Therapeutic Class Review
ADHD Agents and Stimulants

Therapeutic Class

- **Overview/Summary:** 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] The core symptoms of ADHD utilized in the diagnosis of the disorder include hyperactivity, impulsivity, and inattention. Untreated, or undertreated, ADHD is associated with adverse sequelae, including delinquent behavior, antisocial personality traits, substance abuse and other comorbidities[2]. Several central nervous system agents are Food and Drug Administration (FDA)-approved for the treatment of ADHD, including the cerebral stimulants (amphetamines and methylphenidate derivatives), as well as atomoxetine (Strattera®), clonidine extended-release (Kapvay®), and guanfacine extended-release (Intuniv®).[3-22] The cerebral stimulant agents are classified as Schedule II controlled substances due to their potential for abuse.[3-11,14-20,22] Atomoxetine, clonidine extended-release, and guanfacine extended-release are not classified as controlled substances.[12,13,21] Clonidine and guanfacine, extended-release formulations, are approved as adjunctive therapy with stimulant medications as well as monotherapy.[12,13,23] Some cerebral stimulant agents are indicated for the treatment of a variety of sleep disorders. Narcolepsy is a sleep disorder characterized by excessive daytime sleepiness and intermittent manifestations of rapid eye movement (REM) sleep during wakefulness (American Academy of Sleep Medicine, 2007). Obstructive sleep apnea (OSA) is a common chronic disorder that often requires lifelong care. Cardinal features of OSA include obstructive apneas, hypopneas, or respiratory effort related arousals; daytime symptoms attributable to disrupted sleep (e.g., sleepiness, fatigue, poor concentration); and signs of disturbed sleep (e.g., snoring, restlessness, or resuscitative snorts).[24,25] 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.[24] Modafinil (Provigil®) and armodafinil (Nuvigil®) are both FDA-approved to improve wakefulness in adult patients with excessive sleepiness associated with narcolepsy, OSA, and shift work sleep disorder. These agents are classified as Schedule IV controlled substances because they have been shown to have been shown to produce psychoactive and euphoric effects similar to stimulants.[26,27] Sodium oxybate (Xyrem®) is γ-hydroxybutyric acid (GHB), a known drug of abuse. It is approved for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy. It is classified as a Schedule III controlled substance. However, non-medical uses of sodium oxybate are classified under Schedule I.[28] Several generic ADHD agents and stimulants are currently available. Specifically, at least one short-, intermediate-, and long-acting agents are available generically.[29]

Table 1. Current Medications Available in the Class[3-22, 26-28]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Single-Entity Products			
Anorexigenic Agents and Respiratory and Cerebral Stimulants-Amphetamines			
Amphetamine/dextroamphetamine salts (Adderall®*, Adderall XR®*)	Treatment of ADHD	Capsule (Adderall XR®): 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg Tablet (Adderall®): 5 mg	✔

		7.5 mg 10 mg 12.5 mg 15 mg 20 mg 30 mg	
Dextroamphetamine (Procentra®, Dexedrine Spansule®*)	Treatment of ADHD, narcolepsy	Solution (Procentra®): 5 mg/5 mL Sustained-release capsule (Dexedrine Spansule®): 5 mg 10 mg 15 mg Tablet: 5 mg 10 mg	✔
Lisdexamfetamine (Vyvanse®)	Treatment of ADHD	Capsule: 20 mg 30 mg 40 mg 50 mg 60 mg 70 mg	
Methamphetamine (Desoxyn®*)	Exogenous obesity, treatment of ADHD	Tablet: 5 mg	✔
Anorexigenic Agents and Respiratory and Cerebral Stimulants-Miscellaneous			
Armodafinil (Nuvigil®)	Improve wakefulness in patients with excessive sleepiness associated with OSA and narcolepsy, improve wakefulness in patients with excessive sleepiness associated with shift work disorder	Tablet: 50 mg 150 mg 250 mg	-
Dexmethylphenidate (Focalin®*, Focalin XR®)	Treatment of ADHD	Extended-release capsule: 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 (Concerta®*,	Treatment of ADHD, narcolepsy:	Chewable tablet (Methylin®):	✔

Daytrana®, Metadate CD®, Metadate ER®*, Methylin®, Ritalin®*, Ritalin LA®*, Ritalin SR®*)		2.5 mg 5 mg 10 mg Extended-release capsule (Metadate CD®): 10 mg 20 mg 30 mg 40 mg 50 mg 60 mg Extended-release capsule (Ritalin LA®): 10 mg 20 mg 30 mg 40 mg Extended-release tablet (Concerta®): 18 mg 27 mg 36 mg 54 mg Extended-release tablet (Metadate ER®): 20 mg Solution (Methylin®): 5 mg/5 mL 10 mg/5 mL Sustained-release tablet (Ritalin-SR®): 20 mg Tablet (Ritalin®): 5 mg 10 mg 20 mg Transdermal patch (Daytrana®): 10 mg/9 hours (1.1. mg/hour) 15 mg/9 hours (1.6 mg/hour) 20 mg/9 hours (2.2 mg/hour) 30 mg/9 hours (3.3	

		mg/hour)	
Modafinil (Provigil®*)	Improve wakefulness in patients with excessive sleepiness associated with OSA and narcolepsy, improve wakefulness in patients with excessive sleepiness associated with shift work disorder:	Tablet: 100 mg 200 mg	✔
Central α-Agonists			
Clonidine extended-release (Kapvay®)	Treatment of ADHD as monotherapy and as adjunctive therapy to stimulant medications	Extended-release tablet: 0.1 mg 0.2 mg	-
Guanfacine extended-release (Intuniv®)	Treatment of ADHD as monotherapy and as adjunctive therapy to stimulant medications	Extended-release tablet: 1 mg 2 mg 3 mg 4 mg	-
Central Nervous System Agents-Miscellaneous			
Atomoxetine (Strattera®)	Treatment of ADHD	Capsule: 10 mg 18 mg 25 mg 40 mg 60 mg 80 mg 100 mg	-
Sodium oxybate (Xyrem®)	Treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy	Solution: 500 mg/mL (180 mL)	-

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

Evidence-based Medicine

- Data from several clinical trials demonstrate that the ADHD agents and stimulants are effective in the treatment of ADHD, as measured by significant decreases in ADHD rating scale scores compared to placebo. Although comparative trials have been conducted, it is difficult to interpret the results of these trials due to design flaws (e.g., small population, short treatment duration, variable outcomes). Overall, there is insufficient evidence to suggest that one ADHD agent and stimulant is more efficacious than another for the treatment of ADHD. [30-106]
- The majority of efficacy data supporting the use of the ADHD agents and stimulants is derived from placebo-controlled trials. In addition, the majority of trials were conducted in the pediatric population. Limited data exists to demonstrate the efficacy of a variety of cerebral stimulants (amphetamine/dextroamphetamine, dexmethylphenidate, and lisdexamfetamine) and atomoxetine in the adult population.[35,43,57,75,76,90]
- Clonidine extended-release and guanfacine extended-release have been shown to improve ADHD symptoms scores both as monotherapy and as adjunctive therapy to psychostimulants. These agents are FDA-approved for use in ADHD as monotherapy and as adjunctive treatment to stimulants.[53,54,62-69]
- Armodafinil, modafinil, and sodium oxybate have all been shown to be more effective compared to placebo in patients with narcolepsy, OSA, and shift work disorder, as measured by significant improvements in sleepiness scale scores. In addition, sodium oxybate has been shown to significantly reduce the rate of inadvertent naps and cataplexy attacks compared to placebo. Similar

to ADHD, there is insufficient evidence to suggest that one ADHD agent and stimulant is more efficacious than another for the treatment of sleep disorders.[107-134]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - Guidelines recommend the use of FDA-approved agents for initial pharmacologic treatment of ADHD, and preference of one agent over another is not stated.
  - Stimulant medications remain the most effective treatment option for most children with ADHD, and response to one stimulant dose not predict response to another. Other factors associated with treatment decisions include presence of comorbid conditions, patient/family preference, storage/administration issues at school, history and/or presence of substance abuse, pharmacokinetics, and anticipated adverse events.[2,23,135-137]
  - With regard to the use of nonstimulant medications in the treatment of ADHD, atomoxetine is recognized as a good option for patients with comorbid anxiety, sleep initiation disorder, substance abuse, or tics, or if initially preferred by parents and/or the physician.
  - Overall, atomoxetine, clonidine extended-release, and guanfacine are effective in reducing ADHD core symptoms; however, these agents have a smaller evidence base compared to the cerebral stimulants.[23]
  - Methylphenidate is recommended as first-line treatment of ADHD in adults, with atomoxetine and dexamphetamine recommended second line.[136-137]
  - Guidelines for the treatment of narcolepsy, OSA, and shift work disorder have not been updated since FDA-approval of sodium oxybate. Guidelines recommend the use of FDA-approved agents for the treatment of such sleep disorders, with modafinil recommended first-line for the treatment of narcolepsy. [24,138-140]
  - Even though guidelines are published prior to FDA-approval of sodium oxybate, the agent is the only one to be recognized as being an effective option for the treatment of cataplexy due to narcolepsy. Armodafinil, was FDA-approved in 2007; however, its role is not defined within current clinical guidelines.[24,138-140]
- Other Key Facts:
  - Armodafinil (Nuvigil®) is the longer half-life enantiomer of modafinil (Provigil®).
  - At least one short-, intermediate-, and long-acting stimulant is available generically.[29]
  - Due to safety concerns and abuse potential, sodium oxybate (Xyrem®) is available only through restricted distribution, the Xyrem Success Program.

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Therapeutic Class Review
ADHD Agents and Stimulants

Overview/Summary

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] The core symptoms of ADHD utilized in the diagnosis of the disorder include hyperactivity, impulsivity, and inattention. 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[2]. There are several central nervous system agents that are Food and Drug Administration (FDA)-approved for the treatment of ADHD, including the cerebral stimulants (amphetamines and methylphenidate derivatives), as well as atomoxetine (Strattera®), clonidine extended-release (Kapvay®), and guanfacine extended-release (Intuniv®).[3-22] Due to the potential for abuse, the cerebral stimulant agents are classified as Schedule II controlled substances.[3-11,14-20,22] Atomoxetine, clonidine extended-release, and guanfacine extended-release are not classified as controlled substances.[12,13,21] Clonidine and guanfacine, extended-release formulations, are the first ADHD medications to achieve FDA approval as adjunctive therapy with stimulant medications. These agents are also FDA-approved for use as monotherapy.[12,13,23]

Some cerebral stimulant agents are also FDA-approved for the treatment of a variety of sleep disorders. Narcolepsy is a sleep disorder characterized by excessive daytime sleepiness and intermittent manifestations of rapid eye movement (REM) sleep during wakefulness. Obstructive sleep apnea (OSA) is a common chronic disorder that often requires lifelong care. Cardinal features of OSA include obstructive apneas, hypopneas, or respiratory effort related arousals; daytime symptoms attributable to disrupted sleep (e.g., sleepiness, fatigue, poor concentration); and signs of disturbed sleep (e.g., snoring, restlessness, or resuscitative snorts).[24,25] 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.[24] Modafinil (Provigil®) and armodafinil (Nuvigil®) (the longer half-life enantiomer of modafinil) are both FDA-approved to improve wakefulness in adult patients with excessive sleepiness associated with narcolepsy, OSA, and shift work sleep disorder. These agents have been shown to produce psychoactive and euphoric effects similar to stimulants, as well as alterations in mood, perception, thinking and feelings. As a result, these agents are classified as Schedule IV controlled substances.[26,27]

Sodium oxybate (Xyrem®) is γ-hydroxybutyric acid (GHB), a known drug of abuse. It is approved for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy. It is classified as a Schedule III controlled substance. However, non-medical uses of sodium oxybate are classified under Schedule I.[28] Several generic ADHD agents and stimulants are currently available. Specifically, at least one short-, intermediate-, and long-acting agents are available generically.[29] The agents included in this review are listed in Table 1 categorized by medication class and by generic name since there are multiple branded agents that contain the same generic component.

