diseases (e.g., spinal cord injury or multiple sclerosis) and symptoms of overactive bladder and an inadequate response to or poorly tolerated antimuscarinic drugs. • Bladder wall injection with botulinum toxin A may be considered for children and young people with spinal cord disease and symptoms of overactive bladder for who antimuscarinic drugs were ineffective or poorly tolerated. • Bladder wall injection with botulinum toxin A may be considered in adults with spinal cord disease with urodynamic investigations showing impaired bladder storage for whom antimuscarinic drugs were ineffective or poorly tolerated. • Consider bladder wall injection with botulinum toxin A for children and young people with spinal cord disease with urodynamic investigations showing impaired bladder storage and for whom antimuscarinic drugs were ineffective or poorly tolerated. • A catheterization regimen is needed in most people with neurogenic lower urinary tract dysfunction after botulinum toxin A treatment. The patient must be able and willing to manage such a regimen should urinary retention develop after the treatment. • Monitor residual urine volume in patients who are not using a catheterization regimen during treatment with botulinum toxin A. • Monitor upper urinary tract in patients at risk of renal complications (e.g., those with high intravesical pressures on filling cystometry) during treatment. • People should be offered repeated botulinum toxin A injections and have prompt access to repeat injections when symptoms return.

International Scientific Committee: **Evaluation and Treatment of Urinary Incontinence, Pelvic Organ Prolapse, and**	Initial management of urinary incontinence in men
	• For men with stress, urgency or mixed urgency/stress incontinence, initial treatment should include:
	  o Lifestyle interventions.
	  o Supervised pelvic floor muscle training for men with post-radical prostatectomy stress urinary incontinence.

Clinical Guideline	Recommendation(s)
Fecal Incontinence (2010)[26]	o Scheduled voiding regimes for overactive bladder. o Antimuscarinic drugs for overactive bladder symptoms with or without urgency incontinence and the patient has no evidence of significant post-void residual urine. o Alpha adrenergic antagonists (α-blockers) can be added if it is thought that there may also be bladder outlet obstruction. <u>Initial management of urinary incontinence in women</u> • For women with stress, urgency or mixed urgency/stress incontinence, initial treatment should include: o Advice on caffeine reduction and weight reduction. o Supervised pelvic floor muscle training and vaginal cones for women with stress incontinence. o Supervised bladder training for overactive bladder. o If estrogen deficiency and/or urinary tract infection is found, the patient should be treated at initial assessment and then reassessed after a suitable interval. o Antimuscarinics for overactive bladder symptoms with or without urgency incontinence. o Duloxetine may be considered for stress urinary incontinence. <u>Initial management of neurogenic urinary incontinence</u> • Conservative treatment modalities (often in combination): o Intermittent catheterization. o Behavioral treatment. o Timed voiding. o External appliances. o Antimuscarinics. o Alpha-blockers. o Intravesical ES. o Bladder expression. o Triggered voiding. o Indwelling catheter. <u>Management of urinary incontinence in frail older persons</u> • Initial treatment should be individualized and influenced by goals of care, treatment preferences, and estimated remaining life expectancy, as well as the most likely clinical diagnosis. • In some frail elders the only possible outcome may be contained urinary incontinence (managed with pads), especially for persons with minimal mobility (require assistance of >2 persons to transfer), advanced dementia (unable to state their name), and/or nocturnal urinary incontinence. • Conservative and behavioral therapy for urinary incontinence include lifestyle changes, bladder training for more fit alert patients, and prompted voiding for frailer, more impaired patients. • For select cognitively intact patients, pelvic muscle exercises may be considered. Antimuscarinics may be added to conservative therapy of urgency urinary incontinence. • Alpha-blockers may be cautiously considered in frail men with suspected prostatic outlet obstruction. • DDAVP (vasopressin) has a high risk of severe hyponatremia in frail persons and should not be used.
Neurogenic Bladder Society: **Clinical Guidelines for Overactive Bladder**	<u>Behavioral therapy</u> • Behavioral therapy can include lifestyle guidance, bladder training, physical therapy and toileting assistance.

Clinical Guideline	Recommendation(s)
(2009)[2]	• Behavioral therapy is minimally invasive with no adverse reactions and combination therapy with other forms of treatment is also possible. • Behavioral therapy should be considered as the first-line choice for initial treatment of overactive bladder. • The efficacy of combined behavioral therapy and drug therapy over monotherapy has yet to be determined, but it is the recommended treatment approach. <u>Drug therapy</u> • Drug therapy forms the basis of treatment for overactive bladder. • The drugs for which efficacy and safety have been investigated are the antimuscarinic agents. These are most commonly used for the treatment of overactive bladder. • When using antimuscarinic drugs, it is necessary to consider adverse reactions due to blockade of the systemic muscarine receptors <u>Antimuscarinic drugs</u> • Oxybutynin has a direct relaxing effect and paralyzing effect on smooth muscle in addition to its antimuscarinic activity. It has been extensively evaluated and its efficacy has been well demonstrated. The incidence of adverse reactions associated with its antimuscarinic activity is higher than that of other antimuscarinic drugs. It is recommended that treatment is started from a low dose and titrated gradually to determine the optimal dose. Oxybutynin can pass through the blood-brain barrier potentially causing central nervous system adverse events (cognitive impairment, etc.). Caution is required in elderly patients. • Tolterodine has no selectivity for muscarinic receptor subtypes, is well distributed to and has a high binding affinity for the bladder, and as compared to the salivary glands, is highly selective for the bladder. It has been extensively evaluated and there is substantial evidence for efficacy and safety in overactive bladder patients, including the elderly and patients with severe overactive bladder. • Solifenacin is highly selective for the muscarinic receptor M3, and is more highly selective for the bladder than for the salivary glands. It has been shown to be effective for urgency, frequency, and urge urinary incontinence in overactive bladder. • Flavoxate has no antimuscarinic activity, but appears to have a moderate calcium antagonistic action, inhibitory effect on phosphodiesterase, and a local relaxant effect on smooth muscle. Flavoxate has been observed to have almost no adverse reactions, but its efficacy has not been adequately evaluated. • Darifenacin is high selectivity for the M3 receptor subtype, and it has shown a higher selectivity for the bladder than the salivary glands in animal studies. Concern has been raised about adverse reactions involving the salivary glands and gastrointestinal tract, in which M3 receptors are numerous. <u>Antidepressants</u> • Several types of tricyclic antidepressants are indicated for enuresis or nocturnal enuresis, with imipramine being the most commonly used drug. Imipramine appears to be useful for nocturnal enuresis in children, but its usefulness as a therapeutic agent for overactive bladder is yet to be adequately evaluated. <u>Botulinum Toxin</u> • Botulinum toxin is believed to inhibit bladder contraction by blocking the release of acetylcholine from cholinergic nerves, primarily by causing chemical denervation.

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	• Injection of botulinum toxin into the bladder wall is believed to be a promising therapeutic method for overactive bladder, but its usefulness is yet to be adequately explored.
	
	<u>Efficacy of drug therapy for overactive bladder symptoms in benign prostatic hyperplasia patients</u>
	• α_1-blockers are first-line drug therapy for overactive bladder symptoms in benign prostatic hyperplasia patients, but their long-term efficacy in patients without lower urinary tract obstruction has yet to be proven.
	• Randomized controlled studies to demonstrate the efficacy and safety of antimuscarinic drugs for overactive bladder symptoms associated with benign prostatic hyperplasia have yet to be performed.
	• Despite the fact that antimuscarinic drugs may be effective in some benign prostatic hyperplasia patients with overactive bladder symptoms, there is ample risk of causing acute urinary retention or chronic urinary retention.
	• The therapeutic positioning of antimuscarinic drugs for men with lower urinary tract symptoms is uncertain, and they are contraindicated in patients with severe lower urinary tract obstruction or urinary retention.
	• It remains uncertain whether combination therapy with an α_1-blocker and an antimuscarinic drug is superior to α_1-blocker monotherapy in benign prostatic hyperplasia patients with overactive bladder symptoms.
	
	<u>Practical guidelines for drug therapy for overactive bladder: Rules for treatment with anticholinergic drugs, classified by sex and age</u>
	• Overactive bladder in women:
	  o Antimuscarinic drugs can be administered immediately.
	  o If voiding symptoms, as well as overactive bladder symptoms, are present, antimuscarinic drugs should be administered with caution.
	  o Since overactive bladder and impaired detrusor contractility may both be present in elderly women (80 years or older) in particular, patients should be referred to a urological specialist if voiding symptoms are severe or if residual urine is copious (50 mL or more).
	• Overactive bladder in men under 50 years of age:
	  o For overactive bladder in relatively young men, it is recommended that patients be evaluated by a urological specialist at least once, as there may be an underlying comorbid neurological disease or urological disease.
	• Overactive bladder in men aged 50 years or older:
	  o Because there is a high probability of overactive bladder as a complication of benign prostatic hyperplasia, give top priority to starting an α_1-blocker if voiding symptoms are confirmed.
	  o If there is no improvement in overactive bladder symptoms, an antimuscarinic drug can be coadministered. However, since there is not adequate evidence regarding this combination, the patient should also be referred to a urological specialist.

American College of Obstetricians and Gynecologists: **Urinary Incontinence in Women**[27] **(2005)**	• Behavioral therapy (e.g., bladder training and prompted voiding) improves symptoms of urge and mixed incontinence and can be recommended as a noninvasive treatment in many women. • Pelvic floor training appears to be an effective treatment for adult women with stress and mixed incontinence and can be recommended as a noninvasive treatment for many women. • Pharmacologic agents may have a small beneficial effect on improving symptoms of detrusor overactivity in women. • The antimuscarinic drugs, oxybutynin and tolterodine, have been shown to have a small beneficial effect as therapy for urge incontinence. However, for

Clinical Guideline	Recommendation(s)
	many of the outcomes studied, the observed differences between treatment with antimuscarinic medications and placebo may be of questionable clinical significance. No significant difference among these agents was reported. • The most typical side effect of antimuscarinic therapy is dry mouth. Other side effects most frequently reported include blurred vision, constipation, nausea, dizziness, and headache. • Alternative drugs, new drugs, and new formulations of existing drugs are all available, but limited data exist on which to base recommendations. • Oral estrogen regimens cannot be recommended as treatment or prevention for any type of urinary incontinence.
Scottish Intercollegiate Guidelines Network: **Management of Urinary Incontinence in Primary Care: A National Clinical Guideline (2004)**[28]	Behavioral therapy • Pelvic floor muscle exercises should be the first choice of treatment offered to patients suffering from stress or mixed incontinence. • Pelvic floor muscle exercises should be considered as part of a treatment plan for patients with urge urinary incontinence. • Pelvic floor muscle exercise treatment should be considered for patients following radical prostate surgery. • Bladder retraining should be offered to patients with urge urinary incontinence. Pharmacologic therapy of stress incontinence • Published studies have reported conflicting evidence for the efficacy of estrogens in treating stress incontinence. • Imipramine has been used clinically to treat stress incontinence, but there are no studies available to support its use. • Duloxetine should be used only as part of an overall management strategy in addition to pelvic floor muscle exercises. A four-week trial of is recommended for female patients with moderate-to-severe stress incontinence. Patients should be reviewed again after 12 weeks of therapy to assess progress and determine whether it is appropriate to continue treatment. Pharmacologic therapy of detrusor overactivity and urge incontinence • Oxybutynin, tolterodine, trospium and propiverine are effective in reducing detrusor overactivity (urgency and urge incontinence). Comparative studies of the effectiveness of detrusor selective antimuscarinics have shown all the drugs to be equally effective. • The most common side effects of antimuscarinic drugs are dry mouth, blurred vision, abdominal discomfort, drowsiness, nausea and dizziness. • Oxybutynin immediate-release preparation has the highest incidence of side effects. • Several studies have shown sustained-release antimuscarinic preparations are associated with a lower incidence and severity of side effects than immediate-release preparations. • A trial of oxybutynin, propiverine, tolterodine, or trospium should be given to patients with significant urgency with or without urge incontinence. • Antimuscarinic therapy should be tried for a period of six weeks to enable an assessment of the benefits and side effects. Treatment should be reviewed after 6 months to assess continued need. • Studies of the efficacy of flavoxate have shown mixed results; few adverse events were reported. • There is inadequate evidence to support the use of imipramine for the treatment of detrusor overactivity. • There is no evidence to date for combining therapy in a patient with mixed urge and stress incontinence.
European Association of Urology/European	Early management with clean intermittent catheterization • Management of neurogenic bladder in infants has demonstrated that children

Clinical Guideline	Recommendation(s)
Society for Pediatric Urology: **Guidelines on Pediatric Urology: Management of Neurogenic Bladder in Children (2012)**[5]	do not have upper tract deterioration when managed early with clean intermittent catheterization and antimuscarinic medication. • Clean intermittent catheterization should be started soon after birth in all babies, especially in those with signs of possible outlet obstruction. Early intermittent catheterization results in fewer upper tract changes, but also better bladder protection and lower incontinence rates. Medical therapy • Oxybutynin, tolterodine, trospium and propiverine are the most frequently used drugs for the treatment of neurogenic bladder. Most of the studies have been conducted with oxybutynin. • Two different forms of tolterodine have been investigated in children with neurogenic bladder. The extended-release formulation has been found to be as effective as the immediate-release formulation, while being less expensive and only being administered once daily. Despite encouraging clinical outcomes, the level of evidence remains low for antimuscarinic medications due to a lack of controlled studies. • The use of medication to facilitate emptying in children with neurogenic bladder has not been well studied. • The use of α-adrenergic blockade in children with neurogenic bladder has resulted in a good response rate, but the studies lacked controls and long-term followup is warranted. Botulinum toxin injections • Injection of botulinum toxin into the detrusor is an alternative treatment option for neurogenic bladders, which are refractory to Antimuscarinics. The use of botulinum toxin in adults prompted its use in children and even though it has been shown to have beneficial effects on clinical and urodynamic variables, the findings are limited by the lack of prospective controlled trials in children. • Injection of botulinum toxin in therapy-resistant bladders appears to be an effective and safe treatment alternative. Botulinum toxin seems to be more effective in patients who have bladders with obvious detrusor muscle over activity. Stiff bladders without an active component are unlikely to respond to botulinum toxin. No evidence regarding the optimal dose exists and it is unclear how many times this treatment can be repeated in children. • Although the evidence is too low to recommend its routine use in decreasing outlet resistance, injection of botulinum toxin in the urethral sphincter has been shown to be effective in decreasing urethral resistance and improving voiding.

European Association of Urology:
Guidelines on Neurogenic Lower Urinary Tract Dysfunction (2012)[6]
	Treatment goals
	• The primary goals for the treatment of neurogenic lower urinary tract dysfunction are:
	  o Protection of the upper urinary tract.
	  o Improvement of urinary continence.
	  o Improvement of the patient's quality of life.
	  o Restoration of (parts of) the normal lower urinary tract function.
	• Other considerations include the patient's disability, cost-effectiveness, technical complexity, and possible complications.
	
	Assisted bladder emptying
	• Incomplete bladder emptying is a risk factor for urinary tract infections, for developing high intravesical pressure during the filling phase, and for incontinence.
	• Methods to improve the voiding process should be practiced in patients with neurogenic lower urinary tract dysfunction and include the following: third party bladder expression (Credé), voiding by abdominal straining (Valsalva),

Clinical Guideline	Recommendation(s)
	triggered reflex voiding, behavioral modification techniques (bladder training, lifestyle modifications), pelvic floor muscle training, and biofeedback <u>Lower urinary tract rehabilitation</u> • Bladder rehabilitation aims to re-establish bladder function in patients with neurogenic lower urinary tract dysfunction. While improving voluntary control of lower urinary tract dysfunction has been described in non-neurogenic patients, evidence for bladder rehabilitation using electrical stimulation in neurogenic patients is lacking and is based on pilot studies with small patient numbers. • Peripheral temporary electrostimulation suppresses neurogenic detrusor over activity during acute stimulation and it has demonstrated sustained prolonged effects in patients with neurogenic bladder due to multiple sclerosis. In multiple sclerosis patients, a combined approach of pelvic floor muscle training+neuromuscular electrostimulation+biofeedback was more efficacious to electrostimulation alone in achieving a substantial reduction in lower urinary tract dysfunction. • Biofeedback can be used for supporting the voiding pattern modification. • Intravesical electrostimulation may increase bladder capacity; improve bladder compliance as well as the sensation of bladder filling in patients with incomplete spinal cord injuries or meningomyelocele. • Chronic peripheral pudendal stimulation. <u>Drug treatment</u> • An optimal medical treatment for neurogenic lower urinary tract dysfunction is not available and currently, a combination of treatment modalities is the best therapeutic approach. Most drugs only resolve part of the problem, or are adjunct to other measures. • Detrusor over activity can be treated with antimuscarinic agents and they are the first-line choice for treating neurogenic lower urinary tract dysfunction. Antimuscarinic therapy is both safe and effective for the management of neurogenic detrusor over activity. Treatment is generally life-long; however, increased drug tolerance and adverse events are problematic in patients with neurogenic lower urinary tract dysfunction. These patients need a higher dose then other patients with overactive detrusor, which may lead to discontinuation of the therapy because of adverse events. Alternative ways of administration of antimuscarinic agents, such as transdermally and intravesically, should be considered with the goal of reducing adverse effects. • Oxybutynin, tolterodine tartrate, trospium chloride, and propiverine are established, effective, well-tolerated, and safe treatment choices. These agents have different tolerability profiles and an alternative antimuscarinic agent may be prescribed if the patient experiences adverse effects with one. • Darifenacin was recently evaluated in neurogenic overactive bladder secondary to multiple sclerosis and had results similar to other antimuscarinic drugs. • Outcomes for neurogenic detrusor over activity can be maximized by considering a combination of antimuscarinic agents. • In pilot studies, phosphodiesterase inhibitors have shown promising effects on detrusor over activity. • Additional treatment with desmopressin might improve the efficacy of therapy. • In patients with detrusor underactivity, cholinergic drugs (bethanechol chloride and distigmine bromide) may enhance detrusor contractility and promote bladder emptying, but are not used in clinical practice due to a lack of clinical evidence. • Alpha-blockers have been used successfully on occasion for decreasing bladder outlet resistance. These agents may be a preventive measure in spinal

Clinical Guideline	Recommendation(s)
	cord injury to prevent autonomic dysreflexia. • Several drugs have been shown to be effective for the treatment of mild stress incontinence, but there are few studies in patients with neurogenic lower urinary tract dysfunction. <u>External appliances</u> • Social continence may be achieved by collecting the urine when incontinence cannot be resolved by any other methods. • Condom catheters with urine collection devices are a practical method for men. Incontinence pads may also offer a reliable solution. • With both incontinence pads and condom catheters, the patient must be closely observed for a urinary tract infection. <u>Minimal invasive treatment</u> • Intermittent catheterization is the standard treatment of neurogenic lower urinary tract dysfunction and it is effective in patients with: detrusor underactivity or acontractility, detrusor over activity (provided the over activity can be controlled. • Botulinum toxin injection in the detrusor is the most effective minimally invasive treatment to reduce neurogenic detrusor over activity. Therapy causes a long-lasting chemical denervation that lasts approximately nine months. • Antimuscarinics can be administered intravesically to reduce detrusor over activity. This route of administration may decrease adverse effects and a greater amount is sequestered in the bladder.

III. Indications

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

Table 3. FDA-Approved Indications for the Genitourinary Smooth Muscle Relaxants[7-21]

Indication	Darifenacin	Fesoterodine	Flavoxate	Mirabegron	Oxybutynin	Solifenacin	Tolterodine	Trospium
Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency	✔	✔		✔	✔ *†	✔	✔	✔
For symptomatic relief of dysuria, urgency, nocturia, suprapubic pain, frequency and incontinence as may occur in cystitis, prostatitis, urethritis, urethrocystitis and urethrotrigonitis			✔					
Relief of symptoms of bladder instability associated with voiding in patients with uninhibited neurogenic or reflex neurogenic bladder (i.e., urgency, frequency, urinary leakage, urge incontinence, dysuria)					✔ ‡			
Treatment of pediatric patients aged six years and older with symptoms of detrusor overactivity associated with a neurological condition (e.g., spina bifida)					✔ †			

*Transdermal formulations.
† Extended-release oral formulation.
‡Immediate-release oral formulation.

IV. Pharmacokinetics

The pharmacokinetic parameters of the genitourinary smooth muscle relaxants are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Genitourinary Smooth Muscle Relaxants[7-21]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Darifenacin	15 to19	98	Liver; Intestinal wall	Renal (60) Feces (40)	13 to 19
Fesoterodine	52	50	Liver	Renal (70) Feces (7)	4 to 7
Flavoxate	Not reported	Not reported	Not reported	Renal (57)	Not reported
Mirabegron	29 to 35	71	Liver	Renal (55) Feces (34)	50
Oxybutynin	IR: 6 ER: 156 to 187	>99	Liver; Intestinal wall	Renal (<0.1)	Gel: 64.0 ER: 13.2 IR: 2.0 to 3.0 Patch: 6.0 to 7.0
Solifenacin	90	98	Liver	Renal (69.0) Feces (22.5)	45 to 68
Tolterodine	IR: 77	96	Liver	Renal (77) Feces (17)	IR: 2.2 ER: 6.9
Trospium	IR: 9.6	IR: 50 to 85 ER:48 to 78	Liver	Renal (5.8) Feces (85.2)	IR: 18.3 ER: 36.0

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

V. Drug Interactions

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

Table 5. Significant Drug Interactions with the Genitourinary Smooth Muscle Relaxants[7]

Generic Name(s)	Significance Level	Interaction	Mechanism
Genitourinary smooth muscle relaxants (mirabegron)	1	Thioridazine	Coadministration may have additive effects on the prolongation of the QT interval.
Genitourinary smooth muscle relaxants (darifenacin, fesoterodine, flavoxate, oxybutynin, solifenacin, tolterodine, trospium)	2	Potassium preparations	Antimuscarinic agents may slow gastrointestinal motility and cause delay in tablet passage through the gastrointestinal tract.
Genitourinary smooth muscle relaxants (darifenacin, fesoterodine, solifenacin, tolterodine)	2	Imidazoles	Inhibition of cytochrome P450 3A4 by imidazoles may decrease the metabolic elimination of genitourinary smooth muscle relaxants. Plasma concentrations and pharmacologic effects of genitourinary smooth muscle relaxants may be increased.
Genitourinary smooth muscle relaxants (darifenacin, fesoterodine, solifenacin, tolterodine)	2	Macrolides	Inhibition of cytochrome P450 3A4 by macrolides may decrease the metabolic elimination of genitourinary smooth muscle relaxants. Plasma concentrations and pharmacologic effects of genitourinary smooth muscle relaxants may be increased.

Generic Name(s)	Significance Level	Interaction	Mechanism
Genitourinary smooth muscle relaxants (darifenacin, fesoterodine, solifenacin, tolterodine)	2	Protease inhibitors	Inhibition of cytochrome P450 3A4 by protease inhibitors may decrease the metabolic elimination of genitourinary smooth muscle relaxants. Plasma concentrations and pharmacologic effects of genitourinary smooth muscle relaxants may be increased.
Genitourinary smooth muscle relaxants (darifenacin, fesoterodine, solifenacin, tolterodine)	2	Nefazodone	Inhibition of cytochrome P450 3A4 by nefazodone may decrease the metabolic elimination of genitourinary smooth muscle relaxants. Plasma concentrations and pharmacologic effects of genitourinary smooth muscle relaxants may be increased.
Genitourinary smooth muscle relaxants (oxybutynin, trospium)	2	Phenothiazines	The antipsychotic effectiveness of phenothiazines may be decreased by genitourinary smooth muscle relaxants, which may cause additive antimuscarinic toxicity. This may be due to additive central and peripheral antimuscarinic effects, as well as decreased phenothiazine bioavailability.

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

VI. Adverse Drug Events

The most common adverse drug events reported with the genitourinary smooth muscle relaxants are listed in Table 6.

Table 6. Adverse Drug Events (%) Reported with the Genitourinary Smooth Muscle Relaxants[7-21]

Adverse Events	Darifenacin	Fesoterodine	Flavoxate	Mirabegron	Oxybutynin (Oral)	Oxybutynin (Transdermal)	Solifenacin	Tolterodine	Trospium
Cardiovascular									
Arrhythmia	-	-	-	-	1 to 5		-	-	<1
Atrial fibrillation	✔	-	-	-	-	-	-	-	-
Chest pain	-	✔	-	-	1 to 5	✔ §	-	2	✔
Hypertension	≥1	-	-	7.5 to 11.3	1 to 5	-	≤1	-	✔
Hypotension	-	-	-	-	1 to 5	-	-	-	-
Myocarditis	-	-	-	-	-	✔ §	-	-	-
Palpitations	✔	✔	✔	-	1 to 5	-	-	✔	✔
Peripheral edema	≥1	1	-	-	1 to 5	-	-	✔	-
QT_c prolongation	-	✔	-	-	1 to 5	-	✔	-	-
Supraventricular tachycardia	-	-	-	-	-	-	-	-	✔
Syncope	-	-	-	-	-	-	-	-	✔
T-wave inversion	-	-	-	-	-	-	-	-	✔
Tachycardia	✔	✔	✔	-	1 to 5	✔ §	-	✔	1 to 2
Torsade de pointes	-	-	-	-	-	-	✔	-	-
Central Nervous System									
Agitation	-	-	-	-	1 to 5	-	-	-	-
Anxiety	-	-	-	-	-	-	-	1†	-
Confusion	✔	-	✔	-	-	-	✔	✔	-
Delirium	✔	-	-	-	-	-	-	-	✔
Depression	-	-	-	-	1 to 5	-	≤1	-	-
Disorientation	-	-	-	-	-	-	-	✔	-
Dizziness	1 to 2	-	-	-	4 to17	2 to 3‡	≤1	2†, 5γ	-
Drowsiness	-	-	✔	-	-	-	-	-	-
Dysphonia	✔	-	-	-	✔	-	-	-	-
Fatigue	-	-	✔	-	1 to 5	2‡	1 to 2	2†, 4γ	2
Hallucinations	✔	-	-	-	1 to 5	✔ §	✔	✔	✔
Headache	7	-	✔	-	6 to 10	2‡	3 to 6	7†, 6γ	4 to 7
Heat prostration	-	✔	-	-	-	-	-	-	-
Hyperpyrexia	-	-	✔	-	-	-	-	-	-

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

Adverse Events	Darifenacin	Fesoterodine	Flavoxate	Mirabegron	Oxybutynin (Oral)	Oxybutynin (Transdermal)	Solifenacin	Tolterodine	Trospium
Gastritis	-	-	-	-	-	-	-	-	✔
Gastroenteritis	-	<1	-	-	-	2‡	-	-	-
Gastrointestinal obstruction	-	-	-	-	-	-	✔	-	-
Gastroesophageal reflux disease	✔	-	-	-	1 to 5	-	-	-	-
Gastrointestinal motility decreased	-	-	-	-	1 to 5	-	-	-	-
Hoarseness	-	-	-	-	1 to 5	-	-	-	-
Irritable bowel syndrome	-	<1	-	-	-	-	-	-	-
Loose stools	-	-	-	-	1 to 5	-	-	-	-
Nausea	2 to 4	1 to 2	✔	-	2 to 12	-	2 to 3	-	≤1
Taste abnormality	-	-	-	-	1 to 5	-	-	-	✔
Thirst	-	-	-	-	1 to 5	-	-	-	-
Tongue coated	-	-	-	-	1 to 5	-	-	-	-
Vomiting	≥1	-	✔	-	1 to 5	-	≤1	-	✔
Weight gain	≥1	-	-	-	-	-	-	1	-
Xerostomia	19 to 35	19 to 35	✔	-	29 to 71	7 to 8‡, 4 to 10§	11 to 28	23†, 35γ	10 to 22
Genitourinary									
Cystitis	-	-	-	-	1 to 5	-	-	-	-
Dysuria	-	1 to 2	✔	-	1 to 5	2§	-	1†, 2γ	-
Impotence	-	-	-	-	1 to 5	✔ §	-	-	-
Pollakiuria	-	-	-	-	1 to 5	-	-	-	-
Urinary retention	✔	1 to 2	-	-	6	-	≤1	-	≤1
Urinary tract infection	4 to 5	2 to 4	-	5.9	5 to 7	7‡	3 to 5	-	1 to 7
Vaginitis	≥1	-	-	-	-	-	-	-	-
Hepatic									
Alanine transaminase increased	✔	≤1	-	-	-	-	-	-	-
Gamma-glutamyl transferase increased	-	≤1	-	-	-	-	-	-	-
Musculoskeletal									
Arthralgia	≥1	-	-	-	1 to 5	-	-	2	-
Back pain	≥1	1 to 2	-	-	1 to 5	-	-	-	✔
Rhabdomyolysis	-	-	-	-	-	-	-	-	✔
Weakness	<3	-	-	-	3 to 7	-	-	-	-

Adverse Events	Darifenacin	Fesoterodine	Flavoxate	Mirabegron	Oxybutynin (Oral)	Oxybutynin (Transdermal)	Solifenacin	Tolterodine	Trospium
Respiratory									
Asthma	-	-	-	-	1 to 5	-	-	-	-
Bronchitis	≥1	-	-	-	1 to 5	-	-	-	-
Cough	-	1 to 2	-	-	1 to 5	-	≤1	-	-
Dry throat	-	1 to 2	✔	-	1 to 5	-	-	-	-
Nasal congestion	-	-	-	-	1 to 5	-	-	-	-
Nasal dryness	-	-	-	-	1 to 5	-	-	-	1
Nasopharyngitis	-	-	-	-	1 to 5	3‡	-	-	3
Pharyngitis	≥1	-	-	-	-	-	-	-	-
Rhinitis	≥1	-	-	-	2 to 6	-	-	-	-
Sinus congestion	-	-	-	-	1 to 5	-	-	-	-
Sinus headache	-	-	-	-	1 to 5	-	-	-	-
Sinusitis	≥1	-	-	-	1 to 5	-	-	2†	-
Upper respiratory tract infection	-	2 to 3	-	-	1 to 5	-	-	-	-
Special Senses									
Abnormal vision	≥1	-	-	-	-	-	-	1†, 2γ	-
Blurred vision	-	✔	✔	-	1 to 10	-	4 to 5	-	1
Cycloplegia	-	-	-	-	1 to 5	✔ §	-	-	-
Dry eyes	1.5 to 2.0	1 to 4	-	-	3 to 6	-	≤2	3	1 to 2
Eye irritation	-	-	-	-	1 to 5	-	-	-	-
Intraocular pressure increased	✔	-	✔	-	-	-	-	-	-
Keratoconjunctivitis sicca	-	-	-	-	1 to 5	-	-	-	-
Mydriasis	-	-	-	-	1 to 5	-	-	-	-
Vision changes	-	-	✔	-	-	3§	-	-	-
Other									
Anaphylactoid reactions	-	-	-	-	-	-	-	✔	-
Anaphylaxis	-	-	-	-	-	-	✔	-	✔
Angioedema	✔	-	-	-	✔	-	-	✔	-
Angioneurotic edema	-	-	-	-	✔	-	✔	-	✔
Edema	-	-	-	-	1 to 5	-	≤1	-	-
Extremity pain	-	-	-	-	1 to 5	-	-	-	-
Flank pain	-	-	-	-	1 to 5	-	-	-	-
Flu-like syndrome	1 to 3	-	-	-	-	-	-	3	-

Adverse Events	Darifenacin	Fesoterodine	Flavoxate	Mirabegron	Oxybutynin (Oral)	Oxybutynin (Transdermal)	Solifenacin	Tolterodine	Trospium
Fungal infection	-	-	-	-	1 to 5	-	-	-	-
Hyperglycemia	-	-	-	-	1 to 5	-	-	-	-
Hyperkalemia	✔	-	-	-	-	-	-	-	-
Hypersensitivity	✔	-	-	-	-	-	✔	✔	-
Infection	-	-	-	-	-	-	-	1	-
Influenza	-	-	-	-	-	-	≤2	-	2
Lactation suppression	-	-	-	-	1 to 5	✔ §	-	-	-
Leukopenia	-	-	✔	-	-	-	-	-	-
Pain	≥1	-	-	-	1 to 7	-	-	-	-
Pharyngolaryngeal pain	-	-	-	-	1 to 5	-	-	-	-
Renal impairment	✔	-	-	-	-	-	-	-	-

✔ Percent not specified.
- Event not reported or incidence <1%.
†Extended-release formulation.
‡Transdermal gel formulation.
§Transdermal patch formulation.
γ Immediate-release formulation.

VII. Dosing and Administration

The usual dosing regimens for the genitourinary smooth muscle relaxants are listed in Table 7.

Table 7. Usual Dosing Regimens for the Genitourinary Smooth Muscle Relaxants[7-21]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Darifenacin	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency: Tablet (ER): 7.5 to 15 mg once daily	Safety and efficacy in children have not been established.	Tablet (ER): 7.5 mg 15 mg
Fesoterodine	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency: Tablet (ER): 4 to 8 mg once daily	Safety and efficacy in children have not been established.	Tablet (ER): 4 mg 8 mg
Flavoxate	For symptomatic relief of dysuria, urgency, nocturia, suprapubic pain, frequency and incontinence as may occur in cystitis, prostatitis, urethritis, urethrocystitis and urethrotrigonitis: Tablet: 100 to 200 mg three or four times/day	For symptomatic relief of dysuria, urgency, nocturia, suprapubic pain, frequency and incontinence as may occur in cystitis, prostatitis, urethritis, urethrocystitis and urethrotrigonitis in patients ≥12 years of age: Tablet: 100 to 200 mg three or four times/day	Tablet: 100 mg
Mirabegron	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency: Tablet (ER): 25 to 50 mg once daily	Safety and efficacy in children have not been established.	Tablet (ER): 25 mg 50 mg
Oxybutynin	Relief of symptoms of bladder instability associated with voiding in patients with uninhibited neurogenic or reflex neurogenic bladder (i.e., urgency, frequency, urinary leakage, urge incontinence, dysuria): Tablet/syrup (IR): 5 mg two to three times/day; maximum, 5 mg four times/day Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency: Tablet (ER): 5 to 10 mg once daily; maximum, 30 mg/day Transdermal gel in 3% pump container: three pumps should be applied daily Transdermal gel in 10% packets: the contents of one sachet should be applied once daily Transdermal patch: one 3.9 mg/day system applied twice weekly (every	Relief of symptoms of bladder instability associated with voiding in patients with uninhibited neurogenic or reflex neurogenic bladder (i.e., urgency, frequency, urinary leakage, urge incontinence, dysuria) in patients ≥5 years of age: Tablet/syrup (IR): 5 mg twice daily; maximum, 5 mg three times daily Treatment of pediatric patients aged six years and older with symptoms of detrusor overactivity associated with a neurological condition (e.g., spina bifida): Tablet (ER): 5 mg once daily; maximum, 20 mg/day	Syrup: 5 mg/5 mL Tablet (ER): 5 mg 10 mg 15 mg Tablet (IR): 5 mg Transdermal gel: 3% 10% Transdermal patch: 3.9 mg/24 hours

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	three to four days)		
Solifenacin	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency: Tablet: 5 to 10 mg once daily	Safety and efficacy in children have not been established.	Tablet: 5 mg 10 mg
Tolterodine	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency: Capsule (ER): 4 mg once daily Tablet (IR): 2 mg twice daily	Safety and efficacy in children have not been established.	Capsule (ER): 2 mg 4 mg Tablet (IR): 1 mg 2 mg
Trospium	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency: Capsule (ER): 60 mg once daily Tablet (IR): 20 mg twice daily	Safety and efficacy in children have not been established.	Capsule (ER): 60 mg Tablet (IR): 20 mg

ER=extended-release, IR=immediate-release

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the genitourinary smooth muscle relaxants are summarized in Table 8.

Table 8. Comparative Clinical Trials with the Genitourinary Smooth Muscle Relaxants

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Buser et al.[29] (2008) Available antimuscarinic drugs at the time of the analysis, excluding drugs with less direct antimuscarinic effects (e.g. flavoxate)	MA Trials evaluating safety and efficacy in patients being treated for OAB	Efficacy comparison: N=38,662 (76 trials) Safety comparison: N=39,919 (90 trials)	Primary: Perception of cure or improvement, urgency episodes per 24 hours, leakage episodes per 24 hours, urgency incontinence episodes per 24 hours, micturitions per 24 hours, and nocturia episodes per 24 hours and safety outcomes Secondary: Not reported	Primary: 40 mg/day trospium chloride, 100 mg/g per day oxybutynin topical gel and 4 mg/day fesoterodine had the best efficacy, while higher dosages of orally administered oxybutynin and propiverine had the least favorable relationship of efficacy and adverse events. Secondary: Not reported
Chapple et al.[30] (2005) Darifenacin ER 7.5 to 15 mg once daily vs placebo	DB, PG, MC, RCT (Pooled analysis) Men and women ≥18 years of age with symptoms of OAB for ≥6 months, 5 to 50 episodes of incontinence/week, and a high voiding frequency (a mean of ≥8 voids/24 hours) and urgency	N=1,059 (3 trials) 12 weeks	Primary: Median change in the number of incontinence episodes/week Secondary: Number of significant leaks/week, voiding frequency, bladder capacity, frequency and severity of	Primary: The median change in weekly incontinence episodes from baseline was -8.8 (-68.4%) for darifenacin 7.5 mg and -10.6 (-76.8%) for darifenacin 15 mg compared to placebo (-53.8 and -58.3%; P=0.004 and P<0.001 vs placebo, respectively). Secondary: There was a decrease in the number of significant leaks (P<0.001), voiding frequency (P<0.001), number/severity of urgency episodes (P<0.001), and an increase in bladder capacity (P<0.001) with both doses of darifenacin compared to placebo. There was no difference in the number of nocturnal awakenings/week caused by OAB between the darifenacin and placebo groups (P=0.13 and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	(a mean of ≥1 episode/24 hours)		urgency, number of nocturnal awakenings caused by OAB, responder rates, proportion of patients experiencing three or more dry days/week, or at least seven consecutive dry days, in the last two weeks of study treatment, adverse events	P=0.06 for darifenacin 7.5 and 15 mg, respectively). The proportion of patients who achieved a ≥70% reduction from baseline in the number of incontinent episodes/week was 48% for 7.5 mg and 57% for 15 mg darifenacin, compared to 33 and 39% of patients in the placebo group (P<0.001). The proportion of patients who achieved a ≥90% reduction from baseline was 27 and 28% of patients in each of these groups, respectively, compared to 17% of patients in the placebo group (P<0.005). The OR for improvement compared to placebo were consistent for both doses across all responder rates analyzed (OR, 1.8 to 1.9 for 7.5 mg and 1.8 to 2.2 for 15 mg darifenacin; P<0.005). Responder rates for the reduction in urgency episodes also showed significant differences from placebo (P<0.05) for both doses of darifenacin at all levels of response (≥30%, ≥50%, ≥70%, ≥90%). The proportion of patients who attained a normal voiding frequency (<8 voids/day) after 12 weeks of treatment was significantly greater with both doses of darifenacin (7.5 mg, 34%; P=0.029 vs placebo; and 15 mg, 35%; P=0.007 vs placebo) than in the corresponding placebo groups (27 and 28%, respectively). Twenty-four percent of patients treated with darifenacin 15 mg were 'dry' for at least seven days, compared to 16% in the corresponding placebo group (P=0.011). More patients (55 and 61%) had ≥3 dry days/week in the darifenacin 7.5 and 15 mg groups, respectively, than in those taking placebo (43 and 48%, respectively; both P<0.001). The overall incidence of any cause was 54% with darifenacin 7.5 mg and 65.6% with 15 mg darifenacin compared to 48.7% with placebo. The most common all-cause adverse events were dry mouth and constipation, most of which were mild to moderate. The incidence of nervous system adverse events reported by patients taking 7.5 or 15 mg of darifenacin was comparable to placebo. The most common nervous system adverse events were central nervous system-related: dizziness (darifenacin 7.5 mg, 0.9%; 15 mg, 2.1%; vs placebo 1.3%) and somnolence (0.3 and 0.9% vs 0.8%, respectively). The incidence of all-cause cardiovascular adverse events

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				with darifenacin 7.5 mg (6.2%) or 15 mg (3.6%) was also comparable with that of placebo (2.3%).
Foote et al.[31] (2005) Darifenacin ER 7.5 to 15 mg once daily vs placebo	DB, MC, RCT (Pooled analysis) Men and women ≥65 years of age with symptoms of OAB for ≥6 months, 5 to 50 episodes of incontinence/week, and a high voiding frequency (a mean of ≥8 voids/24 hours) and urgency (a mean of ≥1 episode/24 hours)	N=317 (3 trials) 12 weeks	Primary: Median change in the number of incontinence episodes/week Secondary: Number of micturitions/24 hours, bladder capacity, number of urgency episodes per 24 hours, and adverse events	Primary: At week 12, the median reduction in the number of incontinence episodes/week was significantly greater for darifenacin 7.5 mg (-11.2; -66.7%) and darifenacin 15 mg (-10.8; 75.9%) compared to placebo (-4.8; -34.8 and -6.8; 44.8%, respectively; P<0.001). Secondary: There was a significant decrease in the frequency of micturition/24 hours (P<0.001) and urgency episodes (P<0.001), and increased bladder capacity (P<0.001) with both doses of darifenacin compared to placebo. Adverse events were reported by 53.6, 69.1 and 50.9% of patients treated with 7.5 mg darifenacin, 15 mg darifenacin or placebo. The most common treatment-related adverse events, dry mouth, constipation and dyspepsia. The incidence of nervous system and cardiovascular adverse events during darifenacin therapy was similar to that with placebo, and did not increase with increasing dose of darifenacin.
Haab et al.[32] (2006) Darifenacin ER 7.5 to 15 mg once daily	ES, MC, OL Men and women ≥65 years of age who had completed one of two RCTs (feeder studies) who had previously had symptoms of OAB for ≥6 months, 5 to 50 episodes of incontinence/week, and a high voiding frequency (a mean of ≥8 voids/24 hours) and urgency (a mean of ≥1 episode/24 hours)	N=716 2 years	Primary: Safety, tolerability and efficacy Secondary: Not reported	Primary: All-causality adverse events were reported by 80% of patients at some time during the two-year extension and resulted in discontinuation in 8.9% of patients. The most commonly reported adverse events were dry mouth and constipation (23.3 and 20.9%, respectively). There were no relevant changes in any bowel-habit variables from feeder-study end to ES end in the overall group. There were few treatment-related cardiovascular and nervous system adverse events; 0.4, 0.3 and 0.3% of patients reported hypertension, arrhythmias and tachycardia, respectively, while 0.4% of patients each reported hypertonia, somnolence and paresthesia. Abnormal vision was reported in 0.6% of patients. No patient developed treatment-related glaucoma or reported worsening of a pre-existing glaucomatous condition.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				After 24 months of treatment with darifenacin, the median change from baseline of the feeder studies in incontinence episodes/week was -11.0 (84.4%), voids/24 hours was -1.4 (-13.9%), urgency episodes/24 hours was -3.9 (-56.4%), severity of urgency was -15.4 (-28.8%), nocturnal awakenings for OAB/week was -1.5 (-14.3%), and significant leaks/week was -4.7 (-100%). All variables were P<0.001 vs feeder study baseline. Overall, 62.3% of patients achieved a ≥70% reduction in incontinence episodes and 43.8% achieved a ≥90% reduction at two years. Secondary: Not reported
Hill et al.[33] (2007) Darifenacin ER 7.5 to 15 mg once daily	ES, MC, OL Men and women ≥18 years of age who had completed one of two RCTs (feeder studies) who had previously had symptoms of OAB for ≥6 months, 5 to 50 episodes of incontinence/week, and a high voiding frequency (a mean of ≥8 voids/24 hours) and urgency (a mean of ≥1 episode/24 hours)	N=214 2 years	Primary: Safety, tolerability and efficacy Secondary: Not reported	Primary: Dry mouth and constipation were the most common treatment-related (adverse events) adverse events in this older patient population (23.4 and 22.4%, respectively) and were associated with low discontinuation rates (2.3 and 4.2%, respectively). Treatment-related cardiovascular and peripheral/central nervous system adverse events were infrequently reported (1.4 and 3.3%, respectively). After 24 months of treatment with darifenacin, the median change from baseline of the feeder studies in incontinence episodes/week was -11.0 (83.7%), voids/24 hours was -1.2 (-12.4%), urgency episodes/24 hours was -3.7 (-52.0%), severity of urgency was -12.6 (-23.3%), nocturnal awakenings for OAB/week was -1.4 (-10.9%), and significant leaks/week was -4.9 (-100%). All variables were P<0.001 vs feeder study baseline. There were high proportions of responders by all definitions (≥50, ≥70 or ≥90% reductions in incontinence episodes/week), with 74.1%, 60.0% and 44.4%, patients age ≥65 years of age achieving these response levels at 24 months, respectively. Thirty-four percent of older patients experienced normalization of micturition (<8 micturitions/day) after three months of darifenacin treatment and this effect was maintained in approximately the same number of patients at the end of the two-year study (33.8%). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
But et al.[34] (2012) Darifenacin 7.5 mg once daily vs solifenacin 5 mg once daily	MC, OL, RCT Female patients with idiopathic OAB, defined as urgency intensity and urgency urinary incontinence of ≥3 on the UPS and frequency of ≥1 urgency episodes per day who have not received any anticholinergic drugs for at least 6 months	N=100 3 months	Primary: OAB symptoms Secondary: Changes in dose throughout the study, QOL scores, objective assessment of treatment improvement and safety evaluations.	Primary: Analyses of OAB symptoms at baseline were generally similar between the two treatment groups, although urgency (bothersome) scores were higher in the darifenacin group, and frequency scores were higher in the solifenacin group. Following one and three months of treatment, all measured OAB symptoms decreased, with no statistically significant treatment differences being seen between the groups. Nocturia decreased to a greater extent in the solifenacin group at one month and this group also used less incontinence pads than those in the darifenacin group at three months. Secondary: The majority of patients in the solifenacin group who completed the study maintained the same dose post-study (21/25 patients). However, in the darifenacin group only 11 patients who completed then maintained the same dose (11/24 patients). Patients treated with solifenacin indicated a greater improvement in QOL compared to patients treated with darifenacin. Overall patient subjective and objective assessment of treatment improvement was higher for solifenacin compared to darifenacin, with the difference again being statistically significant in favor of solifenacin (P=0.01). Adverse events of dry mouth, constipation, blurred vision, headache, dizziness, concentration problems, memory problems, and insomnia were solicited at the one month and three month assessments, as well as at baseline. Solifenacin showed statistically a decreased incidence of dry mouth after three months of treatment compared to the darifenacin group.
Zinner et al.[35] (2005) Darifenacin ER 15 to 30 mg once daily	DB, PC, RCT, XO Patients 18 to 85 years of age with urge incontinence with ≥4 significant	N=76 2 weeks	Primary: Incontinence episodes/week, urgency episodes/day, severity of urgency	Primary: The mean number of incontinence episodes/week decreased from 20.4 to 10.93 with solifenacin 15 mg (P<0.05 vs placebo), 8.82 with solifenacin 30 mg (P<0.05 vs placebo), 9.45 with oxybutynin (P<0.05 vs placebo), and 14.64 with placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs oxybutynin IR 5 mg three times daily vs placebo	incontinent episodes/week (defined as leakage that would normally require a change of clothing or absorbent pad) and urinary frequency ≥8 voids/24 hours		episodes, and micturitions/day Secondary: Not reported	The mean number of urgency episodes/day decreased from 9.3 to 7.95 with solifenacin 15 mg (P<0.05 vs placebo), 7.59 with solifenacin 30 mg (P<0.05 vs placebo), 8.12 with oxybutynin (P<0.05 vs placebo), and 8.71 with placebo. The mean severity of urgency episodes decreased from 2.00 to 1.93 with solifenacin 15 mg (P<0.05 vs placebo), 1.84 with solifenacin 30 mg (P<0.05 vs placebo), 1.89 with oxybutynin (P<0.05 vs placebo), and 2.03 with placebo. The number of micturitions/day decreased from 10.4 to 9.93 with solifenacin 15 mg (P=NS vs placebo), 8.85 with solifenacin 30 mg (P<0.05 vs placebo), 9.24 with oxybutynin (P=NS vs placebo), and 9.62 with placebo. Dry mouth occurred in a similar percentage of patients receiving darifenacin 30 mg and oxybutynin, which was significantly higher than treatment with placebo or darifenacin 15 mg (P<0.05). There was no significant difference between darifenacin 15 mg and placebo. Constipation occurred more frequently with darifenacin and oxybutynin than placebo. There was no significant difference between darifenacin 15 mg and oxybutynin. Blurred vision and dizziness occurred in 3.3 and 1.6% of patients receiving oxybutynin, respectively. Secondary: Not reported
Chapple et al.[36] (2005) <u>Cohort 1</u> Darifenacin IR 2.5 mg three times daily for 7 days vs oxybutynin 2.5 mg	DB, RCT, XO Patients 18 to 75 years of age with detrusor overactivity within the previous 6 months (either idiopathic or neurogenic with ≥2 associated	N=65 7 days	Primary: Urodynamic parameters, salivary flow, tolerability and safety Secondary: Not reported	Primary: All urodynamic pressure parameters significantly decreased from baseline after seven days' therapy with each treatment. No significant differences between treatments were observed for any dose of darifenacin vs oxybutynin. There were no differences between treatments in responder rates for any of the ambulatory urodynamic parameters. Reduction in salivary flow was significantly less with darifenacin ER (15 and 30 mg) than with oxybutynin (5 mg three times daily). Salivary flow

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
three times daily for 7 days Cohort 2 Darifenacin ER 15 mg once daily for 7 days vs oxybutynin 5 mg three times daily for 7 days Cohort 3 Darifenacin ER 30 mg once daily for 7 days vs oxybutynin 5 mg three times daily for 7 days	symptoms (average of ≥7 micturitions per day, ≥7 episodes of urgency/week, ≥1 urge incontinence episode/week necessitating change of clothing or pads)			was comparable for darifenacin IR (2.5 mg three times daily) and oxybutynin (2.5 mg three times daily). The mean maximum decrease in salivary flow from baseline to day seven was significantly greater with oxybutynin 5 mg three times daily than with darifenacin ER 15 mg (P<0.01). There were no differences in mean heart rate for darifenacin and oxybutynin on day seven. There were no significant differences with darifenacin and oxybutynin for visual nearpoint. The most common adverse events were dry mouth and constipation, which were generally mild or moderate in severity. Dry mouth was reported more frequently in oxybutynin-treated patients than in darifenacin-treated patients. Secondary: Not reported
Wyndaele et al.[37] (2009) Fesoterodine ER 4 to 8 mg once daily	MC, OL Men and women ≥18 years of age with self-reported OAB symptoms for ≥3 months, mean micturition frequency of ≥8 micturitions/24 hours, mean number of urgency episodes ≥3/24 hours, and	N=516 12 weeks	Primary: Number of micturitions, number of UUI episodes, number of micturition-related urgency episodes/24 hours, and the percentage of patients reporting treatment satisfaction at week 12 (‘very	Primary: The change from baseline to week 12 in the number of micturitions was -3.0 (-22%; P<0.0001), -1.7 for the number of UUI episodes (-100%; P<0.0001), and -5.0 for urgency episodes (-57%; P<0.0001). At 12 weeks, 80% of patients who responded to the TSQ reported being satisfied with fesoterodine treatment, with 38.4% of patients being ‘very satisfied’ and 41.4% of patients being ‘somewhat satisfied’. Secondary: The change from baseline to week 12 in the number of nocturnal micturitions was -0.8 (-31%; P<0.0001), -3.5 for severe urgency episodes (-94%; P<0.0001), and -15.2 for frequency-urgency sum/24 hours