Current consensus clinical guidelines for the treatment of children and adolescents with ADHD recommend that stimulants are highly effective for reducing core symptoms of ADHD in children.[2,23,30] Although initial therapy with atomoxetine or extended-release formulations of clonidine and guanfacine may reduce core symptoms of ADHD, there is less evidence to support their use compared to stimulants. The selection of therapy should be based on comorbid conditions, adverse event profiles, compliance issues, risk of drug diversion and patient/parent preference.[31] Stimulants, particularly methylphenidate, are recommended as first-line therapy in adult patient with ADHD.[32] Guidelines for the treatment of narcolepsy, obstructive sleep apnea (OSA), and shift work disorder have not been updated since FDA-

approval of sodium oxybate. Guidelines recommend the use of FDA-approved agents for the treatment of such sleep disorders, with modafinil recommended first-line for the treatment of narcolepsy. Sodium oxybate is the only agent that is recommended as being an effective option for the treatment of cataplexy due to narcolepsy. The role of armodafinil, the R enantiomer of modafinil, was FDA-approved in 2007; however, its role has not been address in the current guidelines.[24,33-35]

Medications

Table 1. Medications Included Within Class Review[3-22,26-28]

Generic Name (Trade name)	Medication Class	Generic Availability
Single-Entity Products		
Anorexigenic Agents and Respiratory and Cerebral Stimulants-Amphetamines		
Amphetamine/dextroamphetamine salts (Adderall®*, Adderall XR®*)	Central nervous system stimulant	√
Dextroamphetamine (Procentra®, Dexedrine Spansule®*)	Central nervous system stimulant	√
Lisdexamfetamine (Vyvanse®)	Central nervous system stimulant	-
Methamphetamine (Desoxyn®*)	Central nervous system stimulant	√
Anorexigenic Agents and Respiratory and Cerebral Stimulants-Miscellaneous		
Armodafinil (Nuvigil®)	Central nervous system stimulant	-
Dexmethylphenidate (Focalin®*, Focalin XR®)	Central nervous system stimulant	√
Methylphenidate (Concerta®*, Daytrana®, Metadate CD®, Metadate ER®*, Methylin®, Ritalin®*, Ritalin LA®*, Ritalin SR®*)	Central nervous system stimulant	√
Modafinil (Provigil®*)	Central nervous system stimulant	√
Central α-Agonists		
Clonidine extended-release (Kapvay®)	α-2 adrenergic agonist	-
Guanfacine extended-release (Intuniv®)	α-2 adrenergic agonist	-
Central Nervous System Agents-Miscellaneous		
Atomoxetine (Strattera®)	Norepinephrine reuptake inhibitor	-
Sodium oxybate (Xyrem®)	Central nervous system agent	-

Table 2. Cerebral Stimulants/Agents Used for ADHD Classified by Duration of Action[3-22,26-28]

Generic Name(s)	Short-Acting	Intermediate-Acting	Long-Acting
Anorexigenic Agents and Respiratory and Cerebral Stimulants-Amphetamines			
Amphetamine/ dextroamphetamine salts	Amphetamine/ dextroamphetamine, Adderall®		Amphetamine/ dextroamphetamine, Adderall XR®
Dextroamphetamine	dextroamphetamine, Procentra®	dextroamphetamine, Dexedrine®	
Lisdexamfetamine			Vyvanse®
Methamphetamine		methamphetamine, Desoxyn®	
Anorexigenic Agents and Respiratory and Cerebral Stimulants-Miscellaneous			
Armodafinil			Nuvigil®
Dexmethylphenidate	dexmethylphenidate, Focalin®		Focalin XR®
Methylphenidate	methylphenidate, Methylin®, Ritalin®	methylphenidate SR, Metadate ER®, Ritalin SR®	methylphenidate, Concerta®, Daytrana®, Metadate CD®, Ritalin LA®

Generic Name(s)	Short-Acting	Intermediate-Acting	Long-Acting
Modafinil			Provigil®
Central α-Agonists			
Clonidine			Kapvay®
Guanfacine			Intuniv®
Central Nervous System Agents-Miscellaneous			
Atomoxetine			Strattera®
Sodium oxybate	Xyrem®		

Indications

Table 3a. FDA-Approved Indication-Anorexigenic Agents and Respiratory and Cerebral Stimulants-Amphetamines[3,4,7-9,20,22]

Indication(s)	Amphetamine/ Dextroamphet-amine Salts	Dextroamphet-amine	Lisdex-amfetamine	Methamphet-amine
Exogenous obesity				√*
Narcolepsy	√†	√		
Treatment of ADHD	√	√	√	√

*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).
†Adderall®.

In addition the Food and Drug Administration-approved indications listed above, dextroamphetamine has been used off-label in the treatment of traumatic brain injury, cocaine dependence and autism.[36]

Table 3b. FDA-Approved Indication-Anorexigenic Agents and Respiratory and Cerebral Stimulants-Miscellaneous[5,6,10,11,14-19,26,27]

Indication(s)	Armodafinil	Dexmethyl-phenidate	Methyl-phenidate	Modafinil
Narcolepsy			√*	
To improve wakefulness in patients with excessive sleepiness associated with OSA, narcolepsy, and shift work disorder	√			√
Treatment of ADHD		√	√	

*Metadate ER®, Methylin®, Ritalin®, and Ritalin SR®.

In addition the Food and Drug Administration-approved indications listed above, methylphenidate has been used off-label in the treatment of traumatic brain injury and depression in the elderly. Modafinil has been used off-label in the treatment children and adults with attention deficit hyperactivity disorder, drug-induced sedation, multiple sclerosis-related nocturnal enuresis and fatigue due to multiple sclerosis, Parkinson's disease and postpoliomyelitis syndrome.[36]

Table 3c. FDA-Approved Indication-Central α-Agonists[12,13]

Indication	Clonidine	Guanfacine
Treatment of ADHD as monotherapy and as adjunctive therapy to stimulant medications	√	√

Clonidine (immediate-release) is used off-label in a variety of conditions including alcohol withdrawal syndrome, diabetic diarrhea, hot flashed, hyperhidrosis, insomnia, methadone withdrawal, postherpetic neuralgia, migraine prophylaxis, restless legs syndrome, smoking cessation, tardive dyskinesia, Tourette syndrome and ulcerative colitis. Guanfacine has also been use in the treatment of Tourette syndrome. [36]

Table 3d. FDA-Approved Indication-Central Nervous System Agents-Miscellaneous[21,28]

Indication(s)	Atomoxetine	Sodium Oxybate
Treatment of ADHD	√	
Treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy		√

In addition the Food and Drug Administration-approved indications listed above, atomoxetine has been used off label in the treatment of binge eating disorder, nocturnal enuresis and obesity, while sodium oxybate has been used in the treatment of fibromyalgia and fatigue.[36]

Pharmacokinetics

Table 4a. Pharmacokinetics-Anorexigenic Agents and Respiratory and Cerebral Stimulants-Amphetamines[3,4,7-9,20,22]

Drug	Absorption	Distribution	Metabolism	Elimination
Amphetamine/ dextro-amphetamine salts	Bioavailability: percent not reported (food: unaffected) Cmax: nd Tmax: 3 hours (IR), 7 hours (ER)	Vd: nd Protein binding: nd	Method: Liver (variable) Metabolites (active): 4-hydroxy-amphetamine, norephedrine	Route: renal (30 to 40% [unchanged], 50% [changed]) (ER) Half-life: 9 to 14 hours (ER) Cl: nd
Dextro-amphetamine	Bioavailability: percent not reported (well-absorbed) (food: unaffected) Cmax: nd Tmax: 60 to 180 minutes (IR), 7 to 8 hours (ER)	Vd: 6.11 L/kg Protein binding: nd	Method: liver (extensive) Metabolites: hippuric acid, benzoic acid, norephedrine, 4-hydroxy-norephedrine, benzyl methyl ketone (activity not reported)	Route: renal (17 to 73%) Half-life: 7 to 34 hours Cl: nd
Lisdex-amfetamine	Bioavailability: percent not reported (rapidly absorbed) (food: increased Tmax by 1 hour) Cmax: nd Tmax: 3.5 hours	Vd: nd Protein binding: nd	Method: blood Metabolites: dextro-amphetamine (active), L-lysine (inactive)	Route: renal (96%) fecal (0.3%) Half-life: <1 hour Cl: nd
Meth-amphetamine	Bioavailability: nd (food: nd) Cmax: nd Tmax: nd	Vd: nd Protein binding: nd	Method: liver (aromatic hydroxylation, N-dealkylation, and domination) Metabolites: 7 metabolites have been identified (activity not reported)	Route: nd Half-life: 4 to 5 hours Cl: nd

Cl=clearance, Cmax=maximum concentration, ER=extended-release, IR=immediate-release, nd=no data, Tmax=time to maximum concentration, Vd=volume of distribution

Table 4b. Pharmacokinetics-Anorexigenic Agents and Respiratory and Cerebral Stimulants-Miscellaneous[5,6,10,11,14-19,26,27]

Drug	Absorption	Distribution	Metabolism	Elimination
Armodafinil	Bioavailability: pe rcent not reported (rapid absorption) (food: minimal effects) Cmax: 1.97 µg/mL (100 mg), 6.37 µg/mL (300 mg) Tmax: 2 hours	Vd: 42 L Protein binding: 60%	Method: Liver (amid hydrolysis) Metabolites (inactive): R-modafinil acid, modafinil sulfones	Route: renal (percent unknown) Half-life: 15 hours Cl: 33 mL/minute
Dexmethyl-phenidate	Bioavailability: 22 to 25% (ER) (food: delayed absorption [IR]) Cmax: nd Tmax: 1.0 to 1.5 hours (IR), 1.5 hours (first peak) and 6.5 hours (second peak) (ER)	Vd: 2.65 L/kg (ER) Protein binding: nd	Method: Liver (extensive) (IR) Metabolites (inactive): d-ritalinic acid (IR)	Route: renal (percent not reported) Half-life: 3 hours Cl: nd
Methyl-phenidate	Bioavailability: 22% (ER capsule), 101 to 101% (SR), (food: high fat meals delays Tmax by 1 hour and may increase AUC up to 30% [IR, ER capsule, ER tablet], no effect [transdermal patch]) Cmax: 4.2 to 15.3 ng/mL (IR), 10.9 to 16.8 ng/mL (ER capsule), 3.7 ng/mL (ER tablet) 39 ng/mL (transdermal patch) Tmax: 1 to 2 hours (IR), 1.5 to 3.0 hours (first peak) and 4.5 to 6.6 hours (second peak) (ER capsule), 6.8 hours (ER tablet),	Vd: 1.8 to 2.65 L/kg (ER capsule) Protein binding: 10 to 33% (ER capsule)	Method: tissues (ER capsule) Metabolites (inactive): ritalinic acid, methylphenidate hydrochloride, hydroxy-methylphenidate, hydroxyritalinic acid (ER capsule)	Route: renal (78 to 97%) fecal (1 to 3%) (ER capsule) Half-life: 2.5 to 3.5 hours (ER capsule), 3 to 4 hours (transdermal patch) Cl: 0.4 to 0.73 L/hour/kg (ER capsule)

Drug	Absorption	Distribution	Metabolism	Elimination
	4.7 hours (SR), 7.5 to 10.5 hours (transdermal patch)			
Modafinil	Bioavailability: percent not reported (rapid absorption) (food: rate is slowed, but extent is unaffected) Cmax: nd Tmax: 2 to 4 hours	Vd: 0.9 L/kg Protein binding: 60%	Method: liver (90%) Metabolites (inactive): modafinil acid, modafinil sulfone, 2-(diphenyl-methylsulfonyl) aceic acid, 4-hydroxy modafinil	Route: renal (80%) fecal (1%) Half-life: 7.5 to 15.0 hours Cl: nd

AUC=area under the curve, Cl=clearance, Cmax=maximum concentration, ER=extended-release, IR=immediate-release, nd=no data, SR=sustained release, Tmax=time to maximum concentration, Vd=volume of distribution

Table 4c. Pharmacokinetics-Central α-Agonist[12,13]

Drug	Absorption	Distribution	Metabolism	Elimination
Clonidine	Bioavailability: pe rcent not reported (food: minimal effect) Cmax: nd Tmax: 6.5 hours	Vd: nd Protein binding: nd	Method: Liver (50%) Metabolites: nd	Route: renal (40 to 60%) Half-life: 22 hours Cl: nd
Guanfacine	Bioavailability: nd (food: increased exposure with high fat foods) Cmax: 1 ng/mL (1 mg) Tmax: 6 hours (range, 4 to 8 hours)	Vd: nd Protein binding: 70%	Method: Liver (50%) Metabolites: guanfacine hydrochloride (activity not reported)	Route: renal (percent not reported) Half-life: 18±4 hours Cl: nd

Cl=clearance, Cmax=maximum concentration, nd=no data, Tmax=time to maximum concentration, Vd=volume of distribution

Table 4d. Pharmacokinetics-Central Nervous System Agents-Miscellaneous[21,28]

Drug	Absorption	Distribution	Metabolism	Elimination
Atomoxetine	Bioavailability: 63 % (food: extent of absorption unaffected) Cmax: nd Tmax: 1 to 2 hours	Vd: 74 to 250 L Protein binding: 98%	Method: liver (CYP2D6) Metabolites: 4-hydroxy-atomoxetine (active), noratomoxetine (inactive), N-desmethyl-atomoxetine (inactive)	Route: renal Half-life: 4 to 5 hours (extensive metabolites), 22 hours (poor metabolizers) Cl: 0.3 to 0.5 L/hour/kg
Sodium oxybate	Bioavailability: 25 % (food: absorption	Vd: 0.19 to 0.58 L/kg Protein binding:	Method: central nervous system, liver (extensive)	Route: renal (1 to 5%), fecal, expiration