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	treated with tolterodine or tolterodine ER for OAB within 2 years who reported being 'somewhat dissatisfied' or 'very dissatisfied' with tolterodine treatment on the TSQ		satisfied' or 'somewhat satisfied' on the TSQ) Secondary: Change from baseline to week 12 in nocturnal micturitions, severe micturition-related urgency episodes, frequency-urgency sum/24 hours, change from baseline in PPBC, UPS and OAB-q scores at week 12	(P<0.0001). Mean PPBC scores improved from 4.9 at baseline to 3.1 at week 12 (P<0.0001). Mean UPS scores improved from 1.8 at baseline to 2.4 at week 12 (P<0.0001). The mean change in OAB-q Symptom Bother score (29-point improvement) from baseline to week 12 was statistically significant (P<0.0001). Mean changes in total HRQOL (26-point improvement) and all four HRQOL domain (Concern, 29-point improvement; Coping, 31-point improvement; Sleep, 25-point improvement; Social Interaction, 17-point improvement) scores were also significant at 12 weeks, compared to baseline (P<0.0001). The improvements for all scales and domains were above the minimally important difference of 10 points, indicating that these changes were clinically meaningful. Dry mouth (23%) and constipation (5%) were the most frequently reported adverse events.
Nitti et al.[38] (2007) Fesoterodine ER 4 to 8 mg once daily vs placebo	DB, MC, PC, RCT Men and women ≥18 years of age with OAB syndrome for ≥6 months, urinary frequency (≥8 micturitions/24 hours) and urinary urgency (≥6 episodes during the 3-day diary period) or UUI	N=836 12 weeks	Primary: Number of micturitions/24 hours, number of UUI episodes/24 hours and treatment response Secondary: Mean volume voided/micturition, daytime micturitions, nocturnal micturitions,	Primary: The mean change from baseline in the number of micturitions/24 hours was significantly improved with fesoterodine 4 mg (-1.61, -14.9%; P<0.001) and fesoterodine 8 mg (-2.09, -16%; P<0.001) compared to placebo (-1.08, -6.9%). The mean change from baseline in the number of UUI episodes/24 hours was significantly improved with fesoterodine 4 mg (-1.65, -67.4%; P<0.001) and fesoterodine 8 mg (-2.28, -81.8%; P<0.001) compared to placebo (-0.96, -40%). Subject-reported treatment response rates with fesoterodine 4 mg (64%) and fesoterodine 8 mg (74%) were significantly higher than those with placebo (45%) at study end point (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			urgency episodes/24 hours and continent days/week	Secondary: Fesoterodine 4 mg showed significant improvements in the mean change from baseline compared to placebo for the number of nocturnal micturitions (P<0.05), urgency episodes (P<0.001) and continent days/week (P<0.001). Fesoterodine 8 mg was significantly better than placebo for MVV/micturition, number of urgency episodes, number of daytime micturitions and continent days/week (each P<0.001). Treatment-emergent adverse events occurred in 55, 61 and 69% of patients receiving placebo, and 4 and 8 mg fesoterodine, respectively. Dry mouth was the most commonly reported adverse event. It was usually mild to moderate in severity and it occurred in 7, 16 and 36% of patients receiving placebo, and 4 and 8 mg fesoterodine, respectively.
Chapple et al.[39] (2007) Fesoterodine ER 4 to 8 mg once daily vs tolterodine ER 4 mg once daily vs placebo	AC, DB, PC, RCT Men and women ≥18 years of age with a medical history of OAB symptoms with urinary urgency for ≥6 months, ≥8 micturitions/24 hours, and either ≥6 urgency episodes or ≥3 UUI/24 hours, and self-reported perception of moderate problems using a Likert scale	N=1,135 12 weeks	Primary: Micturitions/24 hours and treatment response Secondary: Mean volume voided/micturition, daytime micturitions/24 hours, nocturnal micturitions/24 hours, urgency episodes/24 hours, continent days/week, adverse events	Primary: The mean number of micturitions/24 hours was significantly reduced from baseline in patients receiving tolterodine (-1.73, -13.8%; P=0.001 vs placebo), fesoterodine 4 mg (-1.76, -16.7%; P<0.001 vs placebo), and fesoterodine 8 mg (-1.88, -18.6%; P<0.001 vs placebo). Treatment with tolterodine resulted in significantly greater proportion of patients who responded to treatment compared to placebo (P<0.001). The proportion of patients reporting a positive treatment response was significantly greater among patients receiving tolterodine (72%; P<0.001) fesoterodine 4 mg (75%; P<0.001) and fesoterodine 8 mg (79%; P<0.001) compared to placebo (53%). The mean reduction from baseline in UUI episodes/24 hours was significantly greater for patients receiving tolterodine (-1.74, -70%; P=0.008 vs placebo), fesoterodine 4 mg (-1.95, -80%; P=0.001 vs placebo), and fesoterodine 8 mg (-2.22, -87.5%; P<0.001 vs placebo). Secondary: Active treatment significantly increased MVV from baseline (P≤0.002) compared to placebo. The increases in MVV were 2.5, 3.0, and 3.6 times greater than placebo in the patients receiving tolterodine, fesoterodine 4

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				mg, or fesoterodine 8 mg, respectively. The mean number of daytime micturitions/24 hours was significantly reduced from baseline in patients receiving tolterodine (-1.35, -13.6%; P=0.003), fesoterodine 4 mg (-1.37, -14.3%; P=0.001), and fesoterodine 8 mg (-1.48, -16.9%; P<0.001) compared to placebo (-0.60, -9.5%). The mean number of nocturnal micturitions/24 hours did not differ significantly from placebo in patients receiving tolterodine (-0.40, -25%; P=0.815), fesoterodine 4 mg (-0.39, -28.6%; P=0.982), and fesoterodine 8 mg (-0.39, -23.1%; P<0.896). The mean number of urgency episodes/24 hours was significantly reduced from baseline in patients receiving tolterodine (-2.03, -16%; P=0.004), fesoterodine 4 mg (-1.88, -17.6%; P=0.002), and fesoterodine 8 mg (-2.36, -19.1%; P<0.001) compared to placebo (-1.07, -11.1%). Significant improvements in change from baseline compared to placebo in number of continent days/week were observed in patients receiving fesoterodine 4 or 8 mg. The most frequent adverse event was dry mouth, which was mild to moderate in most patients; however, 3% of patients receiving fesoterodine 8 mg reported severe dry mouth.
Chapple et al.[40] (2008) Fesoterodine ER 4 to 8 mg once daily vs tolterodine ER 4 mg once daily vs	AC, DB, PC, RCT (Post-hoc analysis) Men and women ≥18 years of age with a medical history of OAB symptoms with urinary urgency for ≥6 months, ≥8 micturitions/24 hours, and either ≥6 urgency episodes or	N=1,135 12 weeks	Primary: Number of micturitions/24 hours and treatment response Secondary: Mean volume voided/micturition, urgency episodes/24 hours, continent days/week,	Primary: There was no significant difference in the number of micturitions/24 hours or rate of treatment response reported with tolterodine 4 or fesoterodine 8 mg. Fesoterodine 8 mg led to a significant improvement in UUI episodes/24 hours compared to tolterodine 4 mg in 'incontinent patients' (P<0.001). Secondary: Fesoterodine 8 mg led to a significant improvement in MVV/void in 'all patients' and 'incontinent patients' compared to tolterodine (P<0.05). Fesoterodine 8 mg led to a significant improvement in continent

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo Only the results of fesoterodine ER 8 mg vs tolterodine ER 4 mg are reported.	≥3 UUI/24 hours, and self-reported perception of moderate problems using a Likert scale		HRQOL (KHQ and ICIQ-SF), adverse events	days/week (P<0.05) and severe urgency episodes/24 hours (P<0.05) in 'incontinent patients' compared to tolterodine 4 mg. There was no significant difference in the median percent change in number of urgency episodes/24 hours reported in 'all patients' and 'incontinent patients' with fesoterodine 8 mg or tolterodine 4 mg. Scores from the KHQ and ICIQ-SF showed a significant improvement in HRQOL for the groups treated with fesoterodine 8 mg and tolterodine 4 vs placebo. The fesoterodine 8 mg dose produced significant improvements on eight of the nine domains assessed compared to placebo. Tolterodine-treated patients reported significant improvements in six of nine KHQ domains compared to placebo. Both fesoterodine 8 mg and tolterodine 4 mg treatment resulted in a ≥5-point improvement from baseline (which constitutes a meaningful change for the patient) for all domains except General Health. A major improvement in the severity of bladder-related problems from baseline to the end of treatment was reported by 39% of fesoterodine 8 mg and 34% of tolterodine 4 patients (P=0.01 for both groups vs placebo), compared to 25% on placebo. Adverse events reported in ≥2% of patients in the active-treatment groups and occurring more frequently than placebo included dry mouth, constipation, dry eye, dry throat, and elevated levels of alanine aminotransferase. More patients treated with fesoterodine 8 mg had dry mouth than those receiving tolterodine 4 mg or placebo. Most cases of dry mouth were mild or moderate; 3% of patients on fesoterodine 8 mg reported severe dry mouth. More patients on fesoterodine 8 mg reported constipation than those receiving tolterodine 4 or placebo; most cases were mild to moderate. Overall, 3.2% of patients discontinued the study prematurely because of an adverse event: placebo, 2%; tolterodine 4 mg, 3%; fesoterodine 8 mg, 5%.
Ginsberg et al.[41] (2013) Fesoterodine ER 4 mg once daily for 1 week, then 8 mg	DB, DD, RCT Men and women ≥18 years of age with a medical history of OAB	N=4,129 Two 12-week studies	Primary: Change from baseline to week 12 in UUI episodes	Primary: At week 12, women showed significantly greater improvement with fesoterodine than with ER tolterodine (-1.9 vs -1.7; P≤0.007) and placebo (-1.9 vs -1.6; P≤0.001) in UUI episodes. In men, there were no significant differences in improvement in UUI

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
once daily vs tolterodine ER 4 mg once daily vs placebo	symptoms with self-reported symptoms ≥3 months in 3-day baseline diaries and had ≥8 micturitions and ≥1 UUI episode per 24 hours		Secondary: Changes from baseline in three-day bladder diary variables, scores from the PPBC, UPS, and OAB-q, diary-dry rate, proportion of subjects with >0 UUI episodes according to baseline diary and no UUI episodes according to post-baseline diary and safety evaluations	episodes between any treatment groups at week 12 (-1.4 for all groups; P>0.05 for both comparisons). Secondary: At week 12, women showed significantly greater improvement with fesoterodine 8 mg than with ER tolterodine 4 mg and placebo in micturition frequency, urgency episodes, and all other diary endpoints (except nocturnal micturitions vs ER tolterodine), and also in scores on the PPBC, UPS, and all OAB-q scales and domains (all P<0.005). Improvements in men were significantly greater with fesoterodine than with ER tolterodine for severe urgency and the OAB-q Symptom Bother domain and were also significantly greater with fesoterodine than with placebo for micturition frequency, urgency episodes, severe urgency episodes, PPBC responses and scores on all OAB-q scales and domains at week 12 (all P<0.04). The most frequently reported treatment-emergent adverse events in both genders were dry mouth (women: fesoterodine, 29%; ER tolterodine, 15%; placebo, 6%; men: fesoterodine, 21%; ER tolterodine, 13%; placebo, 5%) and constipation (women: fesoterodine, 5%; ER tolterodine, 4%; placebo, 2%; men: fesoterodine, 5%; ER tolterodine, 3%; placebo, 1%).
Van Kerrebroeck et al.[42] (2010) Fesoterodine ER 4 to 8 mg once daily	ES, OL Men and women ≥18 years of age with a medical history of OAB symptoms with urinary urgency for ≥6 months, ≥8 micturitions/24 hours, and either ≥6 urgency episodes or ≥3 UUI/24 hours, and self-reported perception of	N=417 24 to 32 months	Primary: Safety and tolerability Secondary: Bladder diary variables and PROs	Primary: A total of 161 patients (39%) discontinued treatment before or at the 24-month study visit. Primary reasons for discontinuation were adverse events (n=47), withdrawal of consent (n=46), and insufficient clinical response (n=36). A total of 264 patients (63%) received fesoterodine for ≥24 months during the DB and the OL extension phases. Patients received the higher fesoterodine 8 mg dose for an average of 80% of their respective treatment days during OL extension. A total of 315 patients (76%) experienced at least one treatment emergent adverse event, of which 219 cases were related to fesoterodine. The most common treatment emergent adverse event were dry mouth (34%), constipation (7%), and UTI (15%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	moderate problems using a Likert scale			Overall, ≥88% of patients rated treatment tolerance with fesoterodine "good" or "excellent" at months four, 12, and 24. Secondary: Compared to OL baseline, there were significant mean improvements in all diary variables throughout the 24-month extension (all P<0.001). Diary variables included UUI episodes per 24 hours, micturitions per 24 hours, urgency episodes per 24 hours, and MVV per micturition. There were significant improvements in all KHQ domains (P≤0.002), except for general health perception at months 12 and 24. Changes in mean scores typically exceeded the minimally important difference of 5. There were significant mean improvements in ICIQ-SF scores at months four, 12, and 24 (P<0.0001 for all). In the overall population, patient-reported treatment satisfaction was 97% at month 24.
Scarpero et al.[43] (2011) Fesoterodine ER 4 to 8 mg once daily	ES, OL (Pooled analysis) Men and women ≥18 years of age with OAB syndrome for ≥6 months, urinary frequency (≥8 micturitions/24 hours) and urinary urgency (≥6 episodes during the 3-day diary period) or UUI	N=890 (2 trials) 24 to 36 months	Primary: Safety and tolerability Secondary: Bladder diary entries (number of UUI episodes, micturitions, and urgency episodes	Primary: Overall, 55% of men (n=102) and 50% of women (n=349) discontinued treatment within the first 24 months of the OL extension. The most common reasons for discontinuation in men and women were insufficient clinical response (16 and 13%), adverse events (16 and 12%), and withdrawal of consent (14 and 13%). Both men and women were treated with the higher 8 mg dose for the majority of days on OL fesoterodine (89 and 83%). A total of 539 women (77%) and 140 men (76%) experienced ≥1 treatment emergent adverse event. A total of 351 women (50%) and 86 men (47%) experienced ≥1 treatment emergent adverse event that were determined to be related to fesoterodine. The most commonly reported treatment emergent adverse event in men were dry mouth (24%) and constipation (6%), compared to dry mouth (32%) and UTI (18%) in women.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The majority of men and women (≥92 and ≥91%, respectively) reported "good" or "excellent" treatment tolerance at months four, 12, and 24. Secondary: Among women, improvements in all diary variables (mean UUI episodes per 24 hours, micturitions per 24 hours, urgency episodes per 24 hours, and MVV per micturition) were significant at each time point during OL treatment compared to both DB baseline (P<0.0001) and OL baseline (P<0.0001). Among men, improvements in all diary variables were significant at each time point during OL treatment compared to DB baseline (P<0.05). Improvements in micturitions and urgency episodes per 24 hours were significant at months one, four, eight, and 12 compared to OL baseline (P<0.05). At month 24, there were no statistically significant differences from OL baseline for any diary variable.
Kelleher et al.[44] (2008) Fesoterodine ER 4 to 8 mg once daily vs tolterodine ER 4 mg once daily vs placebo	DB, MC, PC, RCT (Pooled analysis) Men and women ≥18 years of age with OAB syndrome for ≥6 months	N=1,971 (2 trials) 12 weeks	Primary: Treatment-related effects on HRQOL using the KHQ (disease-specific questionnaire to assess LUTS), ICIQ-SF (questionnaire to evaluate patients with UI including urinary frequency, urine leakage and perceived impact of these symptoms on patients' daily lives) and a six-point Likert Scale used by patients to rate the severity of problems related to	Primary: The fesoterodine 8 mg group had statistically significant improvements over placebo in eight of nine KHQ domains. Fesoterodine 4 mg and tolterodine showed statistically significant improvements over placebo in seven of nine domains of the KHQ. Fesoterodine 8 mg led to better results than 4 mg in two domains (Emotions and Severity/Coping; P<0.05). There were no significant differences between fesoterodine 8 mg and tolterodine 4 mg. In all treatment groups, all but one KHQ domain (General Health) showed improvements meaningful to the patient (i.e., changes of ≥5 points from baseline). All active-treatment groups reported a significant improvement in the ICIQ-SF score vs placebo (P<0.001). There were no significant differences between active treatment groups. Baseline scores for the six-point Likert scale were 3.6, which indicates moderate to severe problems. At the end of the study, the scores were 2.3 to 2.8, which indicate minor problems. The percentage of patients reporting scores of 1 to 3 was <1% at baseline and increased after 12 weeks. There was also a similar change in scores with placebo. A major improvement in bladder condition (i.e., ≥2-point change) was reported by

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			their bladder condition, and treatment response Secondary: Not reported	33% of patients on fesoterodine 4 mg, 38% on fesoterodine 8 mg, and 34% on tolterodine compared to 21% on placebo (P<0.001). The percentage of patients reporting a positive treatment response was significantly higher in those receiving fesoterodine than those receiving placebo. There were significant differences between the doses in favor of fesoterodine 8 mg at two weeks and 12 weeks. Secondary: Not reported
Herschorn et al.[45] (2010) Fesoterodine ER 4 to 8 mg once daily vs tolterodine ER 4 mg once daily vs placebo	DB, MC, PC, RCT Men and women ≥18 years of age with symptoms of OAB for ≥3 months	N=1,697 12 weeks	Primary: Changes from baseline to week 12 in UUI episodes Secondary: Total and nocturnal voids, urgency episodes, severe urgency episodes, frequency-urgency sum per 24 hours, and MVV per void, UPS, OAB-q, and PPBC	Primary: The mean reduction in the number of UUI episodes/24 hours was significantly greater in the fesoterodine group than in the tolterodine group (P=0.017) and placebo group (P<0.001). The median percentage reduction in UUI episodes was 100% for fesoterodine. Tolterodine ER also produced a significantly greater improvement in UUI episodes than placebo (P=0.011). The diary-dry rate at week 12 was significantly greater for patients receiving fesoterodine than for those receiving tolterodine ER (64 vs 57.2%; P=0.015) or placebo (45%; P<0.001). The difference between tolterodine ER and placebo in diary-dry rate was also significant (P<0.001). Secondary: Fesoterodine produced a significantly greater increase in MVV per void than tolterodine ER (P=0.005) or placebo (P<0.001). Compared to placebo, fesoterodine also significantly reduced voids, urgency episodes, severe urgency episodes, and frequency-urgency sum per 24 hour (all P<0.001 vs placebo). Fesoterodine did not significantly improve nocturnal voids (P=0.327). Compared to tolterodine ER, total voiding, urgency episodes, severe urgency episodes, and frequency-urgency sum per 24 hours were not statistically different. Compared to placebo, tolterodine ER significantly improved total voids, urgency episodes, severe urgency episodes, and frequency-sum per 24 hours (all P<0.001). The categorical change in PPBC score was significantly more favorable in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				the fesoterodine group than in patients on placebo (P<0.001) and tolterodine ER (P<0.001). The change between tolterodine ER and placebo was also significant (P<0.001). The categorical change in UPS was significantly more favorable for fesoterodine than placebo (P<0.001) and tolterodine (P=0.014). The difference between tolterodine ER and placebo was NS. Improvements in the OAB-q scores were significantly greater in the fesoterodine than the placebo group on the Symptom Brother scale, total HRQOL scale, and all four HRQOL domains (all P<0.001). In a post-hoc analysis, improvements with fesoterodine were also significantly greater than tolterodine ER on the Symptom Bother (P<0.001) and total HRQOL (P=0.006) scales and the Concern (P=0.008), Coping (P=0.002), and Social Interaction (P=0.019) domains. Six patients (2%) receiving placebo, 28 (4%) receiving tolterodine ER, and 42 (6%) receiving fesoterodine discontinued treatment due to treatment-emergent adverse effects. The most frequent treatment emergent adverse event in the fesoterodine and tolterodine groups were dry mouth (28 vs 16%), headache (6 vs 3%), and constipation (5 vs 4%). Sixteen (2%) of patients in the fesoterodine group had a non-fatal serious adverse events during treatment, two of which were considered related to fesoterodine. One patient with BPH developed urinary retention requiring catheterization.
Kaplan et al.[46] (2011) Fesoterodine ER 4 to 8 mg once daily vs tolterodine ER 4 mg once daily vs placebo	DB, PC, PG, RCT Men and women ≥18 years of age who have self-reported OAB symptoms for ≥3 months and had a mean of at least one UUI episode and ≥8 micturitions per 24 hours in 3-day bladder diary	N=2,417 12 weeks	Primary: Change in UUI episodes from baseline to week 12 Secondary: Change from baseline in micturitions, nocturnal micturitions, urgency episodes, severe urgency episodes,	Primary: The median percentage reduction in UUI episodes at week 12 was 100% in all groups; however, the treatment differences between the fesoterodine group and the tolterodine ER group (P=0.0093) and placebo (P=0.0001) were significant. Additionally, the difference between groups was shown as early as week four. Secondary: At week 12, fesoterodine 8 mg had significantly greater mean improvements than patients receiving tolterodine ER for micturitions (P=0.0016), urgency episodes (P<0.0001), severe urgency episodes (P<0.0001), and frequency-urgency sum (P<0.0001). Compared to tolterodine, fesoterodine did not improve nocturnal micturition or MVV. Fesoterodine also significantly improved all diary endpoints compared to placebo at week 12 (all P<0.02).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			frequency-urgency sum per 24 hours, three-day diary-dry rate, and MVV per micturition	Tolterodine ER significantly improved UUI episodes (P=0.0228), MVV (P=0.0021), and micturitions (P=0.0407) compared to placebo at week 12. The three-day diary-dry rate at week 12 was significantly better in the fesoterodine group vs tolterodine ER and placebo (P=0.0169 and P=0.0003). PPBC, UPS, and OAB-q scores were better at week 12 with fesoterodine compared to both tolterodine ER and placebo. These changes were also better for tolterodine ER compared to placebo. The most frequent treatment emergent adverse event in all groups were dry mouth, constipation, and headache.
Nitti et al[47] (2013) Mirabegron 100 mg once daily vs mirabegron 50 mg once daily vs placebo	DB, MC, PC, PG, RCT Patients ≥18 years of age, with OAB symptoms for ≥3 months and with an average baseline micturition frequency of ≥8 micturitions/24 hours and ≥3 urgency episodes with or without incontinence during the 3-day micturition diary period	N=1,328 12 weeks	Primary: Change from baseline to end of treatment in the mean number of incontinence episodes per 24 hours, change from baseline to end of treatment in the mean number of micturitions per 24 hours Secondary: Change from baseline to end of treatment in the mean VVPM, change from baseline to week four in the mean number of	Primary: Change from baseline to end of treatment in the mean number of incontinence episodes per 24 hours was -1.63 in the mirabegron 100 mg group, -1.47 in the mirabegron 50 mg group and -1.13 in the placebo group. When compared to placebo the change from baseline was statistically significant in both the mirabegron 100 mg (P<0.05) and 50 group (P<0.05). Change from baseline to end of treatment in the mean number of micturitions per 24 hours was -1.75 in the mirabegron 100 mg group, -1.66 in the mirabegron 50 mg group, and -1.05 in the placebo group. When compared to placebo the change from baseline was statistically significant in both the mirabegron 100 mg (P<0.05) and 50 group (P<0.05). Secondary: Change from baseline to end of treatment in the mean VVPM was 18.0 mL in the mirabegron 100 mg group, 18.2 mL in the mirabegron 50 mg group, and 7 mL in the placebo group. When compared to placebo the change from baseline was statistically significant in the mirabegron 100 mg (P<0.05) and 50 group (P<0.05). Change from baseline to week 4 in the mean number of incontinence episodes per 24 hours was -1.18 in the mirabegron 100 mg group, -1.20 in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			incontinence episodes per 24 hours, change from baseline to week four in the mean number of micturitions per 24 hours, change from baseline to final visit in mean level of urgency, change from baseline to final visit in mean number of urgency incontinence episodes per 24 hours, change from baseline to final visit in grade 3 or 4 urgency episodes per 24 hours, change from baseline to final visit in mean number of nocturia episodes, safety	the mirabegron 50 mg group, and -0.72 in the placebo group. When compared to placebo the change from baseline was statistically significant in the mirabegron 100 mg (P<0.05) and 50 group (P<0.05). Change from baseline to week 4 in the mean number of micturitions per 24 hours was -1.37 in the mirabegron 100 mg group, -1.19 in the mirabegron 50 mg group, and -0.77 in the placebo group. When compared to placebo the change from baseline was statistically significant in the mirabegron 100 mg (P<0.05) and 50 group (P<0.05). Change from baseline to final visit in mean level of urgency was -0.21 in the mirabegron 100 mg group, -0.19 in the mirabegron 50 mg group, and -0.08 in the placebo group. When compared to placebo the change from baseline was statistically significant in the mirabegron 100 mg (P<0.05) and 50 group (P<0.05). Change from baseline to final visit in mean number of urgency incontinence episodes per 24 hours was -1.45 in the mirabegron 100 mg group, -1.32 in the mirabegron 50 mg group and -0.89 in the placebo group. When compared to placebo the change from baseline was statistically significant in the mirabegron 100 mg (P<0.05) and 50 group (P<0.05). Change from baseline to final visit in grade 3 or 4 urgency episodes per 24 hours was -1.76 in the mirabegron 100 mg group, -1.57 in the mirabegron 50 mg group, and -0.82 in the placebo group. When compared to placebo the change from baseline was statistically significant in the mirabegron 100 mg (P<0.05) and 50 group (P<0.05). Change from baseline to final visit in mean number of nocturia episodes was -0.57 in the mirabegron 100 mg and mirabegron 50 mg group compared to -0.38 in the placebo group. When compared to placebo the change from baseline was statistically significant in the mirabegron 100 mg (P<0.05) and 50 group (P<0.05). Mirabegron was well tolerated and the incidence of adverse events was similar across all groups. Adverse events reported in the placebo group,

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				mirabegron 50 mg group and mirabegron 100 mg respectively were hypertension (6.6 vs 6.1 vs 4.9%), UTI (1.8 vs 2.7 vs 3.7), headache (2.0 vs 3.2 vs 3.0%), nasopharyngitis (2.9 vs 3.4 vs 2.5%), URI (2.6 vs 2.7 vs 2.1%), diarrhea (1.3 vs 2.3 vs 2.3%), sinusitis (2.2 vs 2.0 vs 2.1%), dry mouth (1.5 vs 0.5 vs 2.1%), constipation (1.8 vs 1.4 vs 1.6%). Serious adverse events were reported in 2.0, 2.5 and 3.2% of patients in the placebo group, mirabegron 50 mg group and mirabegron 100 mg respectively. Treatment discontinuation due to adverse events was reported in 3.8, 4.1 and 4.4% of patients in the placebo group, mirabegron 50 mg group and mirabegron 100 mg respectively.
Chapple et al[48] (2013) Mirabegron 100 mg once daily vs mirabegron 50 mg once daily vs tolterodine ER 4 mg once daily	DB, MC, RCT Patients ≥18 years of age with OAB symptoms for ≥3 months and with an average baseline micturition frequency of ≥8 micturitions/24 hours and ≥3 urgency episodes with or without incontinence during the 3-day micturition diary period	N=2,444 12 months	Primary: Incidence and severity of treatment-emergent adverse events, vital signs and laboratory tests Secondary: Change from baseline in micturition frequency and urgency frequency at one, three, six, nine and 12 months; OAB-q, PPBC and VAS scores, proportion of treatment responders (≥50% decrease from baseline in the incontinence episodes/24 hours or those with zero incontinence	Primary: The incidence of treatment-emergent adverse events was similar among patients treated with mirabegron 50 mg (59.7%), 100 mg (61.3%) or tolterodine ER (62.6%). Most events were categorized as mild or moderate in severity. The most frequent treatment-related adverse events included hypertension, dry mouth, constipation, and headache, occurring at a similar incidence across all treatment groups, except for dry mouth, which was highest in the tolterodine group. Discontinuations resulting from adverse events were similar between treatment groups, with 6.4, 5.9 and 6.0% of patients treated with mirabegron 50 mg, 100 mg and tolterodine ER 4 mg, discontinuing treatment, respectively. Urinary retention occurred in one patient each in the mirabegron 50 mg and 100 mg group compared to three patients treated with tolterodine ER. Urinary retention requiring catheterization was reported in one patient receiving mirabegron 100 mg and tolterodine ER. There was a higher incidence of cardiac arrhythmias with tolterodine ER 4 mg (6.0%) compared to mirabegron 50 mg (3.9%) and 100 mg (4.1%). Mean changes from baseline in systolic blood pressure with mirabegron 50 mg, 100 mg and tolterodine were 0.2, 0.4 and -0.5 mm Hg for morning measurements and -0.3, 0.1 and 0.0 mm Hg for evening measurements, respectively. The mean changes in diastolic blood pressure were -0.3, 0.4, and 0.1 mm Hg, respectively for morning measurements and 0.0, 0.1 and 0.6 mm Hg, respectively for evening measurements.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			episodes at final visit)	There was a higher incidence of neoplasm (benign, malignant and unspecified including cysts and polyps) in the mirabegron 100 mg group (1.3%) compared to the 50 mg group (0.1%) and tolterodine ER 4 mg (0.5%). Secondary: There were similar improvements between treatments with regard to the mean number of micturitions/24 hours (-1.27 for mirabegron 50 mg, -1.41 for mirabegron 100 mg and -1.39 for tolterodine ER 4 mg; P values not reported). Improvements in the mean number of incontinence episodes/24 hours (-1.01 for mirabegron 50 mg, -1.24 for mirabegron 100 mg and -1.26 for tolterodine ER 4 mg) and MVV (17.5 mL for mirabegron 50 mg, 21.5 mL for mirabegron 100 mg and 18.1 mL for tolterodine ER 4 mg) were similar among treatment groups (P values not reported). At the final visit, the proportion of treatment responders (≥50% reduction from baseline in the mean number of incontinence episodes/24 hours was 63.7, 66.3 and 66.8% for patients treated with mirabegron 50 mg, 100 mg and tolterodine ER, respectively; P values not reported). The proportion of patients who reported zero incontinence episodes at the final visit was 43.4, 45.8 and 45.1%, respectively; P values not reported). Both doses of mirabegron showed numerical improvements on the other secondary efficacy variables including OAB-q symptom bother and QOL, treatment satisfaction, number of nocturia episodes and PPBC.
Khullar et al[49] (2013) Mirabegron 100 mg once daily vs mirabegron 50 mg once daily	AC, DB, MC, PC, PG, RCT Patients ≥18 years of age, with OAB symptoms for ≥3 months and an average baseline micturition frequency of ≥8 micturitions/24	N=1,978 12 weeks	Primary: Change from baseline to end of treatment in the mean number of incontinence episodes per 24 hours, change from baseline to end of treatment in the mean number of	Primary: Change from baseline to end of treatment in the mean number of incontinence episodes per 24 hours was -1.46 in the mirabegron 100 mg group, -1.57 in the mirabegron 50 mg group, -1.27 in the tolterodine SR group and -1.17 in the placebo group. When compared to placebo the change from baseline was statistically significant in the mirabegron 100 mg (P<0.05) and 50 group (P<0.05) but not in the tolterodine SR group (P value not reported). Change from baseline to end of treatment in the mean number of micturitions per 24 hours was -1.77 in the mirabegron 100 mg group, -1.93

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs tolterodine SR 4 mg once daily vs placebo	hours and ≥3 urgency episodes with or without incontinence during the 3-day micturition diary period		micturitions per 24 hours Secondary: Change from baseline to end of treatment in the mean VVPM, change from baseline to week four in the mean number of incontinence episodes per 24 hours, change from baseline to week 4 in the mean number of micturitions per 24 hours, change from baseline to final visit in mean level of urgency, change from baseline to final visit in mean number of urgency incontinence episodes per 24 hours, change from baseline to final visit in grade 3 or 4 urgency episodes per 24 hours, change from baseline to final visit in mean number of nocturia	in the mirabegron 50 mg group, -1.59 in the tolterodine SR group and -1.34 in the placebo group. When compared to placebo the change from baseline was statistically significant in the mirabegron 100 mg (P<0.05) and 50 group (P<0.05) but not in the tolterodine SR group (P value not reported). Secondary: Change from baseline to end of treatment in the mean VVPM was 25.6 mL in the mirabegron 100 mg group, 24.2 mL in the mirabegron 50 mg group, 25.0 mL in the tolterodine SR group and 12.3 mL in the placebo group. When compared to placebo the change from baseline was statistically significant in the mirabegron 100 mg (P<0.05) and 50 group (P<0.05) and tolterodine SR group (P<0.05). Change from baseline to week four in the mean number of incontinence episodes per 24 hours was -1.03 in the mirabegron 100 mg group, -1.04 in the mirabegron 50 mg group, -1.00 in the tolterodine SR group and -0.65 in the placebo group. When compared to placebo the change from baseline was statistically significant in the mirabegron 100 mg (P<0.05) and 50 group (P<0.05) and tolterodine SR group (P<0.05). Change from baseline to week four in the mean number of micturitions per 24 hours was -1.29 in the mirabegron 100 mg group, -1.16 in the mirabegron 50 mg group, -1.10 in the tolterodine SR group and -0.77 in the placebo group. When compared to placebo the change from baseline was statistically significant in the mirabegron 100 mg (P<0.05) and 50 group (P<0.05) and tolterodine SR group (P<0.05). Change from baseline to final visit in mean level of urgency was -0.30 in the mirabegron 100 mg group, -0.31 in the mirabegron 50 mg group, -0.29 in the tolterodine SR group and -0.22 in the placebo group (P values not reported). Change from baseline to final visit in mean number of urgency incontinence episodes per 24 hours was -1.33 in the mirabegron 100 mg group, -1.46 in the mirabegron 50 mg group, -1.18 in the tolterodine SR group and -1.11 in the placebo group (P values not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			episodes, safety	Change from baseline to final visit in grade 3 or 4 urgency episodes per 24 hours was -1.96 in the mirabegron 100 mg group, -2.25 in the mirabegron 50 mg group, -2.07 in the tolterodine SR group and -1.65 in the placebo group (P values not reported). Change from baseline to final visit in mean number of nocturia episodes was -0.56 in the mirabegron 100 mg group, -0.41 in the mirabegron 50 mg group, -0.50 in the tolterodine SR group and -0.45 in the placebo group (P values not reported). Mirabegron and tolterodine SR were well tolerated and the incidence of adverse events was similar across all groups. Adverse events reported in ≥2% of the placebo, mirabegron 50 mg group, mirabegron 100 mg and tolterodine SR group respectively included hypertension (7.7 vs 5.9 vs 5.4 vs 8.1%), nasopharyngitis (1.6 vs 2.8 vs 2.8 vs 2.8%), dry mouth (2.6 vs 2.8 vs 2.8 vs 10.1%), headache (2.8 vs 3.7 vs 1.8 vs 3.6%), influenza (1.6 vs 2.2 vs 2.0 vs 1.4%), UTI (1.4 vs 1.4 vs 1.8 vs 2.0%), constipation (1.4 vs 1.6 vs 1.6 vs 2.0%).
Staskin et al.[50] (2009) Oxybutynin 10% topical gel 1 g applied once daily vs placebo	DB, MC, PC, PG, RCT Patients ≥18 years of age with OAB, urge or mixed urinary incontinence with predominance of UUI episodes as well as ≥8 daily urinary voids and ≥4 daily UUI episodes	N=789 12 weeks	Primary: Change in mean number of daily incontinence episodes Secondary: Mean change in urinary frequency, urinary volume per void, number of nocturia episodes, proportion of patients achieving complete urinary continence and safety	Primary: Patients receiving oxybutynin topical gel reported a significantly greater decrease in the mean number of daily incontinence episodes compared to patients receiving placebo (-3.0 vs -2.5; P<0.0001). Secondary: Oxybutynin topical gel was associated with a significant improvement in the mean number of episodes of urinary frequency (-2.7 vs -2.0; P=0.0017) and voided urinary volume compared to placebo (21.0 vs 3.8 mL; P=0.0018). The difference between groups in the number of nocturia episodes did not reach statistical significance (-0.75 daily for oxybutynin topical gel compared to -0.65 daily for placebo; P=0.1372). Complete urinary continence was demonstrated in 27.8% patients receiving oxybutynin topical gel patients compared to 17.3% of patients randomized to placebo (P value not reported). Compared to placebo, oxybutynin topical gel was associated with a higher

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				incidence of dry mouth (6.9 vs 2.8%; P=0.0060) and application site dermatitis (1.8 vs 0.3%; P=0.0358).
Goldfischer et al.[51] (2013) Oxybutynin 3% topical gel 84 g applied once daily vs Oxybutynin 3% topical gel 56 g applied once daily vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with symptoms of urgency and/or mixed UI and a predominance of urgency incontinence for ≥3 months and who had a history of at least 1 to 2 urinary urgency episodes and ≥8 voids per day; were treatment-naive or had a previous beneficial response to anticholinergic treatment; and, if on anticholinergic medication or any pharmacologic treatment for OAB at screening, were willing to undergo a 2-week washout period.	N=626 12 weeks	Primary: Change from baseline to week 12 in mean number of weekly UI episodes Secondary: Change from baseline to week 12 in daily urinary frequency, average urinary void volume per void, daily UI episodes and change from baseline to week one in these analyses and safety endpoints	Primary: At 12 weeks, the 84 and 56 mg/day arms achieved significantly greater improvement vs placebo in weekly UI episodes (mean change from baseline: -20.4 and -16.4 vs -18.1; P<0.05 and P=0.04, respectively). Secondary: At 12 weeks, the 84 mg/day arm achieved significantly greater improvement vs placebo in daily urinary frequency (-2.6 vs -1.9; P=0.001) and urinary void volume (32.7 vs 9.8; P<0.0001). For oxybutynin gel 56 mg/day, the changes from baseline in these secondary endpoints were not significantly different from placebo. The 84-mg/day arm also reduced the number of daily UI episodes from baseline by a mean of 2.9 episodes, and significant changes from baseline in weekly and daily UI episodes, daily urinary frequency, and urinary void volume were achieved within one week after the start of treatment. The most common treatment-emergent adverse events (>2% of patients) that occurred significantly more often in patients receiving oxybutynin gel than in those receiving placebo, were dry mouth and application site erythema.
Anderson et al.[52] (1999) Oxybutynin ER 5 to 30 mg daily	AC, DB, MC, RCT Community dwelling men and women with urge incontinence or	N=97 Not specified	Primary: Urge incontinence episodes/week Secondary: Proportion of	Primary: The mean number of weekly urge incontinence episodes decreased from 27.4 to 4.8 in the ER group and from 23.4 to 3.1 in the IR group (P=0.6). The percentage reduction in weekly urge incontinence episodes was 84% in the ER group and 88% in the IR group (P=0.71).

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vs oxybutynin IR 5 mg 1 to 4 times/day	mixed incontinence with a primary urge component who had at least 6 urge incontinence episodes a week when not taking medication (who had previously responded to oxybutynin)		participants achieving elimination of urge incontinence episodes, number of incontinence episodes, proportion of those achieving continence, adverse events	Secondary: Of the participants, 52% in the ER group and 51% in the IR group had no urge incontinence episodes at the end of treatment (P=0.7). Total incontinence (urge, stress and other) episodes decreased from 29.3 to 6.0 in the ER group and from 26.3 to 3.8 in the IR group from baseline to the end of the study (P=0.6). The percentage reduction in any incontinence episodes was 82% in the ER group and 88% in the IR group (P=0.5). The proportions of patients who were totally continent was 41% in the ER group and 40% in the IR group (P=0.9). Normal void frequency increased 54% in the ER group and 17% in the IR group (P<0.001). At least one anticholinergic event occurred in 87% of patients in the ER group and 94% of patients in the IR group. The most common anticholinergic event in both groups was dry mouth (68% of the ER group and 87% of the IR group; P=0.04). Fewer participants reported moderate or severe dry mouth with ER oxybutynin (25 vs 46%; P=0.03). There was no significant difference among the treatment groups for other anticholinergic adverse events. There were few reports of moderate to severe dry mouth at the 5 mg dose, and there was a trend in both groups toward increasing frequency of dry mouth as doses increased.
Barkin et al.[53] (2004) Oxybutynin ER 15 mg daily vs oxybutynin IR 5 mg three times daily	DB, MC, PG, RCT Men and women >18 years of age with UUI who demonstrated >7 UI episodes/week and >8 voids/day	N=123 9 weeks	Primary: Void frequency, UI episodes, treatment-related changes in QOL as assessed by the IIQ and UDI, and adverse events Secondary: Not reported	Primary: The mean number of incontinence episodes/week decreased from 24.3 to 10.4 in the ER group (P<0.001 vs baseline) and from 23.0 to 6.1 in the IR group (P<0.001 vs baseline). There was no significant difference among the treatment groups (P=0.404). The mean voluntary micturition episodes/day decreased from 11.4 to 9.6 in the ER group (P<0.001 vs baseline) and from 11.0 to 8.6 in the IR group (P<0.001 vs baseline). There was no significant difference among the treatment groups (P=0.286). There was no significant difference among the treatment groups in mean urine voided/micturition (P=0.533), incidence of urgency (P=0.116), or

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				severity of urgency (P=0.255). There was a significant reduction from baseline in the mean number of pads/day in the ER group (2.3. to 1.7; P<0.001); however, there was no change from baseline in the IR group (2.4 to 1.9; P=NS). Patients in both treatment groups demonstrated significant improvements from baseline in mean IIQ scores (ER; P<0.001, IR; P<0.001) and mean UDI scores (ER; P<0.001, IR; P<0.001). There were no significant differences among the treatment groups. The most frequently reported adverse events in the ER and IR oxybutynin groups were dry mouth (68 and 72%, respectively) and dry throat (31 and 37%, respectively). There was no significant difference in the incidence of moderate and severe dry mouth among the treatment groups (ER, 26% and IR, 42%). More patients in the ER group rated their medication tolerable compared to the IR group (P=0.020). More patients discontinued treatment in the IR oxybutynin group than in the ER oxybutynin group (P=0.047), primarily due to adverse events. Secondary: Not reported
Birns et al.[54] (2000) Oxybutynin ER 10 mg once daily vs oxybutynin IR 5 mg twice daily	DB, MC, PC, RCT Patients 18 to 76 years of age with detrusor instability or detrusor hyperreflexia whose symptoms were stabilized on conventional oral oxybutynin tablets (5 mg twice daily) for 2 weeks	N=130 6 weeks	Primary: Proportion of patients with daytime continence at completion of the study Secondary: Percentage of patients with nighttime continence, median change in the number of	Primary: At the completion of the study, 53% of patients receiving oxybutynin ER were continent during the day compared to 58% of patients receiving oxybutynin IR (P=0.62). Secondary: There was no significant difference between the treatment groups in the percentage of patients with nighttime continence at the completion of the study or the median change in the number of voluntary daytime voids, voluntary nighttime voids, daytime episodes of incontinence and nighttime episodes of incontinence from the week preceding treatment to the completion of the study. Dry mouth and vision abnormalities were more common in patients receiving oxybutynin ER than in those receiving oxybutynin IR; however,

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			voluntary daytime voids, voluntary nighttime voids, daytime episodes of incontinence and nighttime episodes of incontinence from the week preceding treatment to the completion of the study, adverse events	this was NS (P=NS).
Versi et al.[55] (2000) Oxybutynin ER 5 to 20 mg/day vs oxybutynin IR 5 to 20 mg/day	DB, MC, PG, RCT Patients with 7 to 45 urge incontinence episodes/week and ≥4 days of incontinence/week who had previously responded to treatment with antimuscarinic drugs	N=226 Duration not specified	Primary: Number of incontinence episodes and total incontinence episodes Secondary: Not reported	Primary: Urge incontinence episodes decreased from 18.6 to 2.9/week with oxybutynin ER (83% reduction; P<0.001) and from 19.8 to 4.4/week with oxybutynin IR from baseline (76% reduction; P<0.001). There was no significant difference between the treatment groups (P=0.36). Total incontinence episodes decreased from 20.2 to 3.5/week with oxybutynin ER (81% reduction; P<0.001) and from 22.4 to 5.4/week with oxybutynin IR from baseline (75% reduction; P<0.001). There was no significant difference between the treatment groups (P=0.41). There was no significant difference in anticholinergic adverse events among the treatment groups. Dry mouth occurred in 47.7% and 59.1% of patients receiving oxybutynin ER and IR, respectively. Secondary: Not reported
Nilsson et al.[56] (1997) Oxybutynin ER 10 mg daily for 60 days	XO Female patients 37 to 65 years of age with symptoms of urge incontinence and detrusor	N=17 120 days	Primary: Frequency of voluntary voiding, the maximal volume of urine/single void, and the total	Primary: The frequency of voids/24 hour was reduced by 23% with oxybutynin ER and by 24% with oxybutynin IR (P=0.51). Treatment with oxybutynin ER resulted in a 28% reduction in the total weight of pads compared to a 21% reduction with oxybutynin IR (P=0.80).

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vs oxybutynin IR 5 mg twice daily for 60 days	instability		volume of voluntarily voided urine/24 hour Secondary: Not reported	The total volume of voluntary voided urine/day increased by 15% with both treatments (P=0.75), and the maximal volume of urine/void increased by 26% and 34% with oxybutynin ER and oxybutynin IR, respectively (P=0.95). There were no significant differences in adverse events among the treatment groups, including dry mouth (P=0.41), headache (P=1.00), dyspepsia (P=0.26), or vision abnormality (P=0.32). Secondary: Not reported
Appell et al.[57] (2001) Oxybutynin ER 10 mg daily vs tolterodine IR 2 mg twice daily	DB, PG, MC, RCT Participants with OAB who had between 7 and 50 episodes of urge incontinence/week and 10 or more voids/24 hours	N=378 12 weeks	Primary: Number of urge incontinence episodes/week, number of total incontinence episodes/week and micturition frequency episodes/week Secondary: Not reported	Primary: The number of urge incontinence episodes/week decreased from 25.6 to 6.1 in the oxybutynin group and from 24.1 to 7.8 in the tolterodine group (P=0.03). The number of total incontinence episodes/week decreased from 28.6 to 7.1 in the oxybutynin group and from 27.0 to 9.3 in the tolterodine group (P=0.02). Micturition frequency episodes/week decreased from 91.8 to 67.1 in the oxybutynin group and from 91.6 to 71.5 in the tolterodine group (P=0.02). Both drugs improved symptoms of OAB significantly from baseline to the end of the study as assessed by the three main outcome measures (P<0.001). Overall, 92.6 and 95.3% of the patients in the oxybutynin and tolterodine groups, respectively, had fewer incontinence episodes at the end of the study period compared to baseline. The incidence of dry mouth was similar among the treatment groups (28.1% for oxybutynin and 33.2% for tolterodine; P=0.32). Moderate to severe dry mouth was also similar among the treatment groups (10.2% for oxybutynin and 10.9% for tolterodine; P=0.87). Other adverse events were similar among the treatment groups. Overall, the discontinuation rates for

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				adverse events were 7.6% in the oxybutynin group and 7.8% in the tolterodine group (P=0.99). Secondary: Not reported
Sand et al.[58] (2004) Oxybutynin ER 10 mg once daily vs tolterodine IR 2 mg twice daily	DB, RCT Women with urge or mixed incontinence (≥7 and ≤50 urge incontinence episodes/week and ≥10 voids/24 hours)	N=315 12 weeks	Primary: Number of urge incontinence episodes, total incontinence, micturition frequency, tolerability Secondary: Not reported	Primary: The number of urge incontinence episodes decreased from 28.1 to 6.2/week in the oxybutynin ER group compared to a reduction from 28.9 to 8.5/week in the tolterodine IR group (P=0.038). Total incontinence episodes decreased from 25.2 to 7.3/week in the oxybutynin ER group compared to a reduction from 25.1 to 10.1/week in the tolterodine IR group (P=0.030). Micturition frequency decreased from 91.7 to 68.0/week in the oxybutynin ER group compared to a reduction from 91.6 to 71.2/week in the tolterodine IR group (P=0.272). There was no significant difference in dry mouth, central nervous system events or other adverse events among the treatment groups. Secondary: Not reported
Diokno et al.[59] (2003) Oxybutynin ER 10 mg daily vs tolterodine ER 4 mg daily	AC, DB, MC, RCT Women ≥18 years of age with OAB who documented 21-60 UUI episodes/week and ≥10 voids/day	N=790 12 weeks	Primary: Mean weekly UUI episodes, weekly total incontinence episodes and weekly micturition frequency, adverse events Secondary: Not reported	Primary: The mean weekly episodes of UUI decreased from 37.1 to 10.8 in the oxybutynin group and from 36.7 to 11.2 in the tolterodine group (P=0.28). The mean number of total incontinence episodes decreased from 43.4 to 12.3 in the oxybutynin group and from 42.4 to 13.8 in the tolterodine group (P=0.08). Patients receiving oxybutynin had a greater decrease in the mean weekly micturition frequency compared to tolterodine participants (P=0.003). The proportion of participants who reported total dryness (no incontinence episodes) in their last seven-day 24-hour voiding diary was 23.0% in the oxybutynin group compared to 16.8% in the tolterodine group (P=0.03).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The proportion of participants who reported no UUI episodes at the last assessment was 26.7% in the oxybutynin group compared to 20.9% in the tolterodine group (P=0.06). Dry mouth was more common in the oxybutynin group than in the tolterodine group (29.7 vs 22.3%, respectively; P=0.02). Most reports of dry mouth events were mild. Other anticholinergic adverse events (constipation, impaired urination-retention, and blurred vision) and central nervous system adverse effects (dizziness, somnolence, depression, and confusion) occurred at similar frequencies in each group. Adverse events led to discontinuation of study medication by 20 patients receiving oxybutynin and 19 receiving tolterodine. Secondary: Not reported
Reinberg et al.[60] (2003) Oxybutynin ER 5 mg/day vs tolterodine ER 2 mg/day vs tolterodine IR 2 mg/day	OL Pediatric patients with a history of non-neurogenic diurnal urinary incontinence and symptoms of OAB	N=132 Duration not specified	Primary: Urinary frequency, incontinence and safety Secondary: Not reported	Primary: Oxybutynin ER led to a greater reduction in urinary frequency compared to tolterodine IR (P<0.01). Both oxybutynin ER and tolterodine ER were significantly better than tolterodine IR in improving symptoms of diurnal incontinence and urinary frequency (P<0.01 and P<0.05, respectively). Oxybutynin ER was significantly more effective than tolterodine ER in completely resolving diurnal incontinence (P<0.05). There were no significant differences in the peripheral or central nervous system anticholinergic side effects among the treatment groups. Secondary: Not reported
Nelken et al.[61] (2011) Oxybutynin IR 5 mg twice daily	PRO, RCT Women who had ≥10 voids in a 24 hour period, as	N=59 12 weeks	Primary: Change from baseline in number of daily voiding episodes	Primary: After 12 weeks, both groups had a significant decrease in the number of daily voids (14.7 to 11.7 for oxybutynin [P=0.003] and 14.9 to 10.4 for estradiol ring [P<0.001]). The difference between groups was not statistically significant.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs estradiol vaginal ring 7.5 µg/day	recorded in a 72 hour voiding diary, and were postmenopausal		Secondary: Change in vaginal pH levels, vaginal maturation index, and QOL scores, as assessed by the UDI-6 and the IIQ-7	Secondary: There was a significant decrease in UDI-6 (12.1 to 9.4 for oxybutynin [P=0.003] and 11.4 to 7.8 for estradiol [P<0.001]) and IIQ-7 (14.7 to 11.3 for oxybutynin [P=0.02] and 13.2 to 8.1 for estradiol [P<0.001]) scores in both treatment groups. Mean vaginal pH levels in the oxybutynin group remained unchanged after 12 weeks of treatment, but those who received the estradiol ring had a significant decrease in mean pH (6 to 4.9; P=0.002). Mean maturation index did not significantly change in the oxybutynin group, whereas mean maturation index increased significantly after 12 weeks of therapy with an estradiol ring (24.3 to 70.1; P<0.001). Dry mouth, constipation, and blurry vision occurred significantly more in patients who received oxybutynin, whereas more women in the estradiol group reported vaginal discharge.
Davila et al.[62] (2001) Oxybutynin transdermal 2 to 4 patches applied twice weekly vs oxybutynin IR 5 to 7.5 mg orally two or three times daily	DB, MC, PC, RCT Patients ≥18 years of age with a history of urge or mixed urinary incontinence with a predominance of urge symptoms who had symptomatic improvement during a minimum of 6 weeks of oral oxybutynin	N=76 6 weeks	Primary: Average number of daily incontinence episodes, patient-completed VAS for efficacy, dry mouth on an anticholinergic symptoms questionnaire, cystometric comparisons Secondary: Not reported	Primary: The average daily incontinence episodes were reduced by approximately five episodes in both groups (P<0.0001), with no significant difference between transdermal and oral therapy. The change in the mean VAS score for each group was 5.8 vs 6.0 cm for the transdermal and oral groups, respectively (P<0.0001). The difference in mean VAS score between transdermal and oral therapy was 0.1 cm (P=0.9). Dry mouth occurred in 38% of patients in the transdermal group compared to 94% of patients in the oral group (P<0.001). Blurred vision, dizziness, drowsiness, palpitations, nausea and impotence were comparable between the groups. Average bladder volume at first detrusor contraction increased by 66 mL in the transdermal (P<0.0055) and 45 mL in the oral groups (P=0.1428). There was no significant difference among the transdermal and oral groups (P=0.57).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Average maximum cystometric capacity increased 53 and 51 mL in the transdermal (P<0.0011) and the oral (P<0.0538) groups, respectively. Post-void residual volume increased by an average of 13 and 16 mL in the oral and transdermal groups, respectively (P=NS). The most frequent treatment related adverse events were dry mouth, constipation, somnolence, dizziness, blurred vision and impaired urination, which occurred more frequently in the oral group. Secondary: Not reported
Dmochowski et al.[63] (2003) Oxybutynin transdermal delivery system (OXY-TDS) 3.9 mg/day applied twice weekly vs tolterodine ER (TOL-LA) 4 mg daily vs placebo	DB, RCT Patients ≥18 years of age who were receiving pharmacologic treatment for OAB and who had a beneficial response to the pre-study treatment	N=361 12 weeks	Primary: Change from baseline in the number of incontinence episodes/day, average daily urinary frequency, average urinary volume/void, and changes in the QOL instruments Secondary: Not reported	Primary: There was a significant reduction in the number of urinary incontinence episodes/day in patients treated with OXY-TDS compared to placebo (median change -3 vs -2, respectively; P=0.0137). There was a significant reduction in the number of urinary incontinence episodes/day in patients treated with TOL-LA compared to placebo (median change -3 vs -2, respectively; P=0.0011). There was no significant difference between OXY-TDS and TOL-LA in the reduction of incontinent episodes (P=0.2167). The reduction in incontinence episodes corresponded to a 75% improvement in the OXY-TDS group, 75% in the TOL-LA group, and 50% in the placebo group. Complete continence was achieved by 39% of patients in the OXY-TDS group, 38% of patients in the TOL-LA group, and 22% of patients in the placebo group (both, P=0.014 vs placebo). The mean decrease in average daily urinary frequency was -1.9 micturitions/day with OXY-TDS (P=0.1010 vs placebo) -2.2 micturitions/day with TOL-LA (P=0.0025 vs placebo), and -1.4 micturitions/day with placebo. There was no significant difference between OXY-TDS and TOL-LA (P=0.2761).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The median increases in average urinary volume/void was 24 mL with OXY-TDS (P=0.0010 vs placebo), 29 mL with TOL-LA (P=0.0017 vs placebo) and 5.5 mL in the placebo group. There was no significant difference between OXY-TDS and TOL-LA (P=0.7690). The patients' Global Assessment of Disease State scores were significantly improved with OXY-TDS (P=0.0106) and TOL-LA (P=0.0001) compared to placebo. There was no significant difference between OXY-TDS and TOL-LA (P=0.1861). The total IIQ scores improved significantly with OXY-TDS (P=0.0018) and TOL-LA (P=0.0045) compared to placebo. Significant improvements in irritative symptoms of the UDI questionnaire were also observed with OXY-TDS (P=0.0156) and TOL-LA (P=0.0010) compared to placebo. The most common treatment-related adverse events in the OXY-TDS group were application site reactions, including erythema (8.3%) and pruritus (14.0%). Dry mouth (4.1 vs 1.7% with placebo; P=0.2678) and constipation (3.3%) were also reported. Adverse events led to treatment discontinuation in 10.7% of patients receiving OXY-TDS. Anticholinergic adverse events were the most common treatment-related events in the TOL-LA group (13.0%). Dry mouth occurred at a greater rate with TOL-LA (7.3%) than placebo (1.7%; P=0.0379). Constipation occurred in 5.7% of TOL-LA patients. Adverse events led to treatment discontinuation in 1.6% of patients receiving TOL-LA. Secondary: Not reported
Metello et al.[64] (2007) Solifenacin 5 mg once daily	OL Women ≥18 years of age with OAB symptoms (≥8 voids/24 hours and ≥1 incontinence episode/24 hours) for ≥3 months who	N=40 30 days	Primary: Patient self-assessment of improvement after 30 days using the USS in both treatment groups Secondary:	Primary: After 30 days of therapy, treatment with solifenacin led to a significant improvement in USS scores when assessed in all patients (P<0.001). There was no significant difference in USS scores among patients who were drug naïve compared to those who had previously failed trospium. Overall 16% of patients experienced no improvement, 13.5% had mild improvement and 69.5% had great improvement.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	had either not received any previous medication or who had been previously unsuccessfully treated with trospium		Reduction of the daily number of voids and urgency or involuntary leakage episodes	Secondary: Treatment with solifenacin resulted in a significant reduction in urgency episodes, involuntary leakage episodes, and number of voids/24 hours when assessed in all patients (P<0.001). There was no significant difference in these endpoints among patients who were drug naïve compared to those who had previously failed trospium. Overall, 16% of patients had no improvement in the number of involuntary leakage episodes, 11% of patients had mild improvement and 73% of patients had great improvement. For daily urgency episodes, 13.5% of patients had no improvement, 27.0% had a mild reduction, and 59.0% had a great reduction.
Chancellor et al.[65] (2008) Solifenacin 5 to 10 mg once daily	MC, OL Patients ≥18 years of age with symptoms of OAB for ≥3 months who had been treated with tolterodine ER 4 mg for ≥4 weeks, and wished to switch therapy because of a lack of sufficient subjective improvement in urgency (≥3 urgency episodes/24 hours)	N=441 12 weeks	Primary: Change in urgency episodes compared to pre-washout (when patients were receiving tolterodine ER 4 mg) Secondary: Change in micturitions, incontinence episodes, nocturia episodes, and nocturnal voids compared to pre-washout and post-washout; PRO using the PPBC and the OAB-q was also assessed	Primary: The mean change in the number of urgency episodes/24 hours was −3.4 from pre-washout to study end (P<0.001). The median percent change was -75%. Secondary: The mean change in micturitions, incontinence episodes, nocturia episodes, and nocturnal voids from pre-washout to study end was –1.6, –1.9, –0.7, and –0.8, respectively (all, P<0.001). The median percent change from pre-washout was –15.0% for the number of micturitions, –96.4% for incontinence episodes, –40.8% for nocturia episodes, and –40.0% for nocturnal voids. The median change in micturitions, incontinence episodes, nocturia episodes, and nocturnal voids from post-washout to study end was –2.0 (-19.5%), –2.0 (-100%), –0.7 (-43.7%), and –0.7 (-40.0%), respectively (all, P<0.001). The mean PPBC score decreased from pre-washout by 1.2 points (95% CI, –1.3 to –1.1; P<0.001) and from post-washout by 1.2 points (95% CI, –1.3 to –1.0; P<0.001). Patients had significant improvements on the OAB-q at study end compared to both pre-washout and post-washout (all, P<0.001). The mean changes in OAB-q scores at study end relative to pre-washout and post-