Drug	Absorption	Distribution	Metabolism	Elimination
	delayed and decreased by high fat meals) Cmax: nd Tmax: 25 to 60 minutes	<1%	Metabolites (inactive): hemisuccinic, succinic acid	Half-life: 20 to 53 minutes Cl: 7 to 14 mL/minute/kg

Cl=clearance, Cmax=maximum concentration, CYP=cytochrome P450 isoenzyme, nd=no data, Tmax=time to maximum concentration, Vd=volume of distribution

Clinical Trials

Clinical trials demonstrating the safety and efficacy of the ADHD agents and stimulants in FDA-approved indications are outlined in Table 5.[37-141]

Data from several clinical trials demonstrate that the ADHD agents and stimulants are effective in the treatment of ADHD, as measured by significant decreases in ADHD rating scale scores compared to placebo. Although comparative trials have been conducted, it is difficult to interpret the results of these trials due to design flaws (e.g., small population, short treatment duration, variable outcomes). Overall, there is insufficient evidence to suggest that one ADHD agent and stimulant is more efficacious than another for the treatment of ADHD. [37-113]

The majority of efficacy data supporting the use of the ADHD agents and stimulants is derived from placebo-controlled trials. In addition, the majority of trials were conducted in the pediatric population. Limited data exists to demonstrate the efficacy of a variety of cerebral stimulants (amphetamine/dextroamphetamine, dexmethylphenidate, and lisdexamfetamine) and atomoxetine in the adult population. [42,49,64,82,83,97] In a large study by Goodman et al (N=725), adults 18 years of age or older were administered amphetamine/dextroamphetamine salts extended-release 10 to 60 mg daily for 10 weeks. By week 10, the mean ADHD rating scale (ADHD-RS) scores significantly decreased in the amphetamine/dextroamphetamine salts extended-release group compared to baseline, regardless of dose (P<0.0001).[42] In a four-year open label study in adults diagnosed with ADHD, treatment with atomoxetine reduced mean Conners Adult ADHD Rating Scale–Investigator Rated: Screening Version total ADHD symptom scores by 30.2% from baseline to endpoint (-8.8; P<0.001). In a study by Weisler and colleagues, treatment with lisdexamfetamine improved ADHD-RS total scores as early as week one of treatment and continued throughout the eleven month treatment period (P<0.001).[82] In adult patients who were stabilized on immediate-release methylphenidate at baseline, switching to methylphenidate extended-release (Concerta®) has had no effect on Adult ADHD investigator system symptom report scale (AISRS) after six weeks of treatment (11.2 vs 10.7; P=0.80).[97]

Clonidine extended-release and guanfacine extended-release are FDA-approved for use in ADHD as monotherapy and as adjunctive treatment to stimulants.[12,13] In children with ADHD, treatment with clonidine extended-release 0.2 mg or 0.4 mg daily significantly improved ADHD-RS from baseline at eight weeks compared to placebo (P<0.001).[60] In a six-week study evaluating the effect of guanfacine extended-release on psychomotor functioning, there were no significant differences between guanfacine extended-release and placebo groups on measures of psychomotor functioning or alertness on the Cambridge Neuropsychological Test Automated Battery-Choice Reaction Time scale (mean difference, 2.5; P=0.8 for choice reaction time, 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). Moreover, guanfacine extended-release was associated with a significant improvement in ADHD symptoms compared to placebo (P=0.001).[69] In a study by Sallee and colleagues, adolescents randomized to receive guanfacine extended-release 1 mg to 4 mg daily achieved statistically significant reductions in ADHD-RS-IV total scores from baseline compared to placebo. The placebo-adjusted mean endpoint changes from baseline were -6.75 (P=0.0041), -5.41 (P=0.0176), -7.34 (P=0.0016), and -7.88 (P=0.0006) in the guanfacine extended-release 1 mg, 2 mg, 3 mg and 4 mg groups, respectively.[70] Guanfacine extended-release was shown to significantly improve scores on the oppositional subscale of the Conners' parent rating scale-revised: long form compared to placebo over

nine weeks of treatment (*P*<0.001). The mean percentage reductions from baseline were 56.3% with guanfacine extended-release and 33.4% with placebo (*P*<0.001).[72] With regard to monotherapy, these agents have been shown to significantly improve ADHD rating scale scores compared to placebo. Both clonidine extended-release and guanfacine extended-release have only been evaluated in pediatric patients (six to 17 years of age).[60,69-74,77] Similarly, use of these agents as adjunctive treatment to stimulant therapy has been shown to significantly improve ADHD rating scale scores compared to stimulant monotherapy.[61,75,76] Prior to FDA approval of clonidine extended-release and guanfacine extended-release, the immediate-release formulations of these agents were evaluated, and demonstrated variable efficacy, for the treatment of ADHD.[59,68,100]

Armodafinil, modafinil, and sodium oxybate have all been shown to be more effective compared to placebo in patients with narcolepsy, OSA, and shift work disorder, as measured by significant improvements in sleepiness scale scores. In addition, sodium oxybate has been shown to significantly reduce the rate of inadvertent naps and cataplexy attacks compared to placebo. Similar to ADHD, there is insufficient evidence to suggest that one ADHD agent and stimulant is more efficacious than another for the treatment of sleep disorders.[114-141]

Table 5. Clinical Trials

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
Attention Deficit Hyperactivity Disorder				
McCracken et al[37] AMP-IR (Adderall®) 10 mg daily vs AMP-XR (Adderall XR®) 10 to 30 mg daily vs placebo	DB, PC, RCT, XO Children 6 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[38] AMP-IR (Adderall®) 12.5 mg daily vs MPH-IR 25 mg daily vs placebo	DB, PC, PG, RCT Children in grades 1 through 5 diagnosed with ADHD	N=58 3 weeks	Primary: CGI-S (parent and teacher) 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
Pelham et al[39] AMP-IR (Adderall®) 7.5 or 12.5 mg BID vs	DB, PC, RCT, XO Children 5 to 12 years of age diagnosed with ADHD	N=25 6 weeks	Primary: Time course and dose-dependent response information	Primary: Both doses of AMP-IR were generally more efficacious in reducing negative behaviors and improving academic productivity than low-dose MPH-IR (10 mg BID) throughout the course of the entire day. The differences were more pronounced when the effects of MPH-IR were wearing off at midday and late afternoon/early evening (*P*<0.025).

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
MPH-IR (Ritalin®) 10 or 17.5 mg BID vs placebo			Secondary: Not reported	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[40] AMP-IR (Adderall®) vs MPH-IR	MA (4 trials) Patients diagnosed with ADHD	N=216 3 to 8 weeks	Primary: CGI-S (parent, teacher and investigator) Secondary: Not reported	Primary: Combined results showed slightly greater efficacy with AMP-IR vs MPH-IR in clinician and parent ratings (*P*<0.05). No statistically significant difference was found in CGI-S scores with teacher ratings (*P*≥0.26). Secondary: Not reported
Biederman et al[41] AMP-XR (Adderall XR®) 10 to 30 mg daily vs placebo	DB, MC, PC, RCT Children 6 to 12 years of age diagnosed with ADHD (hyperactive-impulsive or combined subtypes)	N=584 3 weeks	Primary: CGI-S (teachers and parents) Secondary: Variation in responses based on morning and afternoon assessments	Primary: Each AMP-XR treatment group had a statistically significant improvement in both CGI-S teacher and parent scales (*P*<0.001). Secondary: The CGI-S teacher scores calculated for the morning and afternoon assessments showed all doses of AMP-XR to be more effective than placebo (*P*<0.001) at each assessment. The CGI-S teacher scores in the AMP-XR group were statistically significantly improved at all time points compared to those in the placebo group (*P*<0.001).
Goodman et al[42]	MC, OL, PRO	N=725	Primary: ADHD-RS,	Primary: At the end of the study, the mean ADHD-RS scores significantly decreased in

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
AMP-XR (Adderall XR®) 10 to 60 mg daily	Adults ≥18 years of age diagnosed with ADHD (any subtype)	10 weeks	CGI-I Secondary: SF-36	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[43] Atomoxetine 1.2 to 1.8 mg/kg/day vs placebo	2 DB, MC, PC, RCT Girls 7 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).
Michelson et al[44] Atomoxetine 1.2 to 1.8 mg/kg/day vs placebo	MC, OL, PC, RCT Children 8 to 18 years of age diagnosed with ADHD	N=297 8 weeks	Primary: ADHD-RS Secondary: CPRS-R, CHQ	Primary: Significant reduction in ADHD-RS was seen in both active groups (*P*<0.001). No difference was seen between the 1.2 and the 1.8 mg/kg/day treatment arms. Secondary: Atomoxetine 1.2 mg/kg showed significant decreases in all scales of CPRS-R (*P*<0.05). Atomoxetine 1.8 mg/kg showed significant increase in all scales of CHQ (*P*<0.05).
Kratochvil et al[45]	DB, MC, PC,	N=101	Primary:	Primary:

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
Atomoxetine 0.5 to 1.8 mg/kg/day vs placebo	RCT Children 5 to 6 years of age diagnosed with ADHD	8 weeks	ADHD-RS Secondary: CGI-S, CGI-I	Atomoxetine significantly reduced mean parent (P<0.009) and teacher (P=0.02) ADHD-RS total score compared to placebo. A total of 40% of children treated with atomoxetine and 22% of children who received placebo had CGI-I scores much to very much improved (P=0.1) with no significant differences between groups. A total of 62% of children treated with atomoxetine had CGI-S scores of moderately or severely ill at the end of the study compared to 77% of children who received placebo. Common adverse events included decreased appetite, gastrointestinal upset, and sedation. Most adverse events were considered mild or moderate by the study investigator.
Spencer et al[46] Atomoxetine up to 90 mg daily vs placebo	DB, MC, PC, RCT (pooled data) Children 7 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 1 and P<0.001 for study 2). Secondary: Atomoxetine displayed a significant mean reduction in CPRS-R:S index over placebo in both studies (study 1: -5.7 vs -2.6; P=0.023 and study 2: -8.8 vs -2.1; P<0.001). Atomoxetine displayed a statistically significant mean change in CGI-S scores over placebo in both studies (study 1: -1.2 vs -0.5; P=0.023 and study 2: -1.5 vs -0.7; P=0.001).
Dittmann et al[47] Atomoxetine 0.5 mg/kg/day for 7 days, followed by 1.2 mg/kg/day (fast titration)	DB, PC, RCT Patients 6 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

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
vs atomoxetine 0.5 mg/kg/day for 7 days, followed by 0.8 mg/kg/day for 7days, followed by 1.2 mg/kg/day (slow titration) vs placebo				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. 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[48] Atomoxetine 0.5 to 1.4 mg/kg/day	OL, PRO Children 6 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.

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
Adler et al[49] Atomoxetine 60 to 120 mg/day	MC, OL Adults diagnosed with ADHD	N=384 4 years	Primary: CAARS-Inv:SV total ADHD symptom score Secondary: CAARS-Self:SV, CGI-ADHD-S, HAM-D-17, HAMA, WRAADDS, SDS	Primary: The mean CAARS-Inv:SV Total ADHD Symptom scores decreased 30.2% from baseline to endpoint (-8.8; *P*<0.001). Secondary: Significant decreases were found on the CAARS-Inv:SV subscales, and the CAARS-Self:SV total and subscales (*P*<0.001). CGI-ADHD-S and WRAADDS scores improved significantly from baseline (-1.1 and -5.0, respectively; *P*<0.001 for both). SDS total and subscale scores improved 25.3% (-3.8; *P*<0.001). A slight increase was noted in HAM-D-17 scores (0.8; *P*=0.004), but this small change is not likely clinically relevant. There was no significant change in HAMA scores (0.4; *P*=0.216). HR, DBP, SBP increased. Weight loss over the course of the study was statistically significant (-0.94 kg; *P*<0.001).
Biederman et al[50] Atomoxetine 0.5 to 1.2 mg/kg/day vs AMP-XR (Adderall XR®) 10 to 30 mg daily	DB, FD, MC, RCT Girls 6 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).