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				washout were –27.4 and –29.5, respectively, for symptom bother; 23.1 and 27.9 for coping; 25.2 and 29.7 for concern; 21.9 and 24.5 for sleep; 11.1 and 15.0 for social interaction; and 21.1 and 25.2 for total HRQOL. The most common adverse events were dry mouth (17.5%), constipation (11.6%), and blurred vision (2.3%).
Zinner et al.[66] (2008) Solifenacin 5 to 10 mg once daily	MC, OL Patients ≥18 years of age with OAB symptoms for ≥3 months who were previously treated with tolterodine ER 4 mg/day for ≥4 weeks, and who wished to switch to solifenacin due to lack of sufficient improvement in urgency episodes while receiving tolterodine (≥3 urgency episodes/24 hours)	N=441 12 weeks	Primary: WPAI-SHP, HUI, and a resource utilization questionnaire administered at pre-washout and week 12 Secondary: Not reported	Primary: Patients reported significantly fewer physician office visits (0.2 vs 1.2; P<0.0001), UTIs (0.1 vs 0.2; P<0.0001), and pads/diapers (7.9 vs 10.7/week; P=0.0009) with solifenacin compared to the pre-washout period. There were no significant differences in the numbers of skin rashes or falls reported at end of the study compared to pre-washout. Patients reported using fluid management as a behavioral management strategy on fewer days with solifenacin compared to when they were taking tolterodine ER 4 mg/day (14.2 vs 18.0 days; P=0.0381). There were no significant differences in other behavioral management strategies. Based on the WPAI-SHP, patients who were working reported a reduction in percent of work time missed (0.2 vs 2.1%; P=0.0017), a reduction in percent of impairment while working (11.3 vs 22.9%; P<0.0001), a reduction in percent of overall work impairment (11.9 vs 24.0%; P<0.0001), and a reduction in percent of activity impairment (18.4 vs 31.6%; P<0.0001) after 12 weeks of therapy with solifenacin. There was no significant difference in the health utility score between pre-washout and end of study based on the HUI 2/3. Secondary: Not reported
Wong et al.[67] (2009) Solifenacin 5 to 10 mg once daily	OL Women with OAB who had previously taken oxybutynin IR	N=9 12 weeks	Primary: Daytime frequency, nocturia, number of incontinence	Primary: The mean number of daytime micturitions was reduced from 11.4 to 7.3 with solifenacin (P=0.0002). The mean number of nocturia episodes was reduced from 2.8 to 0.9 with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	without benefit or developed intolerable adverse effects		episodes, average urinary voided volume, and quality-of-life (OAB-q short form symptom bother) Secondary: Not reported	solifenacin (P=0.0004). The total number of incontinence episodes/day was reduced from 4.9 to 1.9 with solifenacin (P=0.02). The mean micturition volumes were increased from 160 to 280 ml with solifenacin (P=0.002). The symptom severity domain of the OAB-q showed a value of 60.8% at baseline and 32.0% at 12 weeks with solifenacin (P=0.001). The HRQOL domain of the OAB-q showed a value of 45.5% at baseline and 73.3% at 12 weeks with solifenacin (P=0.0006). Secondary: Not reported
Garely et al.[68] (2006) Solifenacin 5 to 10 mg once daily	MC, OL Patients ≥18 years of age with OAB (urgency, urge urinary incontinence, frequency, and/or nocturia for ≥3 months)	N=2,225 12 weeks	Primary: PPBC scale, OAB-q, and a VAS for the degree of bother caused by individual OAB symptoms Secondary: Not reported	Primary: The mean PPBC scale score decreased significantly to 2.9 (mean change, -1.4; 95% CI, -1.49 to -1.38; P<0.001), which corresponded to a perception of "some minor problems" associated with their bladder condition. There were significant improvements in all of the OAB-q scoring domains (symptom severity, coping, concern, sleep, social interaction, and overall HRQoL) with solifenacin (all subscales, P<0.001). Significant improvements in urinary urgency, urge urinary incontinence, frequency, or nocturia were observed with solifenacin on the VAS. For urinary urgency, 88.2% of patients indicated less bothersome symptoms; for urge urinary incontinence, 89.4% of patients indicated less bothersome symptoms; for frequency, 88.3% of patients indicated frequency was less bothersome; for nocturia, 87.5% of patients indicated that nocturia was less bothersome. Anticholinergic adverse events occurred as follows: dry mouth (21.4%), constipation (13.3%), headache (3.4%), blurred vision (2.6%), nausea (1.8%), dyspepsia (1.5%), and dry eyes (1.3%). A total of 9.7% of patients discontinued treatment due to an adverse event. The most frequently

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				reported treatment-emergent adverse events that resulted in discontinuation were dry mouth (1.9%) and constipation (1.9%). Secondary: Not reported
Haab et al.[69] (2005) Solifenacin 5 to 10 mg once daily	ES, OL Patients ≥18 years of age with symptoms of OAB (≥8 micturitions/24 hours and either ≥1 urgency episode/24 hours or ≥1 incontinence episode/24 hours) for >3 months	N=1,633 40 weeks	Primary: Safety and tolerability Secondary: Efficacy	Primary: Dry mouth occurred in 10% of patients receiving solifenacin 5 mg and 17% of patients receiving solifenacin 10 mg. The discontinuation rate due to dry mouth was 0.4%. After 40 weeks, 85% of patients indicated satisfaction with solifenacin tolerability, and 99% of patients rated solifenacin tolerability as either ‘‘satisfactory’’ or ‘‘acceptable.’’ Secondary: The mean number of urgency episodes/24 hours decreased by 63%. For patients with ≥1 episode of urgency/24 hours at baseline, 40% had no symptomatic urgency at end point. The mean number of incontinence episodes/24 hours decreased by 66%. For patients with ≥1 episode of incontinence at baseline, 58% were continent at end point. The mean number of micturitions/24 hours decreased by 2.97 (23%) with solifenacin. A total of 39% of patients had <8 micturitions/24 hours by study end. The mean number of nocturia episodes/24 hours decreased by 32% and the mean volume voided/micturition increased by 31%.
Bolduc et al.[70] (2010) Solifenacin 0.15 to 0.25 mg/kg once daily	OL, PRO Children with OAB (neurogenic and non-neurogenic) who failed intensive medical and behavioral therapy	N=72 ≥3 months	Primary: Efficacy for continence, safety and tolerability Secondary: Not reported	Primary: Subjective continence improved in all cases. Patients/parents rated improvement as 100% (complete dryness in 24 patients, >90% improvement in 42 patients, and a 50 to 89% decrease in six patients). MVV and cystometric bladder capacity improved without deterioration in compliance (P<0.001). Maximum detrusor contraction pressure decreased overall as well (P<0.0001). There were no significant differences in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				response in neurogenic vs non-neurogenic cases. The mean PPBC score at baseline was 4.9 (mod-severe problems), which significantly improved to 1.8 (minor problems) at study end (P<0.0001). No adverse events were reported in 50 patients (70%). The most common adverse event was dry mouth (n=14). Secondary: Not reported
Chapple et al.[71] (2006) Solifenacin 5 to 10 mg once daily vs placebo	DB, MC, PC, RCT (Pooled analysis) Patients ≥18 years of age with OAB (≥8 micturitions/24 hours, and either a mean of ≥1 incontinence episode/24 hours or a mean of ≥1 urgency episode/24 hours)	N=2,848 (4 trials) 12 weeks	Primary: Urgency episodes (mean absolute values and median percentage values), incontinence episodes, micturition frequency, nocturia episodes/24 hours, and volume voided/micturition Secondary: Not reported	Primary: Treatment with solifenacin 5 and 10 mg resulted in a -2.9 (-66.1%) and -3.4 (-70.0%) reduction in urgency episodes, respectively, compared to a -2.0 (-40.0%) reduction with placebo (P<0.001). Treatment with solifenacin 5 and 10 mg resulted in a -1.5 (-100%) and -1.8 (-100%) reduction in incontinence episodes, respectively compared to a -1.1 (-63.6%) reduction with placebo (P<0.001). The frequency of micturition was significantly reduced with solifenacin 5 mg (-2.3; -19.4%) and 10 mg (-2.7; -22.5%) compared to placebo (-1.4; -12.0%; P<0.001). The number of nocturia episodes were significantly reduced with solifenacin 5 mg (-0.6; -35.5%) and 10 mg (-0.6; -36.4%) compared to placebo (-0.4; -25.0%; P<0.05 and P<0.001 for solifenacin 5 and 10 mg, respectively). The volume voided/micturition increased significantly with solifenacin 5 mg (32.3 mL; 19.0%) and 10 mg (42.5 mL; 25.7%) compared to placebo (8.5 mL; 3.1%; P<0.001). The most common adverse events were dry mouth, constipation, and blurred vision. The incidence of dry mouth was higher in the 10 mg solifenacin group compared to the 5 mg group. The numbers of patients discontinuing treatment due to adverse events were are follows: 4.4, 2.8, and 6.8% with placebo, solifenacin 5 mg and solifenacin 10 mg.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Abrams et al.[72] (2005) Solifenacin 5 to 10 mg once daily vs placebo	DB, MC, PC, RCT (Pooled analysis) Subgroup of patients >18 years of age with symptoms of OAB (≥8 micturitions/24 hours or ≥1 urgency episode/24 hours) who did not experience incontinence episodes at baseline	N=975 (4 trials) 12 weeks	Primary: Urgency episodes, micturition frequency, and nocturia episodes/24 hours, and volume voided/micturition Secondary: Not reported	Primary: The mean change from baseline in urgency episodes/24 hours (-3.2, -3.2, -2.1), micturition frequency/24 hours (-2.6, -2.8, -1.6), and volume voided/micturition (24.9 mL, 33.9 mL, 7.0 mL) were significantly greater with solifenacin 5 and 10 mg than placebo, respectively (all P<0.001). The mean change from baseline in nocturia episodes/24 hours was significantly greater for solifenacin 10 mg than placebo (P<0.01). The percentage of patients with resolution of urgency (36.6, 32.9, 24.6%) and normalization of micturitions (29, 34.7, 18.5%) was significantly greater with solifenacin 5 mg and solifenacin 10 mg compared to placebo, respectively (P<0.05 to P<0.001). The percentage of patients with resolution of nocturia (14.1, 20.9, 12.8%) was significantly greater with solifenacin 10 mg compared to placebo (P<0.01). Dry mouth was reported in 3.6, 10.8, and 24.4% of patients receiving placebo, 5 mg solifenacin, and 10 mg solifenacin, respectively. The incidence of constipation was 1.3, 4.0, and 12.2% with placebo, 5 mg, and 10 mg, respectively. Discontinuations due to adverse events for the solifenacin 5 mg group (2.8%) and solifenacin 10 mg group (7.8%) were comparable with or less than that of the placebo group (6.2%). Secondary: Not reported
Millard et al.[73] (2006) Solifenacin 5 to 10 mg once daily vs placebo	DB, MC, PC, RCT (Pooled analysis) Subgroup of patients ≥18 years of age with severe OAB (>3 incontinence episodes/24 hour, >8 urgency	N=2,848 (4 trials) 12 weeks	Primary: Responder rates, urgency episodes, incontinence episodes, micturition, frequency, nocturia episodes/24 hours, and volume voided/micturition	Primary: For those with >3 incontinence episodes/24 hours, the percentage of patients who were continent at study end point was significantly higher with solifenacin 5 mg (28.4%; P<0.01) and 10 mg (30.5%; P<0.001) compared to placebo (15.3%). The mean change in the number of episodes of incontinence and urgency, the frequency of micturitions and volume voided/micturition was significantly greater with solifenacin 5 mg (P<0.01) and 10 mg (P<0.001) than with placebo. For those with >8 urgency episodes/24 hours, the percentage of patients

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	episodes/24 hours, or >13 micturition episodes/24 hours)		Secondary: Not reported	with resolution of urgency at study end point was significantly higher with solifenacin 5 mg (12.4%; P<0.01) and 10 mg (13.9%; P<0.001) compared to placebo (4.6%). The mean change in the number of episodes of incontinence and urgency, the frequency of micturitions and volume voided/micturition was significantly greater with solifenacin 10 mg compared to placebo (P<0.001). For solifenacin 5 mg, the mean change for all efficacy parameters was significantly greater than placebo (P<0.05; except micturition frequency/24 hours). For those with >13 micturitions/24 hours, the percentage of patients who achieved normalization of micturition frequency (<8 micturitions/24 hours) at study end point was significantly higher with solifenacin 10 mg (13.3%; P<0.001) compared to placebo (4.0%). There was no significant difference between solifenacin 5 mg and placebo. The mean change in the number of episodes of incontinence and urgency, the frequency of micturitions and volume voided/micturition was significantly greater with solifenacin 5 mg (P<0.05) and 10 mg (P<0.001) compared to placebo. The incidence of adverse events was comparable among the treatment groups. Dry mouth, constipation, UTI, blurred vision, and nausea occurred at a higher incidence with solifenacin 5 or 10 mg than with placebo. Discontinuations due to adverse events occurred in 4.1, 7.5, and 4.8% of patients in the solifenacin 5 and 10 mg and placebo groups, respectively. Secondary: Not reported
Wagg et al.[74] (2006) Solifenacin 5 to 10 mg once daily vs placebo	DB, MC, PC, RCT (Pooled analysis) Subgroup of patients ≥65years of age with OAB (≥8 micturitions/24 hours, and either a mean of ≥1 incontinence episode/24 hours or	N=1,554 (5 trials) 12 to 40 weeks	Primary: Urgency episodes (mean absolute values and median percentage values), incontinence episodes, micturition frequency, nocturia episodes/24 hours, and volume	Primary: In the 12-weeks studies, elderly patients had significantly greater decreases in the mean number of incontinence episodes/24 hours with solifenacin 5 and 10 mg compared to placebo (P=0.013 and P<0.001, respectively). The median change in the number of incontinence episodes/24 hours was -1.0 (-92.4%) and -1.5 (-91.9%) with solifenacin 5 and 10 mg, respectively, and -0.7 (-50%) with placebo (P<0.001 for 10 mg dose). There was no significant difference between solifenacin 5 mg and placebo. A greater percentage of elderly patients who were incontinent at baseline were continent with solifenacin 5 and 10 mg (49.1 and 47.3%, respectively) compared to placebo (28.9%; P<0.001).

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	a mean of ≥1 urgency episode/24 hours)		voided/micturition Secondary: Not reported	In 12-week studies, elderly patients had significantly greater decreases in the mean number of urgency episodes/24 hours with solifenacin 5 and 10 mg compared to placebo (P<0.001). The median change in the number of urgency episodes was -2.3 (-76.1%) and -2.7 (-66.7%) with solifenacin 5 and 10 mg, respectively, and -1.5 (-33.3%) with placebo (P<0.001 for 10 mg dose). A greater percentage of elderly patients with urgency at baseline had resolution of urgency with solifenacin 5 and 10 mg (34.6 and 24.9%, respectively) compared to placebo (16.9%; P<0.001 for 5 mg and P<0.01 for 10 mg). In 12-week studies, elderly patients had significantly greater decreases in the mean number of micturitions/24 hours with solifenacin 5 and 10 mg compared to placebo (P<0.001). The median change in the number of micturitions was -2.0 (-18.3%) and -2.3 (-22%) with solifenacin 5 and 10 mg, respectively, and -1.0 (-10.3%) with placebo (P=0.008 for the 5 mg dose and P<0.001 for the 10 mg dose. In 12-week studies, elderly patients had a significantly greater increase in the mean volume voided/micturition with solifenacin 5 and 10 mg compared to placebo (P<0.001).The median change in volume voided/micturition was 27.2 (17.8%) and 40.1 (28.5%) with solifenacin 5 and 10 mg, respectively, and 6.2 (3.7%) with placebo (P<0.001). During the 40-week extension trial, elderly patients maintained improvements in the number of incontinence episodes/24 hours, urgency episodes/24 hours, and number of micturitions/24 hours, and experienced an increase in the volume voided/micturition compared to baseline. A total of 59.5% of elderly patients were continent and 37.8% reported resolution of urgency at the end of the study period. During the 12-week trials, the most commonly reported adverse events were dry mouth, constipation, and UTI. Rates of discontinuation were 5.5% in the placebo group, 4.7% in the solifenacin 5 mg group, and 9.3% in the solifenacin 10 mg group. During the 40-week extension, the most common adverse events were dry

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				mouth, constipation, and UTI. A total of 9.2% of patients discontinued therapy due to any type of adverse event. Secondary: Not reported
Kelleher et al.[75] (2005) Solifenacin 5 to 10 mg once daily vs placebo	DB, MC, PC, RCT (Pooled analysis) Patients ≥18 years of age with symptoms of OAB (≥8 micturitions/24 hours and either ≥1 urgency episode/24 hours or ≥1 incontinence episode/24 hours) for >3 months	N=3,237 (3 trials) 12 to 40 weeks	Primary: QOL data using the KHQ Secondary: Not reported	Primary: In the 12-weeks studies, there was a significant improvement in all QOL domains (except personal relationships) with solifenacin compared to placebo (P<0.05 to P<0.001). In the 40-week ES, there was a significant improvement in all QOL domains with solifenacin (17% for the general health perception and 35 to 48% for all the other domains). Secondary: Not reported
Herschorn et al.[76] (2010) Solifenacin 5 mg once daily vs oxybutynin IR 5 mg three times daily	DB, MC, RCT Patients ≥18 years of age with OAB symptoms (>1 urgency episode per 24 hours and ≥8 micturitions per 24 hours for ≥3 months)	N=132 8 weeks	Primary: Incidence and severity of dry mouth reported after direct questioning Secondary: Three-day diary changes in urgency, frequency, incontinence, nocturia, voided volume, PPBC, and the OAB-q	Primary: Significantly fewer patients on solifenacin reported dry mouth after direct questioning compared to oxybutynin IR (35 vs 83%; 95% CI, 33 to 62; P<0.0001). Additionally, in those reporting dry mouth, solifenacin was associated with significantly lower severity than that of oxybutynin IR (P=0.001). Secondary: Patients in both groups showed improvement in bladder diary documented urgency, incontinence, frequency, nocturia, and VVPM from baseline to end of treatment. PPBC and OAB-q scores also significantly improved with both groups. Overall adverse events were significantly fewer with solifenacin than with oxybutynin IR (72 vs 92%; P=0.003). Besides dry mouth, the incidence of other adverse events was 59% for solifenacin and 70% for oxybutynin (P=0.17). Fewer patients that received solifenacin withdrew from the study due to

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				dry mouth compared to oxybutynin IR (3 vs 19%; P=0.003).
Herschorn et al.[77] (2011) Solifenacin 5 mg once daily vs oxybutynin IR 5 mg three times daily	DB, MC, RCT (Subgroup analysis) Patients ≥18 years of age with OAB symptoms (>1 urgency episode per 24 hours and ≥8 micturitions per 24 hours for ≥3 months)	N=132 8 weeks	Primary: Adverse events in patients ≤ 65 years of age and in those >65 years of age Secondary: Not reported	Primary: In both age groups, solifenacin 5 mg/day was associated with numerically fewer episodes of dry mouth compared to oxybutynin IR. Patients receiving oxybutynin IR were >8 times more likely to have dry mouth than those receiving solifenacin, regardless of age (OR, 8.88; 95% CI, 3.91 to 20.17). Additionally, oxybutynin IR caused more severe dry mouth compared to solifenacin. The incidence and severity of other adverse events with solifenacin were similar between age groups. Discontinuation of oxybutynin IR treatment occurred more often than solifenacin, irrespective of age. Although the numbers were low, there was a higher incidence of constipation and fatigue in patients >65 years who received solifenacin compared to oxybutynin IR. Secondary: Not reported
Hsiao et al.[78] (2011) Solifenacin 5 mg once daily vs tolterodine ER 4 mg once daily	OL, RCT Women ≥18 years who had ≥3 month history of OAB symptoms (including urgency, urinary frequency, nocturia or urge incontinence) and a mean of ≥8 micturitions per 24 hours	N=48 12 weeks	Primary: Changes in total voided volume, VVPM, and the episodes of micturition, urgency, incontinence and nocturia in 24 hours Secondary: Not reported	Primary: In the solifenacin group, there was a decrease in the PPBC and the micturition, urgency and incontinence episodes per 24 hours and the VVPM increased at most follow-up visits. In the tolterodine group, there was a decrease in the PPBC and the nocturia episodes per 24 hours, but the heart rate increased at most follow-up visits. There were no between- or within-group differences in the changes of the number of episodes of micturition, urgency, incontinence, nocturia or total voided volume per 24 hours or VVPM at weeks four, eight or 12. Compared to baseline, the volume voided was significantly increased after solifenacin treatment (P=0.04). The strong desire to void and pad test result improved after tolterodine treatment (P=0.02 and P=0.03, respectively). At 12 weeks, there were no between-group differences in changes of urodynamic data and pad test results. Changes in the heart rate differed significantly between these two groups at visit two (solifenacin vs tolterodine ER, -4.3; 95% CI, -7.2 to -1.3 vs

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				3.8; 95% CI, 0.3 to 7.3; P=0.02 and visit three (-3.2; 95% CI, -7.4 to 1.0 vs 4.8; 95% CI, 1.2 to 8.3; P=0.03). There was no difference in the number of patients who experienced adverse events between groups (P=0.23). Ten patients in the solifenacin group experienced adverse events, including dry mouth (n=7), constipation (n=3), palpitations (n=1), dizziness (n=1) and fatigue (n=1). Five patients in the tolterodine group experienced adverse events, including dry mouth (n=3), constipation (n=1), and palpitations (n=1). Secondary: Not reported
Armstrong et al[79] (2007) Oxybutynin XL 10 mg once daily vs tolterodine LA 4 mg once daily vs tolterodine IR 2 mg twice daily	MA of 2 studies Present study is a MA of the OPERA and OBJECT studies (Appell et al[57]and Diokno et al[58])	N=1,168 12 weeks	Primary: Adverse events Secondary: Not reported	Primary: Gastrointestinal adverse events occurred in 41.8, 36.3 and 45.1% of patients receiving oxybutynin XL, tolterodine LA and tolterodine IR therapy, respectively (P value not reported). The most common adverse event was dry mouth, occurring in 29.3, 22.3 and 33.2% of patients receiving oxybutynin XL, tolterodine LA and tolterodine IR therapy, respectively (P value not reported). The incidence of nervous system adverse events in the oxybutynin XL, tolterodine LA, and tolterodine IR groups was comparable (10.2 vs 8.3 vs 10.9%, respectively; P value not reported). Most adverse events were mild or moderate in intensity. Severe drug-related adverse events occurred in 4.3, 1.5 and 2.6% of patients in the oxybutynin XL, tolterodine LA and tolterodine IR groups, respectively. The most common adverse event resulting in early discontinuation from the study was dry mouth, with 1.2, 1.0 and 1.6% of patients discontinuing treatment with oxybutynin XL, tolterodine LA and tolterodine IR, respectively (P value not reported). Secondary: Not reported

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Madhuvrata et al[80] (2012) Fesoterodine 4 to 8 mg once daily vs oxybutynin IR 2.5 to 5 mg twice daily to four times daily vs oxybutynin XL 5 to 20 mg once daily vs tolterodine IR 1 to 2 mg twice daily vs tolterodine LA 2 to 4 mg once daily vs trospium IR 20 mg twice daily vs solifenacin 5 to 10 mg once daily	MA of 86 studies Patients with a symptomatic diagnosis of OAB syndrome with or without a urodynamic diagnosis of detrusor overactivity	N=31,249 Up to 52 weeks	Primary: Condition-specific QOL and psychosocial measures Secondary: Patient observations, quantification of symptoms, clinician's measures, socioeconomics	Primary: There was no significant difference between tolterodine and oxybutynin with regard to QOL (SMD, -0.00; 95% CI, -0.18 to 0.18). The results from three studies reported a statistically significant improvement in QOL for patients treated with solifenacin compared to tolterodine (SMD, -0.12; 95% CI, -0.23 to -0.01). Treatment with fesoterodine was associated with a significant improvement in QOL compared to tolterodine LA (SMD, -0.20; 95% CI, -0.27 to -0.14). Secondary: There was no statistically significant difference between tolterodine and oxybutynin with regard to the proportion of patients reporting a symptomatic cure or improvement (RR, 1.01; 95% CI, 0.93 to 1.11), fewer leakage episodes or voids over 24 hours (WMD, 0.33; 95% CI, -0.08 to 0.73). There was no difference in patient reported cure or improvement between patients receiving oxybutynin or trospium (RR, 1.00; 95% CI, 0.90 to 1.11). Moreover, there was no significant difference between the treatments with regard to cystometric capacity or residual bladder volume. Trospium was associated with fewer treatment withdrawals (RR, 0.66; 95% CI, 0.48 to 0.91) and a lower risk of dry mouth compared to oxybutynin (RR, 0.64; 95% CI, 0. 52 to 0.77). Compared to oxybutynin, tolterodine was associated with significantly lower rates of withdrawal due to adverse events (RR, 0.52; 95% CI, 0.40 to 0.66) and a lower incidence of dry mouth (RR, 0.65; 95% CI, 0.60 to 0.71). Treatment with solifenacin was associated with a higher patient report of cure or improvement compared to tolterodine (RR, 1.25; 95% CI, 1.13 to 1.39). There was a statistically significant reduction in the number of leakage

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vs placebo				episodes/24 hours (WMD, -0.30; 95% CI, -0.53 to -0.08 and urgency episodes/24 hours with solifenacin compared to tolterodine (WMD, -0.43; 95% CI, -0.74 to -0.13). Withdrawal rates due to adverse events and the incidence of dry mouth were similar between solifenacin and tolterodine; however, following the exclusion of one study with tolterodine LA, dry mouth rates were significantly lower with solifenacin compared to tolterodine LA (RR, 0.69; 95% CI, 0.51 to 0.94). Fesoterodine treatment was associated with a higher rate of patient reported cure or improvement compared to tolterodine LA (RR, 1.11; 95% CI, 1.06 to 1.16). Compared to tolterodine LA, patients taking fesoterodine reported significant reductions in leakage episodes (WMD, -0.19; 95% CI, -0.30 to -0.09), frequency (WMD, -0.27; 95% CI, -0.47 to -0.06) and urgency episodes/24 hours (WMD, -0.44; 95%CI, -0.72 to -0.16). Patients receiving treatment with fesoterodine had a higher risk of withdrawal due to adverse event compared to tolterodine LA treatment (RR, 1.45; 95% CI, 1.07 to 1.98) and higher risk of dry mouth (RR, 1.80; 95% CI, 1.58 to 2.05). Similar improvements in leakage episodes and micturitions/24 hours were reported for 1, 2 and 4 mg doses of tolterodine IR administered twice daily. There was a higher incidence of dry mouth with both the 2 and 4 mg doses relative to the lower doses of tolterodine IR. Fesoterodine 8 mg was associated with a greater clinical efficacy (patient reported cure, leakage episodes, micturition/24 hours) compared to the 4 mg fesoterodine. There was no difference in efficacy between the 4 mg and 12 mg doses, although higher dose was associated with a greater incidence of dry mouth. The 8 mg strength was also associated with a higher risk of dry mouth compared to fesoterodine 4 mg. Both tolterodine LA and oxybutynin XL were associated with a lower risk

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				of dry mouth compared to their respective IR formulations; however, no significant differences in cure, improvement, leakage episodes, micturitions/24 hours, or withdrawal events were reported between. There was a lower risk of dry mouth with tolterodine LA compared to oxybutynin XL (RR, 0.75; 95% CI, 0.59 to 0.95). There was no difference in the incidence of dry mouth between transdermal oxybutynin and tolterodine LA, although there was a higher withdrawal rate with transdermal oxybutynin due to a skin reaction at the transdermal patch site at 12 weeks.
Ho et al.[81] (2010) Solifenacin 5 mg once daily vs tolterodine ER 4 mg once daily	OL, PRO, RCT Male or female patients ≥18 years of age with OAB symptoms (urinary frequency, urgency, or urge incontinence) ≥3 months, who experienced frequency (defined as ≥8 micturitions per 24 hours)	N=75 12 weeks	Primary: Change from baseline to endpoint for the mean number of micturitions per 24 hours Secondary: Change from baseline to endpoint for MVV per micturition, mean urgency episode per 24 hours, mean incontinence per 24 hours, PPBC, patient and physician assessment of treatment benefit	Primary: Compared to baseline, both treatment groups showed significant improvements in reducing mean micturition numbers per 24 hours from week four. At week 12, the mean changes were not significantly different between solifenacin and tolterodine (-2.56 vs -2.44; P=0.58). Secondary: Both groups significantly improved urgency and incontinence episodes per 24 hours. At week 12, the mean changes from baseline were not significant for urgency episodes between solifenacin and tolterodine (-1.7 vs -1.15; P=0.37), nor were the mean changes for incontinence episodes (-2.79 vs -4.67; P=0.28). A significant increase in MVV per micturition was only observed in the solifenacin group (27.61±51.74 mL). PPBC was significantly improved with both groups compared to baseline. At week 12, the mean changes from baseline were -1.4 and -1.4 in the solifenacin and tolterodine groups, respectively. The difference between solifenacin and tolterodine was not statistically significant. Patient and physician assessment of treatment benefit showed that improvements were made in both groups compared to baseline, but not between each other. The most common adverse events for solifenacin and tolterodine were dry mouth (18.0 vs 8.3%; P=0.31) and constipation (12.8 vs 2.8%; P=0.2).

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Chapple et al.[82] (2005) Solifenacin 5 to 10 mg once daily vs tolterodine ER 4 mg once daily	DB, MC, RCT Patients ≥18 years of age with OAB symptoms (≥8 micturitions/24 hours, ≥1 incontinence episode/24 hours, or ≥1 urgency episode/24 hours) for ≥3 months	N=1,200 12 weeks	Primary: Micturition frequency Secondary: Urgency episodes, urge incontinence, total incontinence, nocturia, proportion of patients who experienced a 50% reduction in incontinence episodes, pad usage, and QOL using a six-point categorical scale to assess perception of bladder condition	Primary: The mean number of micturitions was reduced with solifenacin (-2.45) compared to treatment with tolterodine (-2.24; P=0.004 for non inferiority). Secondary: Treatment with solifenacin led to a reduction in the number of urgency episodes/24 hours (-2.85) compared to treatment with tolterodine (-2.42; P<0.05). Treatment with solifenacin led to a reduction in the number of urge incontinence episodes/24 hours (-1.42) compared to treatment with tolterodine (-0.83; P<0.01). Treatment with solifenacin led to a reduction in the number of total incontinence episodes/24 hours (-1.60) compared to treatment with tolterodine (-1.11; P<0.01). There was no significant difference in nocturia among the treatment groups (P=0.730). Approximately 74% of patients receiving solifenacin who were incontinent at baseline experienced ≥50% reduction in incontinence episodes compared to 67% of patients receiving tolterodine (P=0.021). The percentage of patients who were incontinent at baseline who became continent at study end point was 59% (solifenacin) and 49% (tolterodine; P=0.006). The mean volume voided/micturition increased with solifenacin (38 mL) compared to tolterodine (31 mL; P=0.010). Solifenacin decreased the number of incontinence pads used compared to tolterodine (P=0.0023). Patient-reported perception of bladder condition was significantly improved with solifenacin compared to tolterodine (P=0.006). Approximately 5.9% of patients receiving solifenacin and 7.3% of patients

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				receiving tolterodine discontinued treatment (for any reason); 1.2% and 2.0% discontinued therapy due to insufficient therapeutic response with solifenacin and tolterodine, respectively. The most common adverse events were dry mouth, constipation and blurred vision. The percentage of patients discontinuing treatment due to adverse events was similar between the treatment groups (3.5% of patients receiving solifenacin and 3.0% of patients receiving tolterodine). A total of 1.2 and 2.0% of patients discontinued therapy due to an insufficient therapeutic response with solifenacin and tolterodine, respectively.
Chapple et al.[83] (2004) Solifenacin 2.5 to 20 mg once daily vs tolterodine IR 2 mg twice daily vs placebo	DB, PC, RCT Patients 18 to 80 years of age with OAB and urodynamic evidence of detrusor overactivity (>8 voids/24 hours and >3 episodes of incontinence or urgency)	N=225 6 weeks	Primary: Number of voids/24 hours Secondary: Volume voided/ void; incontinence episodes/24 hours; urgency episodes/24 hours; and total sum score of Contilife items 1 to 27, sum scores of the five Contilife domains (i.e., daily activities, effort, self-image, emotional consequences, and sexuality), and overall Contilife QOL score	Primary: The mean change in number of voids/24 hours was significantly lower with solifenacin 5 mg (-2,21), 10 mg (-2.47) and 20 mg (-2.75) compared to placebo (-1.03; all P<0.05). There was no significant difference with tolterodine (-1.79) compared to placebo (P=NS). Secondary: The mean volume voided/void was significantly greater for solifenacin 5 mg, 10 and 20 mg than for placebo (all P<0.01). There was no significant difference with tolterodine compared to placebo. There was no significant difference in the mean number of incontinence episodes/24 hours with solifenacin or tolterodine compared to placebo. There was no significant difference in the number of urgency episodes/24 hours with solifenacin or tolterodine compared to placebo. Treatment with solifenacin led to significant improvements over baseline based on the results of the Contilife sum score QOL analysis compared to placebo. There was no significant difference with tolterodine compared to placebo. Treatment with solifenacin led to significant improvements in the daily life activities (all groups; P<0.01), self-image (10 and 20 mg; P<0.05), emotional consequences (5, 10 and 20 mg; P<0.05) and sexuality (10 and 20 mg; P<0.05) compared to placebo. Tolterodine resulted in significant improvements in the daily life activities domain only compared to placebo

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(P<0.05). Solifenacin 10 and 20 mg and tolterodine produced significant improvements over placebo in the Contilife overall QOL score (P<0.05). The most frequently reported adverse event was dry mouth, followed by constipation and blurred vision. The frequency of dry mouth was highest among patients receiving solifenacin 20 mg (38%), tolterodine 2 mg (24%) and solifenacin 5 and 10 mg (14% each). Constipation was reported in 19% of patients taking solifenacin 20 mg.
Chapple et al.[84] (2004) Solifenacin 5 to 10 mg once daily vs tolterodine IR 2 mg twice daily vs placebo	DB, MC, RCT Patients ≥18 years of age with symptoms of OAB (including urgency, urge incontinence, or frequency) for ≥3 months (≥8 voids/24 hours, ≥3 episodes of urgency and/or ≥3 episodes of incontinence)	N=1,081 12 weeks	Primary: Urgency episodes, all incontinence episodes, urge incontinence episodes, voids/24 hours and voided volume/void Secondary: Not reported	Primary: There was a significant decrease in the mean number of urgency episodes/24 hours with solifenacin 5 and 10 mg (-52% and -55%, respectively) compared to placebo (-33%; both P<0.001). There was no significant difference in urgency episodes/24 hours between tolterodine (-38%) and placebo (P=0.0511). Direct comparison of solifenacin 5 and 10 mg with tolterodine resulted in estimated differences of - 0.791 and - 1.015 (95% CI, -1.434 to -0.148, and -1.659 to -0.370), respectively. There was a significant decrease in urge incontinence episodes/24 hours with solifenacin 5 mg (-1.41; P=0.002) and 10 mg (-1.36; P=0.0028) compared to placebo (-0.62). There was no significant difference in urge incontinence episodes/24 hours between tolterodine (-0.91) and placebo (P=0.2390). There was no significant difference in urge incontinence episodes/24 hours between solifenacin and tolterodine (5 mg, -0.487; 95% CI, -0.988 to 0.014 and 10 mg, -0.436; 95% CI, -0.921 to 0.048). There was a significant decrease in all incontinence episodes/24 hours with solifenacin 5 mg (-1.42; P=0.008) and 10 mg (-1.45; P=0.0038) compared to placebo (-0.76). There was no significant difference in all incontinence episodes/24 hours between tolterodine (-1.14) and placebo (P=0.1122). There was no significant difference in all incontinence episodes/24 hours between solifenacin and tolterodine (5 mg, -0.276; 95% CI, -0.761 to 0.208 and 10 mg, -0.316; 95% CI, -0.786 to 0.164). There was a significant decrease in mean number of voids/24 hours with

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				solifenacin 5 mg (-2.19, -17%; P<0.001), solifenacin 10 mg (-2.61, -20%; P<0.001) and tolterodine (- 1.88, -15%; P=0.0145) compared to placebo (-1.20, - 8%). Direct comparison of solifenacin 5 and 10 mg with tolterodine resulted in estimated differences of -0.312 and -0.737 (95% CI -0.844 to 0.219, and -1.269 to -0.204). There was a significant increase in mean volume voided/void with solifenacin 5 mg (32.9 mL, +25.1%), solifenacin 10 mg (39.2 mL, +29.0%), and tolterodine (24.4 mL, +20.3%) compared to placebo (7.4 mL; all, P<0.001). There was no significant difference in mean volume voided/void between solifenacin and tolterodine (5 mg, 8.4 mL; 95% CI, 0.496 to 16.34 and 10 mg, 14.8 mL; 95% CI, 6.855 to 22.72). The percentages of patients discontinuing treatment for an adverse event were 3.7% in the placebo group, 3.2% in the solifenacin 5 mg group, 2.6% in the solifenacin 10 mg group, and 1.9% in the tolterodine group. The incidence of dry mouth was lowest with solifenacin 5 mg (14%). Constipation was reported in 7.2 and 7.8% of patients treated with solifenacin 5 and 10 mg, respectively, in 2.6% of patients treated with tolterodine and in 1.9% of placebo patients. Blurred vision was reported in 3.6% of patients receiving solifenacin 5 mg, 5.6% receiving solifenacin 10 mg, 1.5% receiving tolterodine, and 2.6% receiving placebo. Secondary: Not reported
Yamaguchi et al.[85] (2011) Solifenacin 2.5 mg plus tamsulosin 0.2 mg once daily (TAM+SOL 2.5) vs solifenacin 5 mg plus tamsulosin 0.2	DB, MC, PC, RCT Men ≥50 years of age with LUTS and residual OAB symptoms despite treatment with tamsulosin for ≥6 weeks, ≥2 urgency episodes per 24 hours in a 3-day bladder diary, Qmax	N=638 12 weeks	Primary: Mean change in urgency episodes per 24 hours Secondary: Mean changes in micturitions, nocturia episodes, urgency incontinence episodes, IPSS,	Primary: The mean number of urgency episodes per 24 hours decreased by 2.2 and 2.4 episodes in the TAM+SOL 2.5 and TAM+SOL 5 groups, respectively. TAM+SOL 5 showed a significant improvement in urgency episodes compared to TAM+PBO (P=0.049). Secondary: The number of micturitions per 24 hours was reduced by 1.27 episodes in the TAM+SOL 2.5 group and by 1.06 episodes in TAM+SOL 5 groups, and both of these were significantly better than TAM+PBO (0.22 episodes; P<0.01).

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mg once daily (TAM+SOL 5) vs tamsulosin 0.2 mg once daily plus placebo (TAM+PBO)	≥5 mL/s, and PVR volume <50 mL		IPSS-QOL, and OABSS	Compared to TAM+PBO, TAM+SOL 2.5 and TAM+SOL 5 did not significantly reduce the number of nocturia episodes and urgency incontinence. IPSS storage symptom score was significantly improved in both solifenacin groups compared to placebo. IPSS total score, voiding symptom score, post-micturition symptom score, or QOL were no significantly better compared to placebo. For OABSS, both solifenacin groups significantly improved the total score, daytime frequency score, urgency score, and urgency incontinence score compared to placebo. The most common adverse events were dry mouth (6.2% for TAM+SOL 2.5 vs 11.3% for TAM+SOL 5), constipation (3.8% for TAM+SOL 2.5 vs 10.3% for TAM+SOL 5), increase in PVR ≥50 mL (2.9% for TAM+SOL 2.5 vs 6.1% for TAM+SOL 5), abdominal discomfort (2.4% for TAM+SOL 2.5 vs 1.9% for TAM+SOL 5), and creatinine phosphokinase increase (1.9% for TAM+SOL 2.5 vs 2.3% for TAM+SOL 5). A total of four patients in TAM+SOL 5 had urinary retention requiring temporary cauterization.
Kreder et al.[86] (2002) Tolterodine ER 4 mg once daily	ES, OL Patients ≥18 years of age with urinary frequency (≥8 micturitions/24 hours), urge incontinence (≥5 incontinence episodes/week) and urgency for ≥6 months	N=1,077 12 months	Primary: Safety and tolerability Secondary: Efficacy	Primary: The most common adverse events were autonomic nervous system disorders (13.2%), gastrointestinal disorders (11.4%), general body disorders (14.5%), respiratory disorders (9.8%), urinary disorders (9.1%) and musculoskeletal disorders (6.0%). The most frequently report adverse event was dry mouth, which occurred in 12.9% of patients. Approximately 10% of patients withdrew from the study due to adverse events. The most common adverse events leading to withdrawal were dry mouth (1.8%), headache (0.8%), abdominal pain (0.8%), dizziness (0.7%), UTI (0.7%), dyspepsia (0.6%), constipation (0.6%), xerophthalmia (0.5%), and micturition disorders (0.5%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: The number of urge incontinence episodes/week was significantly decreased with tolterodine compared to baseline (median change, -83%). The number of micturitions/24 hours significantly decreased with tolterodine compared to baseline (median change, -21%). The change in volume voided/micturition significantly increased with tolterodine compared to baseline (median change, 25%). Approximately 75% of patients who received tolterodine perceived improvement after 12 months of therapy.
Takei et al.[87] (2005) Tolterodine ER 4 mg once daily	ES, OL Japanese patients ≥20 years of age with OAB symptoms including urinary urgency, urinary frequency (≥8 micturitions/24 hours) and urge incontinence (≥5 episodes/week) for ≥6 months	N=188 12 months	Primary: Safety and tolerability Secondary: Efficacy	Primary: The most common adverse event was dry mouth (33.5%). The incidence decreased during the course of the OL extension (24.5% during the first three months vs 4.3% during the six to 12-month periods). Approximately 23% of patients withdrew prematurely due to adverse events (10.0%), lack of efficacy (8.0%), consent withdrawal (3.7%), lost to follow-up (0.5%) and protocol violation (0.5%). Secondary: The number of incontinence episodes/week was decreased with tolterodine (mean change, -77.2%). The number of micturitions/24 hours significantly decreased with tolterodine (mean change, -21.3%; P<0.0001). The change in volume voided/micturition significantly increased with tolterodine (mean change, 19.6%; P<0.0001).
Choo et al.[88] (2008) Tolterodine ER 4 mg once daily	OL Patients ≥18 years of age with OAB who had urinary frequency (≥8 micturitions/24	N=60 12 weeks	Primary: Rate of PGA by a visual analogue scale Secondary: Changes in	Primary: The median rate of PGA was: frequency (60%; 95% CI, 46.9 to 63.6), urgency (60%; 95% CI, 46.2 to 64.9), urge incontinence (80%; 95% CI, 34.2 to 80.0), nocturia (50%; 95% CI, 39.4 to 57.6) and tenesmus (30%; 95% CI, 25.4 to 52.2). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	hours) and urgency (≥2 episodes/24 hours) with or without urgency incontinence		symptom severity, voiding diary and PPBC, and willingness to continue treatment	The median percentage reduction in symptom severity was as follows: frequency (45%; 95% CI, 36.2 to 54.4), urgency (55%; 95% CI, 40.1 to 60.4), urgency incontinence (71%; 95% CI, 39.2 to 76.8), nocturia (52%; 95% CI, 40.2 to 59.7) and tenesmus (26%; 95% CI, 16.9 to 50.4). Patients reported that the most troublesome symptoms were daytime frequency (50.0%), nocturia (17.9%), urgency incontinence (16.1%), urgency (10.7%) and tenesmus (5.4%). Frequency (-2.7), urgency (-4.2), urgency incontinence (-1.0), and nocturia (-0.7) were significantly reduced with tolterodine (all, P<0.01). The mean voided volume significantly increased with tolterodine (32 mL; P=0.05). Approximately 90% of patients experienced an improvement of at least one point in their bladder condition, and 62.5% reported improvements of at least two points on the PPBC questionnaire. A total of 73.2% of patients wished to continue treatment after receiving three months of treatment. The most common adverse events were dry mouth (21.7%), constipation or indigestion (10.0%), headache (5.0%), UTI (3.3%) and peripheral edema (1.7%).
Van Kerrebroeck et al.[89] (2001) Tolterodine ER 4 mg once daily vs tolterodine IR 2 mg twice daily vs	DB, MC, PC, RCT Patients ≥18 years of age with urinary frequency (≥8 micturitions/24 hours) and urge incontinence (≥5 incontinence episodes/week) for ≥6 months	N=1,529 12 weeks	Primary: Incontinence episodes/week, number of micturition/24 hours, volume voided/micturition, and the number of pads used/24 hours Secondary: Not reported	Primary: The mean change in incontinence episodes/week was significantly better with tolterodine ER (-11.8; P=0.0001) and tolterodine IR (-10.6; P=0.0005) compared to placebo (-6.9). The median percentage reductions in incontinence episodes/week were: tolterodine ER, 71%; tolterodine IR, 60%; and placebo, 33%. Tolterodine ER was 18% more effective than tolterodine IR (P<0.05). The mean change in number of micturitions/24 hours was significantly better with tolterodine ER (-1.8; P=0.0047) and tolterodine IR (-1.7; P=0.0079) compared to placebo (-1.2). The mean change in volume voided/micturition was significantly greater with tolterodine ER (34 mL; P=0.0001) and tolterodine IR (29 mL;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				P=0.0001) compared to placebo (14 mL). The mean change in number of pads used/24 hours was significantly lower with tolterodine ER (-0.5; P=0.0145) and tolterodine IR (-0.5; P=0.0035) compared to placebo (-0.2). The most common adverse events in all treatment groups were dry mouth, constipation, and headache. With the exception of dry mouth, the incidence of adverse events was comparable between active treatment and placebo. The rate of dry mouth was 23, 30, and 8% for tolterodine ER, tolterodine IR, and placebo, respectively. Patients receiving tolterodine ER had 23% less dry mouth than those taking tolterodine IR (P=0.02). Discontinuation rates due to adverse events were similar in all the treatment groups (tolterodine ER, 5%; tolterodine IR, 5%; placebo, 6%). Secondary: Not reported
Swift et al.[90] (2003) Tolterodine ER 4 mg once daily vs tolterodine IR 2 mg twice daily vs placebo	DB, MC, PC, RCT (Subgroup analysis) Women ≥18 years of age with urinary frequency (≥8 micturitions/24 hours) and urge incontinence (≥5 incontinence episodes/week) for ≥6 months	N=1,235 12 weeks	Primary: Incontinence episodes/week, number of micturition/24 hours, volume voided/micturition, and the number of pads used/24 hours Secondary: Not reported	Primary: The mean change in incontinence episodes/week was significantly better with tolterodine ER (-11.8; P=0.001) and tolterodine IR (-10.1; P=0.001) compared to placebo (-7.2). The difference between tolterodine ER and tolterodine IR was significant (P=0.036). The median percentage reductions in incontinence episodes/week were: tolterodine ER, 71%; tolterodine IR, 57%; and placebo, 33%. The mean change in number of micturitions/24 hours was significantly better with tolterodine ER (-1.9; P=0.001) and tolterodine IR (-1.7; P=0.005) compared to placebo (-1.2). There was no significant difference between tolterodine ER and tolterodine IR. The mean change in volume voided/micturition was significantly greater with tolterodine ER (37.9 ml; P=0.001) and tolterodine IR (32.5 mL; P=0.001) compared to placebo (13.3 mL). There was no significant difference between tolterodine ER and tolterodine IR. The mean change in number of pads used/24 hours was significantly lower with tolterodine ER (-0.6; P=0.001) and tolterodine IR (-0.5; P=0.001)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				compared to placebo (-0.2). There was no significant difference between tolterodine ER and tolterodine IR. Dry mouth, constipation, headache and UTI were the most common adverse events in all treatment groups. With the exception of dry mouth, the incidence of adverse events was comparable between active treatment and placebo. There was no significant difference in dry mouth with tolterodine ER or tolterodine IR (P=0.06). Discontinuation rates due to adverse events were similar in all the treatment groups (tolterodine ER, 5%; tolterodine IR, 5%; placebo, 6%). Secondary: Not reported
Homma et al.[91] (2003) Tolterodine ER 4 mg once daily vs oxybutynin IR 3 mg three times daily vs placebo	AC, DB, PC, RCT, Patients ≥20 years of age with OAB and symptoms of urinary urgency, urinary frequency (≥8 micturitions/24 hours) and urge incontinence (≥5 episodes/week) for ≥6 months	N=608 12 weeks	Primary: Incontinence episodes/week Secondary: Voids/24 hours and mean volume voided/void, median number of incontinence pads used/24 hours, patient perception of bladder condition, patient perception of urgency, and QOL using the KHQ	Primary: The number of incontinence episodes/24 hours was significantly decreased with tolterodine (median -78.6%; P=0.0027) and oxybutynin (median -76.5%; P=0.0168) compared to placebo (-46.4%). There was no significant difference between tolterodine and oxybutynin (P=0.4469). Secondary: The number of voids/24 hours decreased with tolterodine (-2.0; P<0.001) and oxybutynin (-2.1; P=0.0114) compared to placebo (-1.1). There was no significant difference among the treatment groups (P=0.3132). The volume voided/void increased significantly with tolterodine (17.2 mL; P=0.0086) and oxybutynin (22.3 mL; P<0.001) compared to placebo (6.6 mL). The number of pads used/24 hours was not significantly different among the treatment groups. Approximately 72% of patients treated with tolterodine and 73% treated with oxybutynin perceived improvement after 12 weeks of treatment compared to 59% of patients treated with placebo. The difference between tolterodine and placebo was NS (P=0.515). There was no significant difference between tolterodine and oxybutynin (P=0.9394).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Significantly more patients reporting at least some benefit with tolterodine (79%; P=0.0091; little benefit 36%; much benefit, 42%) and oxybutynin (81%; P<0.001; little benefit 29%; much benefit 53%) than with placebo (66%; little benefit 40%; much benefit 25%). There was no significant difference between tolterodine and oxybutynin in the assessment of treatment benefit (P=0.2240). Treatment with tolterodine and oxybutynin resulted in significantly greater mean reductions in both the incontinence impact domain and role limitation domain scores (KHQ questionnaire) compared to placebo. There was no significant difference between the improvements with tolterodine and oxybutynin for either domain. Tolterodine and oxybutynin were associated with improvements in other KHO domains, including physical limitations, social limitations, personal relationships, sleep/energy, severity measures, and the severity of urinary symptoms compared to placebo. The differences in improvements between tolterodine and oxybutynin were NS for any of these domains. Dry mouth was the most common adverse event reported with tolterodine (33.5%), oxybutynin (53.7%) and placebo (9.8%). Dry mouth was more common in patients receiving oxybutynin than tolterodine (P<0.001). Other adverse events occurring in >5% of patients were constipation, abdominal pain/tenderness, dyspepsia, difficulty in voiding and headache. Eye disorders occurred in significantly more patients receiving oxybutynin than tolterodine (P<0.0383). The incidence of nervous system disorders was lower in the tolterodine group (8.4%) than in the oxybutynin group (12.7%) or placebo group (11.5%). More patients on oxybutynin withdrew due to adverse events compared to tolterodine (P<0.001).
Sussman et al.[92] (2002) Trial 1 Tolterodine ER 2 to 4 mg once daily	OL, RCT Patients ≥18 years of age with OAB and symptoms of urinary frequency and urgency with or	Trial 1 N=669 8 weeks Trial 2 N=620	Primary: Patient perception of bladder condition and patient assessment of treatment benefit	Primary: Seventy percent of patients in the tolterodine 4 mg group perceived an improvement in their bladder condition compared to 60% in the tolterodine 2 mg group, 59% in the oxybutynin 5 mg group, and 60% in the oxybutynin10 mg group (all P<0.01 vs tolterodine 4 mg). There was a greater percentage of patients who reported an improved