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Both AMP-XR and atomoxetine were well tolerated. The number of adverse events was similar in both groups. Most adverse events reported were of mild or moderate severity.
Kemner et al[51] Atomoxetine 0.5 mg/kg once daily vs MPH-ER (Concerta®) 18 mg once daily	MC, OL, PRO, RCT Children 6 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] Acute Comparison Trial: Atomoxetine 0.8 to 1.8 mg/kg/day administered BID vs	DB, PC, RCT, XO Children 6 to 16 years of age diagnosed with ADHD (any subtype)	Acute Com-parison Trial: N=516 6 weeks XO Trial: N=178	Primary: ADHD-RS Secondary: CGI-S, CPRS, CHQ, and Daily Parent Ratings of Evening and Morning Behavior-	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

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
MPH-ER (Concerta®) 18 to 54 mg once daily vs placebo XO Trial: Atomoxetine 0.8 to 1.8 mg/kg/day administered BID Patients on MPH-ER were switched to atomoxetine during the XO trial.		6 weeks	Revised	compared to atomoxetine on CGI-S, CPRS and CHQ (*P*=0.004, *P*=0.003, *P*=0.02, respectively). XO Trial The responses to the two treatments in these patients were as follows: 34% responded to either atomoxetine or MPH-ER, but not both; 44% responded to both treatments; 22% did not respond to either treatment. Of the 70 patients who did not respond to MPH-ER in the initial trial, 43% subsequently responded to atomoxetine in the crossover trial. Of the 69 patients who did not respond to atomoxetine in the second trial, 42% had previously responded to MPH-ER. Of the patients classified as MPH-ER, 36% showed significantly worse response on atomoxetine, 18% showed significantly better response on atomoxetine, and 46% showed roughly the same response to treatment with atomoxetine. Of the 70 patients classified as MPH-ER nonresponders, 10% showed significantly worse response, 51% showed significantly better response, and 39% showed roughly the same response to treatment with atomoxetine.
Starr et al[53] Atomoxetine 0.5 mg/kg once daily vs MPH-ER (Concerta®) 18 mg once daily	OL, RCT African-American children 6 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
Wang et al[54]	DB, MC, RCT	N=330	Primary:	Primary:

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
Atomoxetine 0.8 to 1.8 mg/kg/day vs MPH-IR 0.2 to 0.6 mg/kg/day administered BID	Children 6 to 16 years of age diagnosed with ADHD	8 weeks	ADHD-RS Secondary: CPRS-R:S, CGI-S, treatment-emergent adverse events, weight	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).
Kratochvil et al[55] Atomoxetine titrated up to 2 mg/kg/day vs MPH-IR titrated up to 60 mg/day	MC, OL Boys 7 to 15 years of age and girls 7 to 9 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 Brief Fatigue Inventory were seen with both atomoxetine and MPH-IR (*P*<0.05).
Sutherland et al[56]	DB, MC, PC, RCT	N=241	Primary: AISRS	Primary: There was a significantly greater decrease in the AISRS total score for

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
Atomoxetine 40 to 100 mg/day vs atomoxetine 40 to 100 mg/day plus buspirone 15 to 45 mg/day vs placebo	Patients 18 to 60 years of age diagnosed with ADHD	8 weeks	Secondary: Not reported	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 1-7, but only statistically significant at week four (*P*<0.09). The most commonly reported adverse events from both treatment groups included insomnia, dry mouth, headache, and asthenia. Dizziness was most commonly reported for the atomoxetine plus buspirone treatment group. Discontinuations due to treatment-related adverse events were 15.5% for atomoxetine plus buspirone, 11.3% for atomoxetine, and 14.9% for placebo. Secondary: Not reported
Prasad et al[57] Atomoxetine 0.5 to 1.8 mg/kg/day vs standard current therapy	MC, OL, RCT Children 7 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[58] Atomoxetine	MA (9 trials) Patients	N=1,828 Variable	Primary: ADHD-RS	Primary: Atomoxetine significantly improved ADHD-RS scores compared to placebo (*P*<0.01 for all).

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	diagnosed with ADHD	duration	Secondary: CTRS-RS, CPRS-R:S, CGI-S, CHQ	Secondary: Atomoxetine significantly improved CTRS-RS, CPRS-R:S, and CGI-S scores compared to placebo (*P*<0.01 for all). Atomoxetine significantly improved quality of life as measured by the CHQ compared to placebo (*P*<0.01).
Hazell et al[59] Clonidine 0.1 to 0.2 mg/day vs placebo	PC, RCT, TB Children 6 to 14 years of age with ADHD and co-morbid ODD or conduct disorder	N=67 6 weeks	Primary: CBC (subscales conduct and hyperactive index) Secondary: Not reported	Primary: Significantly more children treated with clonidine than placebo improved on the CBC-Conduct scale (21 of 37 vs 6 of 29; *P*<0.01) but not the Hyperactive Index (13 of 37 vs 5 of 29; *P*=0.16). Compared to placebo, clonidine was associated with a greater reduction in standing SBP measured and with transient sedation and dizziness. Study patients treated with clonidine have a greater reduction in a number of unwanted effects associated with psychostimulant treatment compared to placebo. Secondary: Not reported
Jain et al[60] Clonidine ER 0.2 mg/day vs Clonidine ER 0.4 mg/day vs placebo	DB, PC, RCT Patients 6 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

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				0.4 mg/day). Improvements from baseline to week 5 in ADHD-RS hyperactivity score were -4.1 in the placebo group, -7.9 in the clonidine ER 0.2-mg/day group, and -8.8 in the clonidine ER 0.4-mg/day group (*P*<0.0012). Mean improvement in CPRS-R total score was significantly greater than placebo in both clonidine ER groups (*P*<0.01) at weeks three and five. Improvement in CGI-S and CGI-I from baseline to week five was significantly greater in both treatment groups vs placebo (*P*<0.0001 for CGI-S and *P*<0.003 for CGI-I). Significant improvement in PGA score from baseline in both treatment groups vs placebo was observed at week two (*P*<0.001) and was maintained through week seven (*P*<0.02) in the clonidine ER 0.2 mg/day group and through week five in the clonidine ER 0.4 mg/day group (*P*<0.009). The most common treatment-emergent adverse event was mild-to-moderate somnolence. Changes on electrocardiogram were minor and due to the pharmacology of clonidine.
Kollins et al[61] Clonidine ER 0.1 to 0.4 mg/day plus psycho-stimulant vs placebo plus psycho-stimulant	DB, MC, PC, RCT Children and adolescents diagnosed with hyperactive or combined subtype ADHD who had inadequate response to their psychostimulant	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

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	therapy			moderate in severity and included somnolence, headache, fatigue, upper abdominal pain, and nasal congestion.
Wigal et al[62] DXM (Focalin®) 2.5 to 10 mg BID vs MPH-IR 5 to 20 mg BID vs placebo	DB, MC, PC, RCT Children 6 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 PM and 6 PM assessments compared to placebo (*P*<0.0001 and *P*=0.0003 respectively). The MPH-IR group significantly decreased 3 PM SNAP-P assessments compared to the placebo group (*P*=0.0073) but did not reach statistical significance at the 6 PM assessment (*P*=0.064). Both DXM and MPH-IR improved CGI-I scores in significantly more patients than the placebo group (67% [*P*=0.0010] and 49% [*P*=0.0130] compared to 22%, respectively). Both DXM and MPH-IR significantly improved clinic-based math test scores compared to placebo (*P*=0.001 and *P*=0.0041 respectively). DXM significantly improved home-based math test scores compared to placebo (*P*=0.0236). MPH-IR did not reach statistical significance compared to placebo.
Greenhill et al[63] DXM-XR (Focalin XR®) 5 to 30 mg/day vs placebo	DB, MC, PC, RCT Children 6 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

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				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[64] DXM-XR (Focalin XR®) 20 to 40 mg/day vs placebo	DB, MC, PC, RCT Adults 18 to 60 years of age diagnosed with ADHD (any subtype), childhood onset of symptoms, and a baseline ADHD-RS score ≥24	N=184 5 weeks	Primary: ADHD-RS Secondary: ADHD-RS, CGI-I CGI-S, CAARS, Q-LES-Q	Primary: All doses of DXM-XR significantly improved ADHD-RS scores from baseline compared to placebo (*P*<0.05). Secondary: The 20 and 40 mg doses of DXM-XR achieved improved ADHD-RS scores ≥30% and were significant compared to placebo, the 30 mg group did not reach statistical significance. The percent of patients who achieved ≥30% were as follows: DXM-XR 20 mg, 57.9% (*P*=0.017); DXM-XR 30 mg, 53.7% (*P*=0.054); DXM-XR 40 mg, 61.1% (*P*=0.007); and placebo, 34.0%. All doses DXM-XR significantly improved CGI-I scores over placebo (*P*<0.05 for all). The 20 and 40 mg doses of DXM-XR improved CGI-S scores in a greater percent of patients compared to placebo, but the 30 mg group did not reach statistical significance. The percents of patients were as follows: 20 mg, 68.4% (*P*=0.09); 30 mg, 61.1% (*P* value not significant); 40 mg, 64.8% (*P*=0.031); and placebo, 41.5%. All doses of DXM-XR significantly improved CAARS scores compared to placebo (*P*<0.05 for all). None of the groups improved Q-LES-Q scores from baseline nor were there significant differences between groups.
Adler et al[65] DXM-XR (Focalin XR®) 20 to 40 mg/day	DB, MC, RCT Patients 18 to 60 years of age	N=103 6 months	Primary: Long-term safety and tolerability	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.

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo After completion of DB phase, patients could enter an OL extension phase with flexible dosing 20 to 40 mg/day for 6 months.	diagnosed with ADHD		Secondary: ADHD-RS, CGI-I	Secondary: Mean improvements in ADHD-RS scores were -10.2 for study patients switched from placebo to DXM-XR and -8.4 for those maintained on DXM-XR. Improvements in CGI-I scores were reported in 95.1% of study patients switched from placebo to DXM-XR and 95.0% of study patients maintained on DXM-XR.
Stein et al[66] DXM-XR (Focalin XR®) 10 to 30 mg/day vs AMP-XR (Adderall XR®) 10 to 30 mg/day	DB, PC, RCT Patients 9 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: Not reported
Muniz et al[67]	DB, MC, RCT	N=84	Primary:	Primary:

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
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	Children 6 to 12 years of age diagnosed with ADHD and stabilized on MPH ≥2 weeks	10 weeks	SKAMP Secondary: Not reported	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[68] Guanfacine 0.5 mg at bedtime, day 4 added 0.5 mg in the morning, day 8 added 0.5 mg afternoon dose vs placebo	DB, PC, PG, RCT Children 7 to 15 years of age diagnosed with ADHD and tic disorder	N=34 8 weeks	Primary: ADHD-RS, CGI-I, CPRS-R (hyperactivity index), YGTSS, CPT Secondary: Not reported	Primary: Guanfacine was associated with a mean improvement of 37% in the teacher-rated ADHD-RS total score compared to 8% improvement for placebo (*P*<0.01). Nine of 17 patients who received guanfacine were rated on the CGI-I as either much improved or very much improved, compared to 0 of 17 patients who received placebo. The mean CPRS-R on the parent-rated hyperactivity index improved by 27% in the guanfacine group and 21% in the placebo group, not a significant difference. Tic severity decreased by 31% in the guanfacine group, compared to 0% in the

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				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[69] Guanfacine ER 1 to 3 mg once daily vs placebo	DB, MC, PC, RCT Patients 6 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[70] Guanfacine ER 1 to 4 mg once daily vs placebo	DB, MC, PC, RCT Patients 6 to 17 years of age with ADHD and a baseline score of 24 on the ADHD-RS-IV	N=324 9 weeks	Primary: ADHD-RS-IV total score Secondary: CPRS-R, CGI-I, PGA	Primary: The mean reduction in ADHD-RS-IV total scores from baseline to endpoint across all guanfacine ER dose groups was -19.6 compared to -12.2 for the placebo group. The placebo-adjusted mean endpoint changes from baseline were -6.75 (*P*=0.0041), -5.41 (*P*=0.0176), -7.34 (*P*=0.0016), and -7.88 (*P*=0.0006) in the guanfacine ER 1, 2, 3, and 4 mg groups, respectively. Placebo-adjusted mean baseline-to-endpoint changes for symptoms of inattentiveness were: -4.2 (*P*=0.002), -3.0 *P*=0.02), -3.5 (*P*=0.007), and -4.0

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				(*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 8 (-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 8 hours (-9.0; *P*=0.01) postdose. For the 1 mg guanfacine ER dosage group, the placebo-adjusted LSMD in CPRS-R at 8, 12, 14, and 24 hours were -12.8 (*P*=0.0004), -11.4 (*P*=0.002), -10.4 (*P*=0.0077), and -8.9 (*P*=0.02), respectively. Based on CGI-I scores, the percentages of the patients showing clinical improvement were 30% (placebo), 54% (guanfacine ER 1 mg; *P*=0.007 vs placebo), 43% (guanfacine ER mg; *P*=0.1404 vs placebo), 55% (guanfacine ER mg; *P*=0.006 vs placebo), and 56% (guanfacine ER mg; *P*=0.004 vs placebo). Improvements in PGA scores were 30% (placebo), 51% (guanfacine ER 1 mg; *P*=0.030 vs placebo), 36% (guanfacine ER 2 mg; *P*=0.4982 vs placebo), 62% (guanfacine ER mg; *P*=0.002 vs placebo), and 57% (guanfacine ER 4 mg; *P*=0.0063 vs placebo). Mild to moderate treatment-emergent adverse events in patients taking guanfacine ER were somnolence, headache, fatigue, sedation, dizziness, irritability, upper abdominal pain, and nausea. There were no significant differences in sleepiness between the patients taking placebo and guanfacine ER. Guanfacine ER was not associated with abnormal changes in height or weight. SBP, DBP, and pulse rate decreased as the guanfacine ER dose increased and then increased during dose maintenance and tapering. The range

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				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[71] Guanfacine ER 1 to 4 mg once daily	ES, OL Patients 6 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 rated the majority of patients very much improved (29.3%) or much improved (28.8%).