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Trial 2 Oxybutynin ER 5 to 10 mg once daily	without urge incontinence	8 weeks	Secondary: Physician assessment of treatment benefit	bladder condition with tolterodine 4 mg compared to oxybutynin 10 mg (77 vs 65%; P<0.01) in those whose perception of bladder condition was moderate to severe at baseline. There was no significant difference in the perception of their bladder condition among treatment-naïve patients (P=0.11) and those who had received prior antimuscarinic therapy (P=0.11). Secondary: There was no significant difference in patient assessment or physician's assessment of treatment benefit between tolterodine and oxybutynin. Dry mouth was dose-dependent in both trials (tolterodine 2 mg vs tolterodine 4 mg; P=0.09; oxybutynin 5 mg vs oxybutynin 10 mg; P=0.05). Patients treated with tolterodine 4 mg reported a significantly lower severity of dry mouth compared to oxybutynin 10 mg (P=0.03).
Chung et al.[93] (2010) Tolterodine ER 4 mg once daily and dutasteride 0.5 mg once daily	OL Men ≥45 years of age on dutasteride 0.5 mg for at least 6 months who failed alpha-blocker therapy, prostate >30 g, an IPSS ≥12, IPSS QOL item ≥3, ≥8 voids per 24 hours, ≥3 urgency episodes per 24 hours with or without urgency incontinence, and self-rated bladder condition on patient perception of bladder condition of hours at least "some	N=51 12 weeks	Primary: Change in frequency, nocturnal OAB micturition, IPSS, Qmax, change in PVR, adverse events, and episodes of urinary retention requiring a catheter Secondary: Not reported	Primary: Tolterodine ER significantly reduced frequency and urgency. Specifically, tolterodine reduced 24 hours micturition frequency (-3.2; P<0.02), OAB episodes (19.2%; P<0.03), severe OAB episodes (71.4%; P<0.05), and nighttime voiding (-0.9; P<0.003). Patients reported a reduction in 24 hours frequency from baseline 11.9 episodes to 10.2 episodes after three months of dutasteride, which further decreased to 8.7 after 12 weeks of tolterodine ER. IPSS decreased with the initial addition of dutasteride (19.3 to 14.3) and further decreased with the addition of tolterodine ER (7.1; P<0.001). There were no significant decreases in Qmax with the addition of tolterodine ER and tolterodine ER did not significantly increase PVR. Additionally, zero patients required catheterization. Four patients (7.5%) experienced dry mouth, one patient (2%) had constipation, and sexual function decreased in two patients (3.9%). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	moderate bother"			Not reported
Chung et al.[94] (2011) Tolterodine ER 4 mg once daily plus doxazosin 4 mg and/or dutasteride 0.5 mg once daily vs doxazosin 4 mg and/or dutasteride 0.5 mg once daily	OS, PRO, RCT Male patients ≥70 years of age with an IPSS score >8 and a storage subscore of >5, QOL index score >3, total prostate volume >20 mL, Qmax <15 mL/second, and with urodynamic confirmed BPH/BOO	N=153 12 months	Primary: Improvement in IPSS subscores (voiding and storage) at 12 months Secondary: Change in PVR volume, and QOL-I	Primary: The mean IPSS-voiding (8.5 to 2.88 with tolterodine [P<0.001], 9.83 to 4.78 without tolterodine [P<0.001]), IPSS-storage (9.44 to 5.18 with tolterodine [P<0.001], 8.34 to 6.92 without tolterodine [P<0.001]), and IPSS-total (18.1 to 8.06 with tolterodine [P<0.001], 18.2 to 11.7 without tolterodine [P<0.001]) improved similarly in both groups by 12 months follow-up. The patients receiving tolterodine ER experienced a better reduction of IPSS-storage symptoms (4.26 vs 1.42; P<0.001). Secondary: The change of PVR in the patients who received tolterodine ER did not differ significantly from those who did not (15.2 vs 8.9 mL; P=0.69). QoL-I also improved in both groups, but change was not significantly different from each other (1.62 vs 1.46; P=0.551). Both groups demonstrated a significant improvement in Qmax compared to baseline, but there was not a significant difference between the two groups (P=0.275). Intolerable dry mouth, constipation, and dizziness were the most commonly reported adverse events and numerically occurred more in patients who received tolterodine ER.
Abrams et al.[95] (2001) Tolterodine IR 2 mg twice daily	ES, OL Patients ≥18 years of age with urinary frequency (≥8 micturitions/24 hours), urgency, and/or urge incontinence (≥1 incontinence episode/24 hours)	N=714 12 months	Primary: Number of micturitions/24 hours, number of urge incontinence episodes/24 hours, mean urine volume voided/micturition, safety Secondary:	Primary: The number of micturitions/24 hours significantly decreased with tolterodine (-2.4; P=0.0001; mean change, -20%). The number of urge incontinence episodes/24 hours significantly decreased with tolterodine (-1.3; P=0.0001; median change, -74%). The change in volume voided/micturition significantly increased with tolterodine (33 mL; P=0.0001; mean change, 18%). Approximately 69% of patients who received tolterodine perceived

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Not reported	improvement after 12 months of therapy. The most frequently occurring adverse events were autonomic nervous system disorders (46%), general body disorders (22%), gastrointestinal disorders (22%) and urinary disorders (18%). The most frequently report adverse event was dry mouth, which occurred in 41% of patients (27% mild, 10% moderate, 3% severe). The most common adverse events leading to withdrawal were adverse events (15%), withdrawal of consent (13%), lost to follow-up (4%) and other (6%). A total of 34 (5%) patients withdrawing from the study due to dry mouth. Secondary: Not reported
Appell et al.[96] (2001) Tolterodine IR 2 mg twice daily	ES, OL Patients ≥18 years of age with OAB, increased urinary frequency (≥8 micturitions/24 hours) and urge incontinence (≥1 incontinence episode/24 hours) or urinary frequency	N=854 9 months	Primary: Safety and tolerability Secondary: Efficacy	Primary: The most frequently reported adverse events were autonomic nervous system disorders (31%), gastrointestinal disorders (24%) and general body disorders (26%). The most frequently report adverse event was dry mouth, which occurred in 28% of patients (19% mild, 7% moderate, 2% severe). Of those patients enrolled in the OL trial, 30% did not complete nine months of therapy. The most common reasons for withdrawal were adverse events (9%), lack of efficacy (6%), lot to follow-up (6%) and withdrawal of consent (4%). Secondary: The number of micturitions/24 hours significantly decreased with tolterodine (-2.5; P=0.0001; median change, -22%). The number of urge incontinence episodes/24 hours significantly decreased with tolterodine (-2.0; P=0.0001; median change, -76%). The change in volume voided/micturition significantly increased with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				tolterodine (40 mL; P=0.0001; median change, 22%). Approximately 65% of patients who received tolterodine perceived improvement after nine months of therapy. Secondary: Not reported
Kilic et al.[97] (2006) Tolterodine IR 1 mg twice daily vs oxybutynin IR 0.4 mg/kg three times daily	PRO, RCT Children with detrusor instability (most with symptoms of nocturnal enuresis associated with daytime incontinence, frequency, urgency, and/or small bladder volume)	N=60 ≥6 months	Primary: Urodynamic investigations before and after treatment, episodes of UUI, and adverse events Secondary: Not reported	Primary: The tolterodine group had a significant increase in the bladder capacity from 148.5 to 239.33 mL; P<0.001, an increase in compliance from 4.6 to 12.57; P<0.001, and a decrease in the maximum detrusor pressure from 79.43 to 40.4 cm H_20; P<0.001. In the oxybutynin group, a significant increase in bladder capacity from 154.67 to 255.23 mL; P<0.001, an increase in compliance from 5.13 to 13.07; P<0.001, and a decrease in the maximum detrusor pressure from 85.47 to 39.43 cm H_20; P<0.001, were found. Increase in the bladder capacity and compliance during cystometry and reduction in the maximal bladder pressure over the period were similar for tolterodine and oxybutynin groups. While there was not a statistically significant difference between the groups, both had a significant reduction in detrusor instability after six months (100 to 30.0% for tolterodine and 100 to 23.3% for oxybutynin). Clinical response was also similar between tolterodine and oxybutynin (73.3% for tolterodine and 80.0% for oxybutynin; P>0.05). Adverse events were significantly lower in the tolterodine group compared to the oxybutynin group (13 vs 27 events; P=0.027). Eight patients in the oxybutynin group were crossed over to tolterodine due to adverse effects. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Appell et al.[98] (1997) Tolterodine IR 1 to 2 mg twice daily vs oxybutynin IR 5 mg three times daily vs placebo	DB, MC, PC, RCT (Pooled analysis) Patients ≥18 years of age with OAB, increased urinary frequency (≥8 micturitions/24 hours) and urge incontinence (≥1 incontinence episode/24 hours) or urinary frequency	N=1,120 (4 trials) 12 weeks	Primary: Number of micturitions/24 hours, number of incontinence episodes/24 hours, and mean urinary volume voided/micturition Secondary: Not reported	Primary: The number of micturitions/24 hours significantly decreased with tolterodine 1 mg (P<0.001), tolterodine 2 mg (P<0.001), and oxybutynin (P<0.01) compared to placebo. There was no significant difference between tolterodine 2 mg and oxybutynin. The number of incontinence episodes/24 hours significantly decreased with tolterodine (1 and 2 mg) and oxybutynin compared to placebo (P<0.05). There was no significant difference between tolterodine 2 mg and oxybutynin. The change in volume voided/micturition significantly increased with tolterodine (1 and 2 mg) and oxybutynin compared to placebo (P<0.001). Approximately 39% of patients who received placebo, 41% treated with tolterodine 1 mg, 52% treated with tolterodine 2 mg (P=0.003 vs placebo), and 50% treated with oxybutynin (P=0.017 vs placebo) perceived improvement after 12 weeks of treatment. Dry mouth was the most common adverse event (16% of the placebo group, 24% of the tolterodine 1 mg group, 40% of the tolterodine 2 mg group, and 78% of the oxybutynin group). The percentage of patients reporting dry mouth was significantly higher in the oxybutynin group than in the tolterodine or placebo groups (all, P<0.001). The percentage of patients reporting moderate or severe dry mouth was higher in the oxybutynin group (60%) compared to the tolterodine 1 mg group (4%), tolterodine 2 mg group (17%), and placebo group (6%; all, P<0.001). Other commonly reported adverse events included headache, dyspepsia, dizziness, and UTI. Dyspepsia was reported at a higher rate with oxybutynin (11%) than with tolterodine2 mg (6%; P=0.006). The proportion of patients who withdrew because of adverse events was higher in the oxybutynin group than in either of the tolterodine groups or the placebo group (all, P<0.001). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Lee et al.[99] (2002) Tolterodine IR 2 mg twice daily vs oxybutynin IR 5 mg twice daily	DB, MC, PG, RCT Patients ≥18 years of age with OAB and symptoms of urinary urgency and frequency (≥8 micturitions/24 hour) for ≥6 months	N=228 8 weeks	Primary: Number of micturition/24 hours and incontinence episodes/24 hours Secondary: Not reported	Primary: The number of micturitions/24 hours decreased with tolterodine (-2.6) and oxybutynin (-1.8) compared to baseline. There was no significant difference among the treatment groups (P=0.14). In patients who were incontinent at baseline, the number of incontinence episodes/24 hours decreased with tolterodine (-2.2) and oxybutynin (-1.4). There was no significant difference among the treatment groups (P=0.10). Overall, 45% of patients who received tolterodine and 46% of patients who received oxybutynin reported 'much' benefit. There was no significant difference among the groups. The most frequently reported adverse events were autonomic nervous system disorders, gastrointestinal disorders, and urinary disorders. Dry mouth was the most commonly reported adverse event and was significantly higher with oxybutynin than tolterodine (P=0.001). There was a higher frequency of moderate-to-severe dry mouth with oxybutynin (28%) than tolterodine (9%). Secondary: Not reported
Malone-Lee et al.[100] (2001) Tolterodine IR 2 mg twice daily vs oxybutynin IR 5 mg twice daily	DB, MC, RCT Patients ≥50 years of age with OAB, increased urinary frequency (≥8 micturitions/24 hours), and symptoms of urgency and/or urge incontinence (≥1 episode/24 hours)	N=379 10 weeks	Primary: Number of micturition/24 hours, incontinence episodes/24 hours and volume voided/micturition Secondary: Not reported	Primary: The number of micturitions/24 hours decreased with tolterodine (-1.7) and oxybutynin (-1.7). There was no significant difference among the treatment groups (P=0.97). The number of incontinence episodes/24 hours decreased with tolterodine (-1.3) and oxybutynin (-1.8). There was no significant difference among the treatment groups (P=0.065). The change in volume voided/micturition increased with tolterodine (33 mL) and oxybutynin (34 mL). There was no significant difference among the treatment groups (P=0.90). Approximately 45% of patients treated with tolterodine and 41% treated with oxybutynin perceived improvement after 12 weeks of treatment.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There was no significant difference among the treatment groups. Autonomic nervous system disorders and gastrointestinal problems were the most commonly reported adverse events. A higher percentage of patients experienced dry mouth with oxybutynin (61%) than with tolterodine (37%). Severe dry mouth was more common in the oxybutynin group (15%) than in the tolterodine group (4%). The proportion of patients who withdrew because of adverse events was similar in the oxybutynin group (15%) and in the tolterodine group (15%). Secondary: Not reported
Abrams et al.[101] (1998) Tolterodine IR 2 mg twice daily vs oxybutynin IR 5 mg three times daily vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with OAB, increased urinary frequency (≥8 micturitions/24 hours), and symptoms of urgency and/or urge incontinence (≥1 episode/24 hours) for ≥6 months	N=293 12 weeks	Primary: Number of micturition/24 hours, incontinence episodes/24 hours and volume voided/micturition Secondary: Not reported	Primary: The mean change in number of micturitions/24 hours was significantly lower with tolterodine (-2.7; P=0.0022) compared to placebo (-1.6). There was no difference between oxybutynin (-2.3) and placebo (P=0.068). There was also no significant difference between tolterodine and oxybutynin (95% CI, -1.1 to 0.1). The number of incontinence episodes/24 hours significantly decreased with oxybutynin (-1.7; P=0.023) compared to placebo (-0.9). There was no difference between tolterodine (-1.3) and placebo (P=0.22). There was also no significant difference between tolterodine and oxybutynin (95% CI, -0.2 to 1.0). The change in volume voided/micturition significantly increased with tolterodine (38 mL) and oxybutynin (47 mL) compared to placebo (6 mL; P<0.001). Approximately 47% of patients who received placebo, 50% treated with tolterodine, and 49% treated with oxybutynin perceived improvement after 12 weeks of treatment. There was no significant difference among the groups. Dry mouth was the most common adverse event. It was reported at a significantly higher rate with both tolterodine (50%) and oxybutynin

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(86%) than placebo (21%; P<0.001). It was also more common with oxybutynin than tolterodine (P<0.001). The proportion of patients who withdrew because of adverse events was higher in the oxybutynin group (17%) than in the tolterodine (8%) or placebo (12%) groups. Secondary: Not reported
Drutz et al.[102] (1999) Tolterodine IR 2 mg twice daily vs oxybutynin IR 5 mg three times daily vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with OAB, increased urinary frequency (≥8 micturitions/24 hours), and symptoms of urgency and/or urge incontinence (≥1 episode/24 hours)	N=277 12 weeks	Primary: Number of micturition/24 hours, incontinence episodes/24 hours and volume voided/micturition Secondary: Not reported	Primary: The number of micturitions/24 hours significantly decreased with tolterodine (-2.0; P=0.036) compared to placebo (-1.1). There was no difference between oxybutynin (-2.0) and placebo (P=0.066). There was also no significant difference between tolterodine and oxybutynin (95% CI, -0.8 to 0.8). The number of incontinence episodes/24 hours was not significantly different with tolterodine (-1.7; P=0.063) or oxybutynin (-1.7; P=0.10) compared to placebo (-1.0). There was no significant difference between tolterodine and oxybutynin (95% CI, -0.7 to 0.7). The change in volume voided/micturition significantly increased with tolterodine (34 mL; P=0.0075) and oxybutynin (50 mL; P=0.0001) compared to placebo (12 mL). Dry mouth was the most common adverse event (15% of the placebo group, 30% of the tolterodine group, and 69% of the oxybutynin group). The percentage of patients reporting dry mouth was significantly higher in the oxybutynin group than in the tolterodine group (P<0.001). The percentage of patients reporting moderate or severe dry mouth was higher in the oxybutynin group (44%) compared to the tolterodine group (9%), and placebo group (7%). Other more commonly reported adverse events with oxybutynin were headache (10%) and dizziness (11%). Headache occurred in 15% of patients receiving tolterodine. The proportion of patients who withdrew because of adverse events was higher in the oxybutynin group (31%) than in the tolterodine (13%) or

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				placebo (14%) groups. Secondary: Not reported
Leung et al.[103] (2002) Tolterodine IR 2 mg twice daily vs oxybutynin IR 5 mg three times daily	DB, MC, RCT Women ≥18 years of age with OAB, increased urinary frequency (≥8 micturitions/24 hours), and symptoms of urgency and/or urge incontinence (≥1 episode/24 hours)	N=106 10 weeks	Primary: Tolerability Secondary: Efficacy	Primary: The median drug compliance rate was 87.5% with oxybutynin and 75% in with tolterodine (P=0.778). Adverse events occurred in 49.1% of patients treated with oxybutynin and 60.4% of patients treated with tolterodine (P=0.329). The proportion of patients who withdrew was 15.1% with oxybutynin and 17.0% with tolterodine (P=1.0). Secondary: There was no significant difference in frequency of micturition (P=0.965), urgency episodes (P=0.672), incontinence episodes (P=0.993), or pad use (P=0.665) among the treatment groups.
Giannitsas et al.[104] (2004) Tolterodine IR 2 mg twice daily for 6 weeks vs oxybutynin IR 5 mg three times daily for 6 weeks	OL, RCT, XO Patients ≥18 years of age with OAB who were categorized according to the characteristics of the first overactive detrusor contraction during filling cystometrogram: high volume–low pressure (grade-group I), high volume–high pressure (grade-group II), low volume–low	N=128 12 weeks	Primary: Volume voided/micturition, number of micturition/24 hours, incontinence episodes/24 hours, and other urodynamic parameters in the total population and individual severity groups Secondary: Not reported	Primary: <u>Total Study Population</u> The mean volume voided/micturition was significantly increased with tolterodine (40.6 mL) and oxybutynin (43.8 mL) and there was no significant difference among the treatment groups. The mean change in number of micturitions/24 hours was -0.9 with tolterodine and -0.8 with oxybutynin (which reached statistical significance only with tolterodine). There was an increase in the 24 hour volume of urine with both treatments; however it was only statistically significant with oxybutynin. Overactivity index was significantly decreased with tolterodine and oxybutynin; there was no significant difference among the treatment groups. There was a significant increase in bladder volume at first desire to void with tolterodine and oxybutynin, which was significantly higher with oxybutynin. The volume at first overactive detrusor contraction and maximum cystometric capacity were significantly increased with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	pressure (grade-group III) and low volume–high pressure (grade-group IV)			tolterodine and oxybutynin; there was no significant difference among the treatment groups. There was no significant change in pressure of first overactive contraction with tolterodine or oxybutynin. <u>Low volume–High pressure Overactivity (Group IV)</u> The mean volume voided/micturition was significantly increased with tolterodine (39.7 mL) and oxybutynin (54.2 mL) and there was no significant difference among the treatment groups. The mean change in number of micturitions/24 hours was -0.9 with tolterodine and -1.0 with oxybutynin; there was no significant difference among the treatment groups. There was an increase in the 24 hour volume of urine with both treatments; however it was only statistically significant with oxybutynin. Overactivity index was significantly decreased with oxybutynin. Volume at first desire to void was significantly increased with oxybutynin and volume at first overactive contraction was significantly increased with tolterodine. There was no significant change in pressure of first overactive contraction with tolterodine or oxybutynin. <u>Low volume–Low pressure Overactivity (Group III)</u> The mean volume voided/micturition was significantly increased with tolterodine (48.8 mL) and oxybutynin (43.1 mL) and there was no significant difference among the treatment groups. There were no significant changes in the rest of voiding diary parameters in this group. Overactivity index was significantly reduced with tolterodine only. Volume at first desire to void was increased significantly with tolterodine and oxybutynin; there was no significant difference among the treatment groups. There were no significant changes for pressure of first overactive contraction and cystometric capacity with tolterodine or oxybutynin. <u>High volume–High pressure Overactivity (Group II)</u>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Changes in clinical parameters did not reach statistical significance. Overactivity index was reduced by tolterodine and oxybutynin; there was no significant difference among the treatment groups. Oxybutynin achieved an increase in volume at first desire to void and volume at first overactive contraction. There were no significant changes in max cystometric capacity and pressure of first overactive contraction. <u>High volume–Low pressure Overactivity (Group I)</u> The small number of patients in this group did not allow for statistical analyses to be performed. Secondary: Not reported
Harvey et al.[105] (2001) Tolterodine IR 1 to 2 mg twice daily vs oxybutynin IR 2.5 to 5 mg three times daily	MA Patients ≥18 years of age with OAB, increased urinary frequency (≥8 micturitions/24 hours), and symptoms of urgency and/or urge incontinence (≥1 episode/24 hours)	4 trials 12 weeks	Primary: Incontinent episodes/24 hours, quantity of pad used/24-hour period, micturitions/24 hours, and voided volume/micturition Secondary: Adverse events	Primary: The mean change in number of micturitions/24 hours was not significantly different between tolterodine and oxybutynin (WMD, 0.00; 95% CI, -0.38 to 0.38). The number of incontinence episodes/24 hours significantly favored oxybutynin compared to tolterodine (WMD, 0.41; 95% CI, 0.04 to 0.77). The change in volume voided/micturition significantly favored oxybutynin (–8.24 mL; 95% CI, –14.11 to –2.38). This translates to an average increase in the volume voided/micturition of more than 8 mL among patients using oxybutynin compared to patients using tolterodine. Secondary: Dry mouth was significantly lower with tolterodine than oxybutynin (RR, 0.54; 95% CI, 0.48 to 0.61), including moderate to severe dry mouth (RR, 0.33; 95% CI, 0.24 to 0.45). There were fewer patients who withdrew from studies due to dry mouth with tolterodine compared to oxybutynin (RR, 0.63; 95% CI, 0.46 to 0.88).
Staskin et al.[106] (2004) Trospium 20 mg	DB, MC, PC, RCT Patients with OAB	N=658 12 weeks	Primary: Central nervous system adverse effects and daytime	Primary: After 12 weeks of treatment, 2.5% of patients receiving placebo and 1.5% of patients receiving trospium exhibited a clinically significant increase (3 points or greater) from baseline in their SSS scores. There was no