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				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
Connor et al[72] Guanfacine ER 1 to 4 mg once daily vs placebo	DB, MC, PC, RCT Patients 6 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). 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[73] Guanfacine ER 2 to 4 mg once daily vs	DB, MC, PC, RCT Patients 6 to 17 years of age with ADHD combined	N=345 8 weeks	Primary: ADHD-RS-IV total score observed during the last treatment week	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.

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placebo	subtype, predominantly inattentive subtype, or predominantly hyperactive-impulsive subtype		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)	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 (*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

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				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[74] Guanfacine ER 2 to 4 mg once daily	ES, OL Patients 6 to 17 years of age with ADHD combined subtype, predominantly inattentive subtype, or predominantly hyperactive-impulsive subtype	N=240 24 months	Primary: Safety Secondary: ADHD-RS-IV, PGA, CHQ-PF50	Primary: Somnolence (30.4%), headache (26.3%), fatigue (14.2%), and sedation (13.3%) were the most frequently reported adverse events. Changes from baseline to endpoint in SBP, DBP, and pulse rate were -0.8 mm Hg, -0.4 mm Hg, and -1.9 beats per minute, respectively. Mean changes in pulse rate and QRS intervals were generally unchanged across study visits. Hypotension was reported in 2.9% of patients and bradycardia was reported in 2.1% of patients. There were no unexpected changes in mean height or weight. Approximately 7.0% of patients reported weight increase possibly or probably related to study drug. Weight decrease was not reported. Appetite increase was reported by 2.1% of patients, appetite decrease by 3.3% of patients, and anorexia by 0.8% of patients. Secondary: The mean ADHD-RS-IV total score was significantly reduced from baseline to endpoint (-18.1; *P*<0.001 vs baseline). 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.

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				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[75] Guanfacine ER 1 to 4 mg once daily, added to existing stimulant therapy	MC, OL Patients 6 to 17 years of age with ADHD (combined, predominantly inattentive, or predominantly hyperactive-impulsive subtype) and who were on a stable regimen of either MPH or AMP ≥1 month with suboptimal control of ADHD symptoms	N=75 9 weeks	Primary: ADHD-RS-IV, CPRS-R, CGI-I, CGI-S, CHQ-PF50, and PGA Secondary: Not reported	Primary: The most common treatment-related adverse events were fatigue (34.7%), headache (33.3%), upper abdominal pain (32.0%), irritability (32.0%), somnolence (18.7%), and insomnia (16.0%). Most adverse events were mild to moderate in severity. The incidences of the treatment-emergent adverse events were comparable between both psychostimulant subgroups except for fatigue (28.6% in the guanfacine ER plus MPH subgroup vs 18.2% in the guanfacine ER plus AMP subgroup) and irritability (14.3% in the guanfacine ER plus MPH subgroup vs 33.3% in the guanfacine ER plus AMP subgroup). Twenty patients have a decrease in BP judged to be of clinical interest. Twelve patients exhibited orthostatic BP decreases. None of the patients with BP decreases reported syncope or lightheadedness. At baseline, the mean PDSS score was 15.0. Decreases were observed at visit six (-4.8) and end point (-3.1). During treatment, there was an increase from screening in the number of patients reporting clinically significant dullness, tiredness, and listlessness on the PSERS. There was a decrease in the number of patients with clinically significant loss of appetite and trouble sleeping. The psychostimulant subgroups were generally comparable. Significant decreases from baseline (psychostimulant only) to end 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%.

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				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[76] Guanfacine ER 1 to 4 mg/day in the morning plus placebo at bedtime vs placebo in the morning and guanfacine ER 1 to 4 mg/day in the afternoon vs placebo Patients continued stable dose of psycho-	DB, MC, PC, RCT Children and adolescents 6 to 17 years of age diagnosed with ADHD	N=461 9 weeks	Primary: ADHD-RS Secondary: CGI-S, CGI-I	Primary: At the end of the study, guanfacine ER treatment groups showed significantly greater improvement from baseline ADHD-RS total scores compared to placebo plus psychostimulant (guanfacine ER in the morning; *P*=0.002; guanfacine ER in the evening; *P*<0.001). Secondary: Significant benefits of guanfacine ER treatment compared to placebo plus psychostimulant were observed on the CGI-S (guanfacine ER in the morning; *P*=0.013, guanfacine ER in the evening; *P*<0.001) and CGI-I (guanfacine ER in the morning; *P*=0.024, guanfacine ER in the evening; *P*=0.003). At study endpoint, small mean decreases in pulse, SBD, and DBP were observed in guanfacine ER treatment groups compared to placebo plus psychostimulant group. The most common treatment-emergent adverse events were mild to moderate in severity and included headache, somnolence and upper respiratory infections.

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
stimulant given in the morning.				
Faraone et al[77] Guanfacine ER 1 to 4 mg once daily	MA Patients 6 to 17 years of age with ADHD (combined subtype, predominantly inattentive subtype, or predominantly hyperactive-impulsive subtype)	N=813 6 to 9 weeks	Primary: Predictors of efficacy and sedation using various models 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). *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

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
Biederman et al[78] LDX 30 to 70 mg/day vs placebo	DB, MC, PC, RCT Children 6 to 12 years of age diagnosed with ADHD and with an ADHD-RS score of ≥28	N=209 4 weeks	Primary: ADHD-RS Secondary: CPRS-R, CGI-S, CGI-I	Primary: ADHD-RS scores were significantly greater with each of the three LDX doses compared 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[79] LDX 30 to 70 mg/day vs placebo AMP-XR 10 to 30 mg was used as a control arm.)	DB, MC, PC, RCT, XO Children 6 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).
Findling et al[80] LDX 30 to 70 mg/day 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	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).

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
			adverse events	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[81] LDX 30 to 70 mg/day	MC, OL, SA Children 6 to 12 years of age diagnosed with ADHD	N=274 12 months	Primary: ADHD-RS Secondary: CGI-S	Primary: Mean ADHD-RS total score improved by 27.2 points (*P*<0.001). Mean ADHD-RS inattentive subscale score improved by 13.4 points (*P*<0.001). Mean ADHD-RS hyperactivity score improved by 13.8 points (*P*<0.001) After improvements during the first four weeks, improvements in ADHD-RS scores were maintained throughout eleven months of treatment. Secondary: Improvement in scale scores seen in >80% of study patients at endpoint and >95% of completers at 12 months were rated as improved. Adverse event included insomnia and vomiting and considered mild or moderate by the study investigator. There were no clinical meaningful changes in BP or electrocardiographic parameters.
Weisler et al[82] LDX 30 to 70 mg/day	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:

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				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.
Mattingly et al[83] LDX 30 to 70 mg/day	Post-hoc analysis of Weisler et al[82] Study Grade: Not applicable 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 1 or 2). Of the 93 patients with predominantly inattention symptom cluster at baseline, 74 were classified as clinical responders at trial end. All 13 patients who had predominantly hyperactivity/impulsivity symptom cluster at baseline were classified as clinical responders at endpoint. At endpoint, 236 of patients who had combined type ADHD at baseline, 196 were classified as clinical responders. Secondary: Not reported Safety: There were 191 patients included in the safety analysis, and 158 patients discontinued treatment. The reasons for discontinuation were as follows: 28 due

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				to treatment-emergent adverse events, 11 due to lack of efficacy, 27 due to protocol violation, 41 lost to follow up, 42 withdrew consent, one due to physician decision, seven due to other reasons, and one due to death. Overall, 87.7% of patients experienced a treatment-emergent adverse event. Most events were rated as mild to moderate in severity, and severe events occurred in 12% of the safety population. There were 12 severe treatment-emergent adverse events in ten patients were considered possibly or probably treatment-related. At trial end, small but significant increases were noted in SBP and pulse. Limitations: Not applicable Conclusion: LDX was effective in patients with predominantly inattention, hyperactivity/ impulsivity, and combined ADHD symptom clusters. Groups exhibiting specific predominant subtype symptoms did not differ in clinical response to LDX.
Wigal et al[84] MPH-ER (Concerta®) 18 to 54 mg/day vs placebo	DB, PC, RCT Children 9 to 12 years of age diagnosed with ADHD	N=78 5 months	Primary: PERMP, SKAMP, TOVA, Finger Windows forward and backward subtest Secondary: Not reported	Primary: MPH-ER significantly improved performance on the number of problems attempted and number of problems correctly answered on the PERMP compared to placebo (*P*<0.001). MPH-ER significantly improved performance on inattention, deportment, and total ratings of the SKAMP measure (*P*<0.001) as compared to placebo. Children taking MPH-ER had statistically significantly better scores than children taking placebo on response time (*P*<0.000). MPH-ER significantly improved performance on memory as compared to placebo. Most common adverse effects included decreased appetite, upper abdominal pain, headache and irritability. Most adverse events were considered mild or

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				moderate by the study investigator. Secondary: Not reported
Casas et al[85] MPH-ER (Concerta®) 54 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.
Wilens et al[86] MPH-ER (Concerta®) 18 to 54 mg/day	MC, OS, PRO Children 6 to 13 years of age	N=432 1 year	Primary: HR and BP after one year	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

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
	diagnosed with ADHD		Secondary: Not reported	end point. Secondary: Not reported
Mattos et al[87] MPH-ER (Concerta®) 18 to 72 mg/day	MC, OL Men and women 18 to 65 years of age diagnosed with ADHD	N=60 12 weeks	Primary: ASRS, AAQoL, STAI, HAMD, CGI-I Secondary: Not reported	Primary: ADHD symptom severity improved with the ASRS scores (total score, inattention and hyperactivity) significantly reduced from baseline to weeks four, eight, and 12 (P<0.001). AAQoL subscales (P<0.001), as well as AAQoL total score (P<0.001), significantly improved from baseline to week 12. A significant reduction in STAI, CGI-I, and HAMD, scores were observed (P<0.0001). The most common adverse events included appetite changes (25%), dry mouth (16.7%), headache (11.7%), irritability (5%) and insomnia (5%). Adverse events were mild to moderate in severity as reported by the study investigators. Secondary: Not reported
Cox et al[88] MPH-ER (Concerta®) 36 mg once daily on days 1 to 5, followed by 72 mg once daily on days 6 to 17 vs AMP-XR (Adderall XR®) 15 mg once daily on days 1 to 5, followed	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	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

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
by 30 mg once daily on days 6 to 17 vs placebo			Secondary: Not reported	MPH-ER as better for driving performance (*P*=0.008). Secondary: Not reported
Yang et al[89] MPH-ER 18 to 54 mg/day vs atomoxetine 0.5 to 1.4 mg/kg/day	RCT, SB Children and adolescents 7 to 14 years of age diagnosed with ADHD	N=142 4 to 6 weeks	Primary: RCFT, Digit span, Stroop color word test Secondary: Not reported	Primary: Both MPH-ER and atomoxetine significantly improved visual memory, verbal memory, and word inference time. Visual and verbal memory was not significantly different from the control group at post-treatment assessment (*P*>0.05). Although word interference time was more improved than the control group, there was no statistically significant difference (*P*>0.05). Secondary: Not reported
Wolraich et al[90] MPH-ER (Concerta®) 18 to 54 mg/day vs MPH-IR 5 to 15 mg TID vs placebo	DB, PC, PG, RCT Children 6 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	Primary: Both MPH-ER and MPH-IR demonstrated a statistically significant improvement in the Iowa Conners I/O and O/D rating scale scores compared to placebo at week one and at the end of the study (*P*<0.001). There was no significant difference in the mean Iowa Conners scale scores between the MPH-ER and MPH-IR groups at week one (*P*=0.838) or at the end of the study (*P*=0.539). Secondary: Teacher and parent SNAP-IV scores were significantly better for patients in the MPH-ER and MPH-IR groups than for those in the placebo group (*P*<0.001). There was not a significant difference in SNAP-IV scores between the MPH-ER and MPH-IR groups.

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
			and teachers)	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).
Pelham et al[91] MPH-ER (Concerta®) 18 to 54 mg/day vs MPH-IR 5 to 15 mg TID vs placebo	DB, PC, RCT, XO Children 6 to 12 years of age diagnosed with ADHD (any subtype) who were taking MPH prior to study entry	N=68 1 week	Primary: Iowa Conners I/O and O/D rating scales (teacher and parents), SKAMP scale (teacher) Secondary: Not reported	Primary: MPH-ER and MPH-IR were better than placebo in the Iowa Conners I/O and O/D rating scale scores from teachers and parents (*P*<0.05). MPH-ER scored significantly better than MPH-IR in the parent Iowa Conners I/O rating scales (*P*<0.05). In the SKAMP scales, MPH-ER and MPH-IR were similar in efficacy, but both were significantly better than placebo. Secondary: Not reported
Gau et al[92] MPH-ER (Concerta®) 18 to 36 mg/day vs MPH-IR 5 to 10 mg TID	OL, RCT Children 6 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

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				much or much improved (84.4%) than the MPH-IR group (56.3%) (*P*=0.014) based on the CGI score.
Lopez et al[93] MPH-ER (Concerta®) 18 to 36 mg/day vs MPH-XR (Ritalin LA®) 20 mg/day vs placebo	DB, PC, RCT Children 6 to 12 years of age diagnosed with ADHD who were previously stabilize on MPH (equivalent dose of 10 mg BID)	N=36 28 days	Primary: SKAMP scales Secondary: Not reported	Primary: Both MPH-ER and MPH-XR statistically improved SKAMP scale scores compared to placebo (*P*<0.001). Secondary: Not reported
Swanson et al[94] MPH-ER (Concerta®) 18 to 54 mg/day vs MPH-XR (Metadate CD®) 20 to 60 mg/day vs placebo	DB, MC, PC, RCT, XO Children 6 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[95] MPH-ER (Concerta®) 18 mg	MC, RCT, SB, XO Children 6 to 12	N=54 6 weeks	Primary: SKAMP-A rating subscale	Primary: All doses of the study medications significantly improved SKAMP-A scores from baseline at all time points, compared to placebo (*P*<0.038).

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
vs MPH-ER (Concerta®) 36 mg vs MPH-ER (ER-MPH) 20 mg vs MPH-ER 40 mg vs placebo All medications were dosed once per study day (6 consecutive Saturdays). Patients continued their regular ADHD medications on Sunday through Thursday of the study weeks, with no medications allowed on Friday.	years of age diagnosed with ADHD and stabilized on MPH (20 to 40 mg/day)		Secondary: SKAMP-D and SKAMP-C rating subscales and written math tests	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.
Jahromi et al[96] MPH-IR 0.125 mg/kg/	DB, RCT, XO Children 5 to 13	N=33 4 weeks	Primary: JAMES, Caregiver-Child	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

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
dose BID for 1 week (low dose) vs MPH-IR 0.25 mg/kg/ dose BID for 1 week (medium dose) vs MPH-IR 0.50 mg/kg/ dose BID for 1 week (high dose) vs placebo for 1 week	years of age with PDD and hyperactivity		Interaction measure (competing demands and clean-up task) captured social communi-cation, self-regulation and affective behavior Secondary: Not reported	dose showed significant improvement compared to placebo (*P*<0.05); no significant differences found between placebo and the medium or high doses. No significant improvement in self-regulation for the competing demands task when comparing best dose MPH to placebo (*P*=0.09); significant improvement in self-regulation behaviors comparing low dose MPH (*P*<0.05) and medium dose effect (*P*<0.01) compared to placebo; no improvement found in high dose MPH over placebo. No significant improvement in self-regulation behaviors for the clean-up task for any of the three dose levels of MPH compared to placebo, or between placebo and the best dose of MPH (*P*>0.05). Significant improvement in affective behavior for the competing demands task when comparing medium MPH dose (*P* <0.05) and high MPH dose compared to placebo (*P*<0.05); no improvement found in best dose of MPH compared to placebo (*P*=0.09); or low dose (*P*=0.07). No significant improvement on affective behavior for the clean-up task and any MPH dose (*P*>0.05). Secondary: Not reported
Spencer et al[97] MPH-IR TID 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 OROS-MPH had no effect on AISRS score at the study endpoint (11.2 vs 10.7; *P*=0.80). Study patients stabilized on MPH-IR and switched to OROS-MPH remained satisfied over 71% of the time. MPH-IR treatment group missed significantly more doses than the OROS-MPH treatment group (7.3 vs 3.3; *P*=0.02). Secondary:

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				Not reported
Efron et al[98] MPH-IR 0.3 mg/kg/ dose BID vs DEX-IR 0.15 mg/kg/ dose BID Patients received 1 drug for 2 weeks then crossed over to the other stimulant for 2 weeks.	DB, RCT, XO Children 5 to 15 years of age diagnosed with ADHD	N=125 4 weeks	Primary: SERS Secondary: Not reported	Primary: There was a statistically significant decrease in the mean number of side effects in the MPH-IR group vs the DEX-IR group (8.19 vs 7.19; *P*=0.03) based on the results of the SERS questionnaire which assess the 17 most common side effects of stimulants including trouble sleeping, decreased appetite and anxiousness. Mean severity of side effects statistically significantly improved in the MPH-IR group compared to the DEX-IR group (3.24 vs 3.73; *P*<0.01). A majority of parents rated their children as improved compared to their "usual selves" in both of the treatment groups (68.8% in the DEX-IR groups and 72% in the MPH-IR). Secondary: Not reported
Pelham et al[99] MPH-IR 10 mg BID vs MPH-SR (Ritalin SR®) 20 mg/day vs DEX-SR (Dexedrine®) 10 mg/day vs pemoline 56.25 mg/day	DB, PC, RCT, XO Boys 8 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, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo				
Palumbo et al[100] MPH-IR 5 to 60 mg/day vs clonidine 0.05 to 0.6 mg/day vs MPH-IR plus clonidine vs placebo	DB, MC, PC, RCT Children 7 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[101] MPH-XR (Metadate CD®) 20 to 60 mg/day vs placebo	DB, MC, PC, RCT Children 6 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

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				significant in the MPH-XR group vs the placebo group (9.7 vs 2.5%; *P*=0.007).
McGough et al[102] MPH transdermal patch 10 to 27 mg/day vs placebo	OL, RCT (first 5 weeks) then DB, PC Children 6 to 12 years of age diagnosed with ADHD	N=80 7 weeks	Primary: Evaluate time course effects of MTS vs PTS via SKAMP-A, SKAMP-D, PERMP, ADHD-RS-IV, CPRS-R, CGI-I, and PGA rating scales Secondary: Acute efficacy and tolerability of MTS	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[103]	DB, DR, MC,	N=36	Primary:	Primary:

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
MPH transdermal patch: 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 ≥12 hours daily Each patient received single applications of MPH transdermal patch 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 AM or 7 AM).	RCT Children 7 to 12 years of age diagnosed with ADHD	8 days	MTS efficacy and influence of exposure time on morning effects Secondary: Not reported	All doses of MPH transdermal patches were significantly improved vs placebo on measures of social behavior in recreational settings, classroom functioning, and parent ratings of evening behavior (P<0.05). Beneficial effects of MPH transdermal patches were observed at all time points after application of the patch and were still seen for three 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[104] MPH transdermal patch: 12.5 cm^2, 25 cm^2, and 37.5 cm^2 plus behavior modification Each participant had 2 days on each treatment without concomitant behavior modification and 4 days on each treatment with behavior modification.	DR, RCT Children aged 6 to 12 years diagnosed with ADHD	N=27 6 weeks	Primary: Proportion that reached individual target goals in Daily Report Card scores Secondary: Not reported	Primary: The percentage of individualized target criteria met by children in their Daily Report Card assessment was significantly (P<0.05 for all) higher with MPH transdermal patch 12.5, 25, and 37.5 cm^2 vs placebo, both without behavior modification (41.9, 63.1, and 66.2 vs 20.8%) and with behavior modification (73.7, 87.5, and 86.2 vs 54.7%; all P<0.05). Response rates were higher in the MPH transdermal patches 25 cm^2 group than in the 12.5 cm^2 group, both with and without behavior modification (P<0.05 for both); increasing the size of the patch to 37.5 cm^2 added no further advantage. Secondary: Not reported
Faraone et al[105] MPH transdermal patch	DB, MC, PC, RCT	N=268 5 weeks	Primary: CSHQ	Primary: No significant difference in the severity of sleep problems was observed among the treatment and placebo groups (P≥0.233).

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
10 to 30 mg/day worn for 9 hours per day or MPH-ER (Concerta®) 18 to 54 mg/day vs placebo	Children 6 to 12 years of age diagnosed with ADHD (predominantly hyperactive-impulsive, predominantly inattentive, or combined type)		Secondary: Not reported	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[106] MPH transdermal patch 10 to 30 mg/day or MPH (OROS-MPH) 18 to 54 mg/day vs placebo	DB, PC, RCT Children 6 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, OROS-MPH, and placebo at baseline (43.0, 43.8, and 41.9, respectively), but not at endpoint (18.8, 21.8, and 32.1, respectively). Mean change from baseline in ADHD-RS scores was greater in study patients receiving MPH transdermal patch and OROS-MPH 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 OROS-MPH showed improvements over placebo in mean total parent and teacher scores from baseline to endpoint. More study patients receiving MPH transdermal patch and OROS-MPH 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.

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
Chou et al[107] MPH (OROS-MPH) 18, 36, or 54 mg once daily	OS Study Grade: Not applicable Children 6 to 19 years of age with ADHD who have received MPH-IR for ≥1 month	N=521 10 weeks (6 weeks forced-titration phase to achieve remission, followed by a 4 week main-tenance phase)	Primary: Symptomatic remission Secondary: Changes in efficacy and satisfaction	Primary: Using the forced-titration of MPH (OROS-MPH) 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. Safety: Among the items on the Barkley SERS, poor appetite was the only one exacerbated on visit three, but improved on later visits. The other side effects gradually decreased in intensity throughout the trial period, and the difference from baseline reached significance from visit three to trial end. At trial end, there was a decrease in both mean body weight (-0.85 kg) and mean respiratory rate (-0.44/minute), and an increase in mean pulse rate (5.09 beats per minute) in comparison with baseline with significance (P<0.001). Five percent of patients withdrew from the trial because of adverse events, and these patients mostly left due to poor appetite and insomnia. Three patients experienced at least one serious adverse event that was not deemed to be treatment-related. Limitations: Not applicable

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				Conclusion: Results suggest remission as a treatment goal for ADHD therapy by providing an optimal dosage of medication for children and adolescents with ADHD through using an effective and tolerable forced-titration scheme.
Faraone et al[108] AMP-IR, AMP-XR, atomoxetine, bupropion, DEX-IR, DEX-ER, DEXM-IR, modafinil, MPH-ER, MPH-IR, MPH-XR, MPH transdermal patch, 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 nonstimulant 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[109] ADHD medications vs nonusers	RETRO Children 3 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[110] AMP and MPH vs	RETRO Patients 6 to 21 years of age diagnosed with	N=171,126 Variable duration	Primary: Cardiac events (inpatient diagnosis of chest pain,	Primary: There were 0.92 new cardiac events and 3.08 new cardiac symptoms per 1,000,000 days of current stimulant use. Current stimulant use compared to no stimulant use was not associated with

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
nonusers	ADHD who were prescribed AMP or MPH		cardiac dysrhythmia or transient cerebral ischemia) and cardiac symptoms (tachycardia, palpitations, or syncope) Secondary: Not reported	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 amphetamine use. Secondary: Not reported
Schelleman et al[111] AMP, atomoxetine, MPH	RETRO Patients 3 to 17 years of age with a prescription for an AMP, atomoxetine, or MPH	N=219,954 Variable duration	Primary: Sudden death, ventricular arrhythmia, stroke, MI Secondary: Not reported	Primary: No significant difference between incident users and nonusers was observed in the rate of sudden death or ventricular arrhythmia (HR, 1.60; 95% CI, 0.19 to 3.60) or all-cause death (HR, 0.76; 95% CI, 0.52 to 1.12). None of the strokes identified during exposed time to ADHD medications were validated. No MIs were identified in ADHD medication users. No significant difference between prevalent users and nonusers was observed (HR for validated sudden death or ventricular arrhythmia, 1.43; 95% CI, 0.31 to 6.61; stroke, 0.89; 95% CI, 0.11 to 7.11; stroke/MI, 0.72; 95% CI, 0.09 to 5.57; and all-cause death, 0.77; 95% CI, 0.56 to 1.07). Secondary: Not reported
Hanwella et al[112]	MA (5 trials)	N=2,762	Primary:	Primary:

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
Atomoxetine vs MPH	Children and adolescents 6 to 16 years of age diagnosed with ADHD	Variable duration	ADHD-RS Secondary: Not reported	The MA did not find a significant difference in efficacy between MPH and atomoxetine when comparing SMD in ADHD-RS scores (SMD, 0.09; 95% CI, -0.08 to 0.26). There was no significant difference in response rates between the two medications (RR, 0.93; 95% CI, 0.76 to 1.14). Treatment effects between the formulations of MPH showed a significant SMD in ADHD-RS favoring OROS-MPH (SMD, 0.32; 95% CI, 0.12 to 0.53). MPH-IR was not superior to atomoxetine (SMD, -0.04; 95% CI, -0.19 to 0.12). There was no significant difference in acceptability between atomoxetine and MPH (RR, 1.22; 95% CI, 0.87 to 1.71). Secondary: Not reported
Bloch et al[113] 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
Narcolepsy				
Harsh et al[114] Armodafinil 150 to 250 mg once daily	DB, MC, PC, RCT Patients 18 to 65	N=196 12 weeks	Primary: MWT 0900-1500 sleep latency, CGI-C	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

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	years of age diagnosed with narcolepsy		Secondary: MWT 1500-1900 sleep latency, CGI-C, CDR, ESS, BFI	comparisons). Secondary: Mean MWT 1500–1900 sleep latency increased 1.5, 1.6, and 1.6 minutes in the 150 mg, 250 mg, and armodafinil combined groups, respectively, and decreased 1.2 min from baseline in the placebo group. The differences for the armodafinil combined group 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. 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;

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				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.
No authors listed US Modafinil in Narcolepsy Group[115] Modafinil 200 to 400 mg/day vs placebo	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. 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.
No authors listed US Modafinil in Narcolepsy Group[116]	DB, MC, PC, RCT	N=271 9 weeks	Primary: MWT, CGI-C	Primary: MWT improved for both modafinil groups vs the placebo group (*P*<0.001) at each follow-up visit (weeks three, six, nine).