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
twice daily vs placebo			sleepiness using the SSS Secondary: Not reported	significant difference between the treatment groups. In a subgroup analysis based on age (<65 and ≥65 years of age; <75 and ≥75 years of age), there was no significant difference in SSS scores among the treatment groups. Approximately 5.8% of patients receiving trospium and 5.2% of patients receiving placebo reported at least one central nervous system adverse event. Somnolence was reported by 0.3% of patients receiving trospium and 0.6% of patients receiving placebo. Sedation was reported by 0.3% of patients receiving placebo and no patients reported sedation with trospium. Secondary: Not reported
Halaska et al.[107] (2003) Trospium (TCl) 20 mg twice daily vs oxybutynin IR (OXY) 5 mg twice daily	AC, DB, MC, RCT Patients ≥18 years of age with urge syndrome, urge incontinence, urge incontinence as one component of mixed incontinence, or urge incontinence due to a neurological condition (detrusor hyperreflexia)	N=358 52 weeks	Primary: Safety and efficacy Secondary: Not reported	Primary: Blood chemistry, nitrogenous metabolites, uric acid, and sodium and potassium were not adversely affected by either treatment. Systolic and diastolic blood pressure were unaffected by the treatments. A pulse rate of >100 beats/min was noted in 27 patients treated with TCl (10.1%) as compared to six patients in the OXY group (6.7%). In the TCl group at 26 and 52 weeks of treatment, 49 and 63% of the trial physicians assessed tolerability as very good, respectively. In the OXY group, the assessment by the trial physicians at the same points showed very good tolerability in 36 and 42% of patients, respectively. Appraisal by the patients led to similar results. Adverse events were observed in 64.8% of patients in the TCl group and 76.7% of patients in the OXY group. Dry mouth was the most common adverse event and was reported by 33% of patients treated with TCl and 50% of those treated with OXY. UTI was reported by 12% of patients receiving TCl and 11% of patients receiving OXY. For the adverse events taken as a whole, the differences between TCl and OXY were significant with regards to time to event (P<0.01). There was also a significant difference between the two treatment groups in favor of TCl for the overall total of adverse events having probable or possible connections

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				with the trial medication (P=0.02), for all gastrointestinal adverse events with this classification (P=0.02) and for dryness of the mouth (P<0.01). When the number of adverse events is viewed in relation to the total number of patients treated and the duration of treatment, the risk of occurrence of an adverse event/patient/week is 0.027 for TCl and 0.045 for OXY (RR, 0.6 in favor of TCl). Patients treated with TCl showed increases in maximum cystometric bladder capacity of 92 mL at 26 weeks and 115 mL at 52 weeks. The OXY group showed increases of 117 and 119.4 mL respectively. The changes from baseline were significant in both treatment arms (P=0.001). There was no significant difference between the treatment groups. The increase in volume at the first unstable contraction was 46.0 mL with TCl and 36.7 mL with OXY. There was no significant difference between the treatment groups. There was no significant difference between the treatment groups in the volume at the first sensation to void, as well as of other urodynamic parameters. The frequency of micturition in the TCl group decreased by 1.2 micturitions/day at two weeks, 2.9 micturitions/day at 26 weeks and 3.5 micturitions/day at 52 weeks. In frequency of micturitions in the OXY group decreased by 1.5 micturitions/day at two weeks, 3.4 micturitions/day at 26 weeks and 4.2 micturitions/day at 52 weeks. Episodes of urgency in the TCl group decreased by 1.6 at two weeks, 3.2 at six weeks and 3.5 at 52 weeks. In the OXY group, episodes of urgency decreased by 1.7 at 2 weeks, 3.2 at 26 weeks and 3.6 at 52 weeks. After 52 weeks of treatment, 29 and 17% of the physicians considered the therapeutic outcome for the TCl and OXY groups as ‘‘cure’’, respectively. The results were similar with regards to patient assessments. Secondary: Not reported

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Madersbacher et al.[108] (1995) Trospium (TCl) 20 mg twice daily vs oxybutynin IR (Oxy) 5 mg three times daily	DB, MC, RCT Patients with detrusor hyperreflexia	N=95 2 weeks	Primary: Maximum bladder capacity and maximum voiding detrusor pressure during micturition Secondary: Bladder compliance, residual urine, adverse events	Primary: Maximum bladder capacity in the TCl group increased significantly by 96.6 mL (P<0.001). In the Oxy group, maximum bladder capacity increased by 163.0 mL (P<0.001). There was no significant difference between the treatment groups (P=0.057). Maximum detrusor pressure during micturition decreased by 35.4 cmH_20 (P<0.001) in the TCl group and 38 cmH_20 (P<0.001) in the Oxy group. There was no significant difference between the treatment groups (P=0.63). Secondary: Bladder compliance increased by 16.96 mL/cm H_20 (P<0.001) in the TCl group and by 22.56 mL/cmH_20 in the Oxy group (P<0.001). There was no significant difference between the treatment groups (P=0.43). Residual urine increased by 76.45 mL in the TC1 group and 114.08 in the Oxy group. There was no significant difference between the treatment groups (P=0.19). There was no significant difference between the treatment groups with regards to the frequency of hyper-reflexive waves (P=0.16). There were no significant changes in blood pressure among the treatment groups. The rate of adverse events was similar in both groups. Dry mouth occurred in 54% of patients in the TCl group and 56% of patients in the Oxy group. The severity grading showed that dryness of the mouth deteriorated to 'severe' in 4% of patients receiving TC1 and 23% of patients receiving Oxy. Withdrawal from the trial occurred more frequently in patients taking Oxy (16%) than in those taking TCl (6%). The Oxy patients withdrew earlier (after an average of 7.1 days) than the TCl patients (after an average of 14.3 days).
Zinner et al.[109] (2011) Trospium ER 60 mg once daily	ES, OL Patients ≥18 years of age with symptoms of OAB	N=944 48 weeks	Primary: Changes in the mean number of toilet voids per day and UUI episodes	Primary: There were reductions from baseline in the number of daily toilet voids and UUI episodes in both the placebo-to-trospium and trospium-to-trospium groups. The mean change in number of toilet voids per day was -3.2 (-24.5%) in the placebo-to-trospium group and -3.4 (-25.5%) in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	for ≥6 months who met the following criteria: urinary frequency ≥30 toilet voids per 3 days, ≥1 severe urgency severity rating per 3 days, and ≥3 UUI episodes per 3 days		per day Secondary: Urgency severity associated with toilet voids, voided volume per void, daily urgency frequency associated with toilet voids, OAB-PGA, KHQ, and OAB-q	trospium-to-trospium group at week 48. The median change in the number of UUI episodes per day was -2.3 in both groups (-85.7%). Secondary: Urgency severity associated with toilet voids, voided volume per void, and daily urgency frequency associated with toilet voids all improved in both groups. Significant improvements in OAB-PGA findings were present with both groups. Patients in the placebo-to-trospium and trospium-to-trospium groups reported improvements from baseline in individual questions addressing toilet void frequency (84.1 and 85.1%, respectively), UUI (79.9 and 82.6%, respectively), and urgency severity (79.2 and 81.6%, respectively). Overall OAB symptoms improved in approximately 84% of patients. KHQ and OAB-q demonstrated improvements with both groups at week 48. Overall, 552 patients (58.5%) experienced ≥1 treatment emergent adverse events, of which 197 were considered at least possibly related to study medication. Dry mouth (n=60) and constipation (n=59) were the most common adverse events reported.
Bolduc et al.[110] (2009) Combination antimuscarinic therapy (oxybutynin 10 to 30 mg, tolterodine ER 4 mg, and/or solifenacin 5 to 10 mg)	OL, PRO Children with OAB, persistent incontinence and a partial urodynamic response to an optimal dose of a well-tolerated, ER antimuscarinic drug	N=33 ≥6 months	Primary: Efficacy for continence Secondary: Safety and tolerability	Primary: Continence improved in all cases. A total of 17 (52%), 14 (42%), and two patients (6%) rated 100% improvement (complete dryness), a >90% decrease in incontinence episodes and a 50 to 89% decrease, respectively. MVV in three-day diaries improved from 165 to 330 mL. Cystometric bladder capacity improved from 192 to 380 mL without any deterioration in compliance and maximum detrusor contraction pressure decreased from 77 to 18 cm H_20 (P<0.01). Secondary: Overall, 12 patients (36%) reported no adverse effects, 16 (48%) reported mild adverse effects (dry mouth, constipation, blurred vision, and headache), and 5 (15%) had a moderate adverse effect (dry mouth). No

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				patients discontinued therapy due to adverse effects.
Chapple et al.[111] (2008) Darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, trospium	MA Patients ≥18 years of age with OAB	73 trials ≥2 weeks	Primary: Incontinence episodes/day, number of micturitions/day, urgency episodes/day, volume voided/micturition, proportion of patients returning to continence, proportion of patients undergoing global improvements in their storage LUTS Secondary: Tolerability, safety, and HRQOL	Primary: Antimuscarinic agents were significantly more effective than placebo with regards to the mean change in the number of incontinence episodes/day. Pooled differences in mean changes ranged from 0.4 to 1.1 incontinence episodes per day. Tolterodine 2 mg IR was not more effective than placebo; however, the 4 mg ER/IR formulations were more effective than placebo. There were no significant differences among the antimuscarinic agents with the exception of fesoterodine 8 mg/day. One study found that this agent was more effective than tolterodine ER 4 mg/day (P=0.03). Antimuscarinic agents were significantly more effective than placebo with regards to the mean change in the number of micturitions/day. Pooled differences in mean changes ranged from 0.5 to 1.3 episodes per day. Three trials favoring solifenacin 10 mg/day over tolterodine IR 4 mg/day (P=0.01). Four trials favored solifenacin 10 mg/day over solifenacin 5 mg/day (P=0.02). Otherwise, there were no significant differences among the antimuscarinic agents. Fesoterodine, propiverine, solifenacin, and tolterodine were significantly more effective than placebo with regards to the mean change in the number of urgency episodes/day (when this outcome was reported). Pooled differences in mean changes ranged from 0.64 to 1.56 episodes per day. Some trial data favored solifenacin 10 mg/day over tolterodine IR 4 mg/day (P<0.01) and solifenacin 5 mg/day over tolterodine IR 4 mg/day (P=0.01). Otherwise, there were no significant differences among the antimuscarinic agents. Antimuscarinic agents were significantly more effective than placebo with regards to the mean change in the volume voided/micturition (when this outcome was reported). Differences in pooled mean changes were 13 to 40 ml. Solifenacin 10 mg/day was favored over tolterodine IR 4 mg/day (P<0.01); solifenacin 10 mg/day was favored over solifenacin 5 mg/day (P<0.01); fesoterodine 8 mg/day was favored over tolterodine ER 4 mg/day (P=0.03); and oxybutynin IR 15 mg/day was favored over tolterodine IR 4 mg/day (P<0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The proportions of patients who had improvements in their bladder condition was significantly higher for fesoterodine 4 and 8 mg/day than for placebo (P=0.01and P=0.01, respectively). Otherwise, there were no significant differences among the antimuscarinic agents. Secondary: Compared to placebo, treatment with oxybutynin IR (15 and 7.5 to 10 mg/day) was associated with significantly higher risk of withdrawal due to any cause (P=0.04 and P<0.01, respectively). Otherwise, there was no significant difference in the proportions of patients who withdrew for any causes between active treatments and placebo. Oxybutynin IR 7.5 to 10 mg/day was associated with a significantly greater risk of withdrawal due to any cause than oxybutynin ER 5 mg/day (P=0.03); oxybutynin IR 7.5 to 10 mg/day was associated with a greater risk of withdrawal than tolterodine ER 4 mg/day (P<0.01) and tolterodine IR 4 mg/day (P=0.04); oxybutynin IR 15 mg/day was associated with a greater risk of withdrawal than tolterodine IR 4 mg/day P<0.01) and oxybutynin ER 15 mg/day (P=0.04). Tolterodine ER 4 mg/day was associated with a significantly lower risk of withdrawal due to an adverse event than placebo (P=0.02). Formulations associated with a significantly higher risk of withdrawal due to adverse events than placebo were as follows: oxybutynin IR 7.5 to 10 mg/day (P=0.01), oxybutynin IR 15 mg/day (P<0.01), and solifenacin 10 mg/day (P=0.04). Tolterodine ER 4 mg/day was associated with lower risk of withdrawal due to an adverse event compared to oxybutynin transdermal delivery system 3.9 mg/day (P=0.01) and oxybutynin IR 15 mg/day (P<0.01); tolterodine IR 4 mg/day was associated with a lower risk than oxybutynin IR 15 mg/day (P<0.01); and oxybutynin ER 5 mg/day was associated with a lower risk than oxybutynin ER 15 mg/day (P=0.04). Otherwise, there were no significant differences among the antimuscarinic agents. Every antimuscarinic agent was associated with a significantly greater risk of adverse events than placebo, except tolterodine IR 2 mg/day (P=0.97) and oxybutynin transdermal delivery system 3.9 mg/day (P=0.07). The pooled RR for any adverse event in comparison to placebo varied between

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				1.13 and 2.00. The risk of adverse events was significantly lower with tolterodine IR 2 mg/day than with oxybutynin ER 5 mg/day (P<0.01) and lower with tolterodine IR 4 mg/day than with oxybutynin IR 7.5 to 10 mg/day (P<0.01) and oxybutynin IR 15 mg/day (P<0.01). There was a higher risk of adverse events with fesoterodine 8 mg/day than with fesoterodine 4 mg/day (P=0.04) and tolterodine ER 4 mg/day (P=0.04). There was a higher risk of adverse events with oxybutynin IR 7.5 to 10 mg/day than with trospium 40 mg/day (P=0.02). Dry mouth was the most frequently reported adverse event and occurred in 29.6% of patients receiving antimuscarinic therapy compared to 7.9% of patients receiving placebo. The following adverse events were reported at statistically significantly higher levels in first-named active treatments than in second-named active treatments: blurred vision (solifenacin 10 mg/day vs solifenacin 5 mg/day, solifenacin 10 mg/day vs tolterodine IR 4 mg/day); constipation (solifenacin 5 mg/day vs tolterodine ER and IR 4 mg/day, darifenacin 15 mg/day vs tolterodine IR 4 mg/day); fatigue (tolterodine ER 4 mg/day vs fesoterodine 4 or 8 mg/day); nausea (oxybutynin IR 15 mg/day vs oxybutynin ER 15 mg/day); and vomiting (tolterodine ER 4 mg/day vs oxybutynin ER 7.5 to 10 mg/day). Significant differences in HRQOL were reported for darifenacin, fesoterodine, oxybutynin transdermal delivery system, solifenacin, tolterodine ER and IR, and trospium compared to placebo.
Hay-Smith et al.[112] (2009) Darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, trospium	MA Patients with OAB with or without a urodynamic diagnosis of detrusor overactivity	N=11,332 (49 trials) Variable duration	Primary: QOL, patient's observations, symptoms, objective measurements, adverse events Secondary: Not reported	Primary: <u>Oxybutynin vs tolterodine (10 studies)</u> There was no significant difference between the groups in the proportion of people reporting cure/improvement (47% with tolterodine vs 44% with oxybutynin; RR, 1.06; 95% CI 0.89 to 1.26). There was no significant difference between IR tolterodine and ER oxybutynin with regards to the change in the number of leakage episodes/24 hours (WMD, -0.15; 95% CI, -0.47 to 0.16). There was no significant difference between IR tolterodine and ER oxybutynin with regards to the change in micturitions/24 hours (WMD, -0.25; 95% CI, -0.61 to 0.10).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There were fewer withdrawals with tolterodine therapy (7%) compared to treatment with oxybutynin (12%; RR, 0.57; 95% CI, 0.43 to 0.75). Dry mouth was significantly lower with tolterodine than oxybutynin (RR, 0.60; 95% CI, 0.54 to 0.66). <u>Oxybutynin vs trospium (four studies)</u> Two trials reported on maximum cystometric capacity and residual volume and there was no significant difference between the groups. Dry mouth was significantly lower with trospium than oxybutynin (RR, 0.74; 95% CI, 0.59 to 0.93). <u>ER vs IR oxybutynin (four trials)</u> There was no significant difference in patient's perception of improvement (one trial). There was no significant difference between the groups in the number of leakage episodes/24 hours. There was a lower maximum cystometric capacity and larger volume at first contraction in the ER formulations; however, only volume at first contraction was significant. There was no significant difference in residual volume measured using ultrasound. There was no significant difference in withdrawals due to adverse events between IR and ER groups. Dry mouth was significantly lower with the ER preparations (RR, 0.77; 95% CI, 0.66 to 0.91). <u>ER vs IR tolterodine (one trial)</u> There was no significant difference between the ER and IR formulations with regards to leakage episodes or micturitions/24 hours. There was no significant difference in withdrawals due to adverse events. There were fewer reports of dry mouth for those using the ER preparation.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				ER oxybutynin vs IR tolterodine (one trial) There was no significant difference in the number of leakage episodes/24 hours. There was a significant difference in favor of oxybutynin for the number of micturitions/24 hours. There was no significant difference in the number of withdrawals due to adverse events among the treatment groups. There was no significant difference in the rate of dry mouth among the treatment groups. ER tolterodine vs IR oxybutynin (one trial) The risk of dry mouth was less for those taking ER tolterodine compared to oxybutynin IR. Tolterodine ER vs oxybutynin ER (two trials) There was no significant difference in change in leakage episodes or micturitions/24 hours (one trial). There was no statistically significant difference between the groups in withdrawals due to adverse events. There was no significant difference in the rate of dry mouth among the treatment groups; however, there was clinical heterogeneity noted among the studies. One study found significantly fewer reports of dry mouth with oral ER tolterodine than oral ER oxybutynin. There was no difference in risk of dry mouth between oral ER tolterodine and transdermal ER oxybutynin. Secondary: Not reported
Maman et al.[113] (2014) Darifenacin, fesoterodine, mirabegron, oxybutynin,	MA Patients ≥18 years of age with a diagnosis of OAB, may be referred to as detrusor	N=27,309 (44 trials) Variable duration	Primary: Efficacy outcomes including micturition frequency, incontinence and urgency urinary	Primary: The results from 26 studies (22,040 patients) showed that the effect of mirabegron 50 mg did not differ significantly in terms of micturition frequency from other treatments, except solifenacin 10 mg, which was more effective (mean difference vs mirabegron 50 mg of -0.584). The estimated mean difference of tolterodine compared to mirabegron was not significant (0.157 micturition episodes per day).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
solifenacin, tolterodine, trospium	overactivity or urinary urgency		incontinence; safety outcomes including dry mouth, constipation and blurred vision Secondary: Not reported	The results from 17 studies (13,101 patients) showed improvement with mirabegron 50 mg in the daily number of incontinence episodes per 24 hours from baseline to end of study was not significantly different from improvements with tolterodine 4 mg, oxybutynin 10 mg, darifenacin 7.5 mg and 15 mg and fesoterodine 4 mg and 8 mg. Mirabegron 50 mg was statistically superior to placebo with a mean difference estimated at 0.493 incontinence episodes per day. The results of 18 studies (16,044 patients) showed that mirabegron 50 mg was significantly less efficacious than solifenacin 10 mg in terms of urgency urinary incontinence (mean difference vs mirabegron 50 mg of -0.422 urgency incontinence episodes per day) and did not differ significantly from other antimuscarinics. All 44 trials (27,309 patients) reported a similr incidence of dry mouth with mirabegron 50 mg to placebo (OR, 1.344). All antimuscarinics were associated with a significantly higher risk of dry mouth compared with mirabegron 50 mg. The OR for the occurrence of dry mouth with antimuscarinics compared with mirabegron 50 mg ranged from 5.213 with solifenacin 5 mg to 40.702 with oxybutynin IR 15 mg. Data of 41 studies (25,257 patients) reported incidence of constipation associated with mirabegron 50 mg was comparable with placebo (OR, 0.732). Other antimuscarinics except darifenacin 15 mg, fesoterodine 8 mg, solifenacin 5 mg, solifenacin 10 mg and trospium 60 mg had similar incidences of constipation. The 25 studies (14,348 patients) available reported blurred vision being relatively rare and no significant difference in risk of developing blurred vision was found between treatments arms. Secondary: Not reported

Drug regimen abbreviations: ER=extended-release, IR=immediate-release, LA=long acting, SR=sustained-release, XL=extended release
Study abbreviations: AC=active control, CI=confidence interval, DD=double-dummy, DB=double-blind, ES=extension study, MA=meta-analysis, MC=multicenter, NS=not significant, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RR=relative risk, XO=crossover

Miscellaneous abbreviations: BPH=benign prostatic hyperplasia, BOO=bladder outlet obstruction, HRQOL=health-related quality of life, ICIQ-SF=International Consultation on Incontinence Questionnaire–Short Form, IIQ=incontinence impact questioner, IPSS=international prostate symptoms score, IPSS-QOL=international prostate symptoms score quality of life, KHQ=King's Health Questionnaire, LUTS=lower urinary tract symptoms, MVV=mean voided volume per void, OAB=overactive bladder, OAB-PGA=Overactive Bladder Patient Global Assessment questionnaire, OAB-q=Overactive Bladder Questionnaire, OABSS=Overactive Bladder Symptom Scores, PPBC=Patient Perception of Bladder Condition Questionnaire, PGA=patient global assessment, PRO=patient reported outcome, PVR=postvoid residual, Qmax=maximum flow rate, QOL=quality of life, QOL-I=Quality of Life Index, SMD=standard mean difference, SSS=Stanford Sleepiness Scale, TSQ=Treatment Satisfaction Questionnaire, UDI=urogenital distress inventory, UPS=Urgency Perception Scale, URI=upper respiratory infection, USS=Urinary Sensation Scale, UTI=urinary tract infection, UUI=urgency urinary incontinence, VAS=visual analog scale, VVPM=volume voided per micturition, WMD=weighted mean difference

Additional Evidence

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

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

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

IX. Cost

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

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

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

Rx=prescription

Table 9. Relative Cost of the Genitourinary Smooth Muscle Relaxants

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Darifenacin	extended-release tablet	Enablex®	$$$$	N/A
Fesoterodine	extended-release tablet	Toviaz®	$$$$	N/A
Flavoxate	tablet	N/A	N/A	$$$
Mirabegron	extended-release tablet	Myrbetriq®	$$$$	N/A
Oxybutynin	extended-release tablet, syrup, tablet, transdermal gel, transdermal patch	Ditropan XL®*, Gelnique®, Oxytrol®	$$$$$	$$$
Solifenacin	tablet	Vesicare®	$$$$	N/A
Tolterodine	extended-release capsule, tablet	Detrol®*, Detrol LA®	$$$$$	$$$$
Trospium	extended-release capsule, tablet	Sanctura®*, Sanctura XR®*	$$$$	$$$$

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

X. Conclusions

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

therapy.[2,4] Antimuscarinic drugs with antimuscarinic effects increase bladder capacity, decrease urgency and are useful for the treatment of urge incontinence.[4] Beta-3 adrenergic receptor agonists increase bladder capacity via relaxation of the detrusor smooth muscle. This novel mechanism may improve tolerability compared to antimuscarinic agents.[21,114] Flavoxate, oxybutynin, tolterodine, and trospium are available in a generic formulation.

Several guidelines provide recommendations on the use of the genitourinary smooth muscle relaxants for the treatment of urinary incontinence and overactive bladder. Antimuscarinic agents are the primary treatment for patients with overactive bladder symptoms (with or without urge incontinence), in addition to lifestyle modifications and behavioral therapy.[2,22-24,26-28] In general, the guidelines do not identify a single preferred agent for initial therapy. However, several recent guidelines provide general recommendations.[23-24,27] For example, two guidelines from the American Urological Association and the European Association of Urology favor the use of extended-release preparations.[23-24] In addition, guidelines from the National Institute of Health and Clinical Excellence recommend immediate-release oxybutynin, immediate-release tolterodine or once-daily darifenacin as initial therapy. Several guidelines also recommend the use of transdermal oxybutynin if anticholinergic side effects are experienced with initial therapy.[23-24,27]

In clinical trials, the genitourinary smooth muscle relaxants have been shown to modestly improve urinary symptoms, including frequency, urgency, nocturia and incontinence episodes.[29-112] The majority of the studies were six to 12 weeks in duration; however, a few long-term (up to 36 months), open-label, non-comparative studies have also been conducted. There were relatively few active-controlled studies found in the medical literature with flavoxate, darifenacin, fesoterodine, solifenacin or trospium. The majority of the active-controlled studies compared oxybutynin and tolterodine. Several studies have demonstrated similar efficacy with the genitourinary smooth muscle relaxants for most, but not all, of the outcomes assessed. In general, studies directly comparing immediate-release and extended-release formulations of the same drug found no differences in efficacy.[52-56,62,90] Studies directly comparing immediate-release formulations of different drugs, as well as studies directly comparing extended-release formulations of different drugs, also demonstrated similar efficacy.[30,33,40,45,59-60,78,81,97-104,107-108] Few studies have demonstrated greater efficacy with one genitourinary smooth muscle relaxant over another.[29,41,46,49,58-59,76,80,84,92] The use of the genitourinary smooth muscle relaxants for the treatment of urinary incontinence and overactive bladder has also been associated with an improvement in quality of life.[40,44,53,75,83-84,91]

Adverse events occur frequently with the genitourinary smooth muscle relaxants due to their antimuscarinic effects, which often leads to discontinuation of therapy. The most common adverse events include dry mouth, blurred vision, abdominal discomfort, drowsiness, nausea and dizziness. These agents may also cause confusion or memory impairment in the elderly.[4] The incidence of adverse events varies among the agents and depends upon the formulation used (extended-release, immediate-release or transdermal). Adverse events tend to be higher with the immediate-release formulations compared to extended-release formulations. In general, dry mouth occurs at a higher rate with oral oxybutynin than with the other agents.

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

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

XI. Recommendations

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

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