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
Modafinil 200 to 400 mg/day vs placebo	Adults 17 to 67 years of age diagnosed with narcolepsy		Secondary: MSLT, ESS	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[117] Modafinil 200 to 400 mg/day 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.
Billiard et al[118] 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

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				placebo group (*P*<0.05).
Boivin et al[119] 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, ≥2 sleep onset REM periods and MSLT <5 minutes	N=10 12 weeks	Primary: Subjectively assessed sleepiness, FCRTT, PLM, nocturnal sleep organization Secondary: Not reported	Primary: Subjective sleepiness was significantly reduced in the modafinil group compared to the placebo group (*P*<0.05) based on home questionnaires. Modafinil significantly reduced the number of gaps and % of error at the FCRTT (*P*<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[120] 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 month	N=40 5 weeks	Primary: ESS, tolerability Secondary: Not reported	Primary: Mean ESS scores were <12 for all groups at the end of the study: 11.3 in the no-washout group, 8.2 for in the washout group, and 10.1 in the taper-down/titrate-up group. 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 taper/titrate group. Secondary: Not reported
No authors listed US Xyrem MC Study Group[121] Phase 1 (2 weeks):	DB treatment withdrawal study design (alternative to conventional DB,	N=55 4 weeks	Primary: Cataplexy attacks, treatment-emergent	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).

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
Continue sodium oxybate at the dose previously prescribed. Phase 2 (2 weeks): Continue sodium oxybate treatment at previously prescribed dose vs conversion to placebo	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		adverse events Secondary: Not reported	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
No authors listed Xyrem International Study Group[122] 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: 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 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:

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				Not reported
No authors listed Xyrem International Study Group[123] 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
Black et al[124] 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 3 and 4 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 1 sleep and the frequency of nocturnal awakenings were each significantly decreased at the 6 and 9 g/night doses.

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				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[125] Sodium oxybate 4.5 to 9 g/day in 2 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: FOCS 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 FOCS (*P*<0.001), as well as in the activity level (*P*<0.001), vigilance (*P*<0.001), general productivity (*P*=0.002), and social outcomes (*P*<0.001) subscales. Effect sizes escalated from small effects for the 6 g per day dose of sodium oxybate to large effects for the 9 g/day dose. Secondary: Not reported
Wang et al[126] 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

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				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 1 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[127] Sodium oxybate 6 to 9 g/day vs modafinil 200 to 600 mg/day vs sodium oxybate 6 to 9 g/day plus modafinil 200 to 600 mg/day vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with narcolepsy taking 200 to 600 mg of modafinil daily for the treatment of EDS	N=270 8 weeks	Primary: MWT Secondary: ESS, CGI-C	Primary: Following the switch from modafinil to placebo, the mean average daytime sleep latency on the MWT decreased from 9.74 minutes at baseline to 6.87 minutes after eight weeks (*P*<0.001). In the sodium oxybate group, there was no decrease in sleep latency, suggesting that this medication was as efficacious in treating EDS as previously administered modafinil. In the sodium oxybate plus modafinil group, there was an increase in daytime sleep latency from 10.43 minutes to 13.15 minutes (*P*<0.001), suggesting that this combination of drugs produced an additive effect. Secondary: The sodium oxybate group showed a decrease in median average EES scores, from 15 to 12 (*P*<0.001). The sodium oxybate 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.

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				The placebo and the modafinil-treated study patients demonstrated no significant change in symptoms.
Black et al[128] Sodium oxybate 6 g/day vs modafinil 200 to 600 mg/day vs sodium oxybate 6 g/day plus 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 3 and 4 sleep (43.5 and 24.25 minutes, respectively; *P*<0.001 for each) and delta power (*P*<0.001 for each) and significant decrease in the number of nocturnal awakenings in sodium oxybate (*P*=0.008) and sodium plus modafinil (*P*=0.014) treated study patients. No significant changes in PSG parameters were noted in patients treated with placebo or modafinil alone. Patients who had been randomized to placebo demonstrated a significant decrease in MWT sleep latency at eight weeks (*P*<0.001) once they had been switched to placebo following stable chronic modafinil treatment. A slight worsening of EDS indicated by increased ESS scores, was noted in placebo-treated patients (*P*=0.011) after stopping baseline modafinil, and ESS scores continued unchanged in the group that was randomized to continue modafinil treatment. Sodium oxybate-treated patients and sodium oxybate plus modafinil-treated patients experienced significant improvements in ESS scores (*P*<0.001 for each). There was no change in ESS scores in the group maintained on modafinil alone. Secondary: Not reported
Obstructive Sleep Apnea				

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
Hirshkowitz et al[129] 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).
Roth et al[130] 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	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.

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
	excessive sleepiness despite effective, regular, and stable use of CPAP treatment			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, 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[131] Armodafinil 200 mg/day	DB, PC, PG, RCT Patients 18 to 65	N=249 18 months	Primary: CGI-C as related to sleepiness,	Primary: The proportion of patients with least minimal improvement on CGI-C was significantly greater in the armodafinil group (69%) compared to the placebo group (53%; *P*=0.012).

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	years of age diagnosed with obstructive sleep apnea		mean change from baseline in MWT to mean sleep latency at final visit Secondary: ESS	Mean MWT sleep latency was increased following armodafinil (2.6 minutes) compared to placebo (1.1 minutes), but was not statistically significant (*P*=0.30). Secondary: Mean ESS scores were significantly reduced in study patients treated with armodafinil (-6.3) compared to patients treated with placebo (-4.8; *P*=0.003). The most common adverse effects included headache, dry mouth and insomnia. Most adverse events were considered mild or moderate by the study investigator.
Black et al[132] Modafinil 200 to 400 mg/day vs placebo	DB, MC, PC, RCT Adults 18 to 70 years of age with OSA/ hypopnea syndrome and having residual excessive sleepiness during CPAP therapy	N=305 12 weeks	Primary: MWT, ESS Secondary: CGI-C, FOSQ	Primary: Modafinil significantly improved mean sleep latency on the MWT compared to placebo (*P*<0.001). Modafinil significantly decreased the ESS scores compared to placebo (*P*<0.001). There were no significant differences in MWT or ESS scores seen between the two modafinil treatment groups (*P*>0.15 for each). Secondary: At the end of the study, modafinil had significant improvements in CGI-C compared to placebo (*P*<0.001). Modafinil improved mean FOSQ scores compared to placebo (*P*<0.02) for vigilance, general productivity, and activity level.
Weaver et al[133] Modafinil 200 to 400 mg/day vs	2 DB, MC, PC, RCT (Pooled analysis) Patients 24 to 76 years of age diagnosed with	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

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
placebo	OSA and residual excessive sleepiness associated with CPAP			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 1 point for significantly more patients who received modafinil (*P*<0.05). Secondary: Not reported
Williams et al[134] 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 1/reaction time and lapses, both *P*<0.0002), and subjective sleepiness (*P*<0.01). Secondary: Not reported
Shift Work Disorder				
Czeisler et al[135] Armodafinil 150 mg/day administered 30 to 60 minutes before the start of work shift vs placebo	DB, MC, PC, RCT Patients 18 to 65 years of age who exhibited signs and symptoms of SWD of moderate or greater severity, as documented by a CGI-S rating of 4 or higher for sleepiness on	N=254 12 weeks	Primary: MSLT, CGI-C Secondary: KSS, CDR	Primary: Armodafinil improved mean nighttime sleep latency (2 to 8 AM) by 3.1 to 5.3 minutes compared to an increase of 0.4 to 2.8 minutes at in patients receiving placebo at the final visit (*P*<0.001). Of the patients who received armodafinil, 79% were rated as improved in the CGI-C ratings compared to 59% of the patients who received placebo at the final visit (*P*=0.001). Secondary: Patient-reported levels of sleepiness during the night shift on the KSS were reduced with armodafinil compared to placebo at all visits. Armodafinil improved most items assessed in the electronic diaries, including the maximum level of sleepiness during the night shift and commute home, and

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
	work nights, including the commute to and from work			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). Adverse events included headache, nausea, nasopharyngitis, and anxiety. Most adverse events were considered mild or moderate by the investigator.
Tembe et al[136] Armodafinil 150 mg administered 1 hour prior to night shift vs modafinil 200 mg	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	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

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
administered 1 hour prior to night shift			Secondary: Improvement in mean SSS grades, compliance, patients' as well as physicians' global assessment for efficacy, safety	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.
Czeisler et al[137] Modafinil 200 mg/ day administered 30 to 60 minutes before the start of work shift vs placebo	DB, MC, PC, RCT Adults 18 to 60 years of age diagnosed with SWD and worked each month at least five night shifts for ≤12 hours, with ≥6 hours or worked between 10 PM and 8 AM and at least three shifts occurring consecutively	N=204 3 months	Primary: MSLT, CGI-C, Psychomotor Vigilance Test Secondary: Not reported	Primary: The modafinil group produced a significant increase in overall mean MSLT from 2.1 minutes at baseline to 3.8 minutes at endpoint compared to the placebo change of 2.04 to 2.37 minutes (*P*=0.002). The modafinil group significantly improved the CGI-C test scores with 74% of the patients rated as at least minimally improved compared to 36% in the placebo group (*P*<0.001). The modafinil group produced a significant decrease in mean number of lapses of attention during the Psychomotor Vigilance Test from baseline vs the placebo group (*P*=0.005). Secondary: Not reported
Miscellaneous				
Black JE, Hull et al[138] Armodafinil 100 to 250 mg/day (OSA) or 100 to 250	DB, MC, OL Men and women 18 to 65 years of age with a	N=743 ≥12 months	Primary: Tolerability and efficacy (CGI-C, ESS, BFI)	Primary: Discontinuations due to adverse events occurred in 13% of study patients during the initial study period. Most adverse events were mild to moderate in severity and included headache

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
mg/night 30 minutes to 1 hour before night shift but no later than 23:00 (SWD)	diagnosis of OSA, SWD, or narcolepsy		Secondary: Not reported	(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
Schwartz et al[139] Armodafinil 100 to 250 mg/day (OSA and narcolepsy) or 100 to 250 mg/day 30 minutes to 1 hour before the start of night shift but no later than 23:00 (SWD)	MC, OL Patients 18 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.

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				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[140] 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[141] Modafinil 300 mg/ day vs placebo	DB, MC, PC, RCT Patients ≥18 years of age diagnosed with myotonic muscular dystrophy type 1 experiencing hypersomnia	N=28 2.5 years	Primary: MWT Secondary: MLST, ESS, global assessment (patient and physician), HAMD, SF-36	Primary: At 4 weeks, the mean MWT score was 16.4 minutes in the modafinil group and 15.8 minutes in the placebo group (*P*=0.71). Secondary: There were no significant differences between the treatment groups in MSLT latency, ESS or treatment efficacy scores. There were no significant differences between the groups in disturbances of personality and mood or quality-of-life. A total of eight patients reported at least one adverse event, including digestive, neurologic and skin symptoms. The adverse events were considered mild or moderate by the study investigator.

†Study grading according to Agency for Healthcare Research and Quality (AHRQ) (See Appendix I for definition of ratings). Studies falling outside of the grading criteria defined by AHRQ will be noted as "Not Applicable". This indicates that the grading criteria did not appropriately fit the design of the included study, but that it was included due to the potential value of the presented data.
Drug regimen abbreviations: AMP=mixed amphetamine salts, BID=twice a day, DEX=dextroamphetamine, DXM=dexmethylphenidate, ER=extended release, ES=extension study, FD=forced dose, IR=immediate release, LDX=lisdexamfetamine, MPH=methylphenidate, OROS=osmotic-release oral system, SR=sustained release, TID=three times a day, XR=extended release
Study regimen abbreviations: CI=confidence interval, DB=double blind, DD=double dummy, HR=hazard ratio, MA=meta-analysis, MC=multicenter, OL=open-label, OR=odds ratio, OS=observational study, PC=placebo-controlled, PG=parallel-group, PRO=prospective trial, RCT=randomized-controlled trial, SA=single arm, SB=single blind, TB=triple blind, XO=cross-over trial

Miscellaneous 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, CAARS=Conners adult ADHD rating scale, CAARS-Inv:SV=Conners Adult ADHD Rating Scale–Investigator Rated: Screening Version, CAARS-Self:SV=Conners Adult ADHD Rating Scale–Self Rated: Screening Version, CADS-T=Conners ADHD/DSM IV scale-teacher version, CADS-P=Conners ADHD/DSM IV scale-parent version, CANTAB-CRT=Cambridge Neuropsychological Test Automated Battery-Choice Reaction Time, CANTAB-SWM=Cambridge Neuropsychological Test Automated Battery-Working Memory and Strategy Performance, CASQ-P=Conner's abbreviated symptom questionnaire for parents, CASQ-T=Conner's abbreviated symptom questionnaire for teachers, CBC=Conner's behavior checklist, CDR=Cognitive Drug Research, CGAS=Children's Global Assessment Scale, CGI=Clinical Global Impression, CGI-ADHD-I=Clinical Global Impressions-ADHD-Improvement scale, CGI-ADHD-S=Clinical Global Impressions-ADHD-Severity scale, CGI-C= Clinical Global Impressions of change, CGI-I= Clinical Global Impressions of improvement, CGI-S= Clinical Global Impressions of severity, CHIP-CE=Child Health and Illness Profile-Child Edition, CHQ=Child Health Questionnaire, CHIP-CE=Child Health and Illness Profile-child edition, CHQ=Child Health Questionnaire, CPAP=continuous positive airway pressure, 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, DBP=diastolic blood pressure, DSST=Digit Symbol Substitution Task/Coding Test, EDS=excessive daytime sleepiness, ESS=Epworth sleep scale, FCRTT=four-choice reaction time test, FOSQ=Functional outcomes of sleep questionnaire, HAMA=Hamilton Anxiety Rating Scale, HAMD=Hamilton Depression Rating Scale, GTSS=Global tic severity scale, HAM-D-17=Hamilton 17-item Depression Rating scale, HR=heart rate, HSPP=Harter Self-Perception Profile, HMVTS=Hopkins motor/vocal tic scale, I/O=inattention/over activity, IDS=Impaired Driving Score, ITT=intention to treat, JAMES=Joint Attention Measure from the ESCs (Early and Social Communication Scale), KSS=Karolinska Sleepiness Scale, LS=least squares, LSMD=least squares mean difference, MI=myocardial infarction, MSLT=multiple sleep latency test, MWT=maintenance of wakefulness test, O/D=oppositional/defiance, PDSS=Pediatric Daytime Sleepiness Scale, PDD=pervasive developmental disorders, PERMP=permanent product measure of performance, PGA=parent global assessment, PLM=periodic leg movements, POMS-DD=depression-dejection subscale of profile of mood states, PSERS=Pittsburgh Side Effects Rating Scale, PSG=Polysomnogram, PSQ=Parental Satisfaction Questionnaire, Q-LES-Q=quality of life, enjoyment, and satisfaction questionnaire, REM=rapid eye movement, RCFT=Rey Complex Figure Test, SAICA=Social Adjustment Scale for Children and Adolescents, SDS=Sheehan disability scale, SF-36=36-item Short Form Health Survey, SERS=side effect ratings scale, SKAMP=Swanson, Kotkin, Agler, M-Flynn, and Pelham, SKAMP-A=SKAMP-Attention, SKAMP-D=SKAMP-Deportment, SMD=standardized 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, SSS=Stanford sleepiness score, STAI=State and trait anxiety inventory, SWD=Shift Work Disorder, TOVA=test of variables of attention, STSSS=Shapiro Tourette syndrome severity scale, 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.

Table 6. Special Populations[3-22,26-28,36]

Drug	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category*	Excreted in Breast Milk
Anorexigenic Agents and Respiratory and Cerebral Stimulants-Amphetamines					
Amphet-amine/ Dextro-amphetamine salts	Not studied in elderly patients (IR). Safety and efficacy in children <3 years of age have not been established (IR). Safety and efficacy in children <6 years of age have not been established (ER).	No dosage adjustment required.	No dosage adjustment required.	C	Yes; advise to refrain from nursing.
Dextro-amphetamine	Safety and efficacy in elderly patients have not been established. Safety and efficacy in children <3 years of age have not been established (IR, solution). Safety and efficacy in children <6 years of age have not been established (ER).	No dosage adjustment required.	No dosage adjustment required.	C	Yes; advise to refrain from nursing.
Lisdexamfetamine	Limited experience in the elderly; use with caution. Safety and efficacy in children <6 years of age have not been established.	No dosage adjustment required.	No dosage adjustment required.	C	Yes; advise to refrain from nursing.
Methamphetamine	Safety and efficacy for the treatment of ADHD in children <6 years of age have not been	No dosage adjustment required.	No dosage adjustment required.	C	Yes; advise to refrain from nursing.

Drug	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category*	Excreted in Breast Milk
	established. Safety and efficacy for use as an anorectic agent in children <12 years of age have not been established.				
Agents and Respiratory and Cerebral Stimulants-Miscellaneous					
Armodafinil	Limited experience in the elderly; consider-ation should be given to the use of a lower dose in elderly patients. Safety and efficacy in children <17 years of age have not been established.	No dosage adjustment required.	Hepatic dosage adjustment required; with severe hepatic dysfunction, reduce the dose by one half of that recom-mended for healthy patients.	C†	Unknown; use with caution.
Dexmethyl-phenidate	Safety and efficacy in elderly patients have not been established (IR). Not studied in elderly patients (ER). Safety and efficacy in children <6 years of age have not been established.	Not studied with renal dysfunction.	Not studied with hepatic dysfunction.	C	Unknown; use with caution.
Methylphenidate	Safety and efficacy in elderly patients have not been established. Safety and efficacy in children <6 years of age have not been established.	Not studied with renal dysfunction.	Not studied with hepatic dysfunction.	C	Unknown; use with caution.
Modafinil	Limited experience in the elderly; consider-	No dosage adjustment required.	Hepatic dosage adjustment	C†	Unknown; use with caution.

Drug	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category*	Excreted in Breast Milk
	ation should be given to the use of a lower dose in elderly patients. Safety and efficacy in children <17 years of age have not been established.		required; with severe hepatic dysfunction, reduce the dose by one half of that recom-mended for healthy patients.		
Central α-Agonists					
Clonidine	Safety and efficacy have not been established. Safety and efficacy in children <6 years of age have not been established.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	B	Unknown; use with caution.
Guanfacine	Safety and efficacy have not been established. Safety and efficacy in children <6 years of age have not been established.	Not studied in renal dysfunction. Monitor patients.	Not reported.	C	Yes; use with caution.
Central Nervous Agents-Miscellaneous					
Atomoxetine	Safety and efficacy have not been established. Include dosage adjustments. The potential risks with clinical need must be balanced when used in children or adolescents.	No dosage adjustment required.	Hepatic dosage adjustment required; with moderate dysfunction, initial and target doses should be reduced to 50% of the normal dose; with severe dysfunction, initial and target doses should be reduced to 25% of normal.	C	Unknown; use with caution.

Drug	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category*	Excreted in Breast Milk
Sodium oxybate	Limited experience in the elderly; monitor elderly patients closely for impaired motor and/or cognitive function. Safety and efficacy in children <16 years of age have not been established.	Not studied with renal dysfunction.	Hepatic dosage adjustment required; with comp-romised liver function, the starting dose should be decreased by one half.	B	Unknown; use with caution.

ER=extended-release, IR=immediate-release
* Pregnancy Category B=No evidence or risk in humans, but there remains a remote possibility. Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women. Pregnancy Category C=Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
†A pregnancy registry has been established to collect information on the pregnancy outcomes of women exposed to armodafinil and modafinil. Healthcare providers are encouraged to register pregnant patients, or pregnant women may enroll themselves by calling 1-866-404-4106 (toll free).

Adverse Drug Events

Table 7a. Adverse Drug Events (%)-Anorexigenic Agents and Respiratory and Cerebral Stimulants-Amphetamines[3,4,7-9,20,22,36]

Adverse Events	Amphetamine/ Dextroam-phetamine Salts	Dextro-amphetamine	Lisdex-amfetamine	Meth-amphetamine
Cardiovascular				
Blood pressure increased	-	-	3	-
Cardiomyopathy	√*	√	√	-
Heart rate increased	-	-	2	-
Hypertension	√*	√	√	√
Myocardial infarction	√†	√	√	-
Palpitations	√*/2 to 4†	√	√	√
Sudden death	√†	√	√	-
Tachycardia	√*/6†	√	√	√
Central Nervous System				
Aggressive behavior	√*†	√	-	-
Agitation	8†	-	3	-
Anxiety	8†	-	6	-
Depression	√*†	-	√	-
Dizziness	2 to 7†	√	5	√
Dyskinesia	√*†	√	√	-
Dysphoria	√*†	√	√	√
Euphoria	√*†	√	√	√
Fever	5†	-	2	-
Headache	√*/26†	√	12	√
Insomnia	12 to 27†	√	4 to 27	√

Adverse Events	Amphetamine/ Dextroam-phetamine Salts	Dextro-amphetamine	Lisdex-amfetamine	Meth-amphetamine
Irritability	√*†	-	10	-
Labile affect	-	-	3	-
Mania	-	√	√	-
Nervousness	6†	-	-	-
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†	√	5 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†	-	-	-
Other				
Anaphylaxis	√†	-	√	-
Angioedema	-	-	√	-
Blurred vision	√*†	√	√	-
Dysmenorrhea	2 to 4†	-	-	-
Dyspnea	2 to 4†	-	2	-
Growth suppression	-	-	-	√

Adverse Events	Amphetamine/ Dextroam-phetamine Salts	Dextro-amphetamine	Lisdex-amfetamine	Meth-amphetamine
Hypersensitivity reactions	-	-	√	-
Infection	2 to 4†	-	-	-
Tolerance	-	-	-	√
Weakness	2 to 6†	-	-	-

-Event not reported.
√Percent not specified.

Table 7b. Adverse Drug Events (%)-Anorexigenic Agents and Respiratory and Cerebral Stimulants-Miscellaneous[5,6,10,11,14-19,26,27,36]

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

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

Adverse Event(s)	Armodafinil	Dexmethyl-phenidate	Methyl-phenidate	Modafinil
Libido decreased	-	-	√	-
Polyuria	1	-	-	-
Pyuria	-	-	-	1
Hematologic				
Agranulocytosis	-	-	-	√
Anemia	-	√	√	-
Eosinophilia	-	-	-	1
Leukopenia	-	√	√	-
Pancytopenia	√	-	√	-
Thrombocytopenic purpura	-	√	√	-
Hepatic				
Hepatic coma	-	√	√	-
Liver function test abnormalities	√	√	√	2
Musculoskeletal				
Arthralgia	-	√	√	-
Back pain	-	-	-	6
Respiratory				
Cough	-	-	√	-
Dyspnea	1	-	√	-
Epistaxis	-	-	-	1
Lung disorder	-	-	-	2
Nasal congestion	-	-	√/6†	-
Nasopharyngitis	-	-	√/5†	-
Pharyngitis	-	-	√	4
Pharyngolaryngeal pain	-	4 to 7	√	-
Respiratory tract infection	-	-	√	-
Rhinitis	-	-	√	7
Sinusitis	-	-	√	-
Special Senses				
Abnormal vision	-	-	-	1
Accommodation difficulties	-	√	√	1
Amblyopia	-	-	-	1
Blurred vision	-	√	√	1
Dry eyes	-	-	√	-
Eye pain	-	-	-	1
Mydriasis	-	-	√	-
Other				
Accidental injury	-	-	√	-
Allergic contact sensitization	-	-	√†	-
Anaphylaxis	√	-	√†	√
Dysmenorrhea	-	-	√	-
Edema	-	-	-	1
Flu-like syndrome	1	-	-	4
Growth suppression	-	-	√	-
Hypersensitivity reactions	-	√	√	√
Necrotizing vasculitis	-	√	√	-
Pain	1	-	-	-

Adverse Event(s)	Armodafinil	Dexmethyl-phenidate	Methyl-phenidate	Modafinil
Thirst	1	-	-	-
Viral infection	-	-	28†	-

-Event not reported.
√Percent not specified.

Table 7c. Adverse Drug Events (%)-Central α-Agonists[12,13,36]

Adverse Event(s)	Clonidine	Guanfacine
Cardiovascular		
Atrioventricular block	√	√
Bradycardia	≤4	-
Cardiac arrhythmia	√	-
Chest pain	√	-
Congestive heart failure	√	-
Electrocardiogram abnormalities	√	-
Hypertension	-	√
Hypotension	-	4
Orthostatic hypotension	√	-
Pallor	√	-
Palpitations	1	-
Reynaud's phenomenon	√	-
Sinus arrhythmia	-	√
Syncope	√	√
Tachycardia	1	-
Central Nervous System		
Abnormal sleep-related event	1 to 3	-
Aggressive behavior	√	-
Agitation	√	√
Anxiety	√	√
Behavioral change	√	-
Crying	1 to 3	-
Delirium	√	-
Depression	-	√
Dizziness	2 to 5	2
Emotional disorder	3 to 4	-
Fatigue/lethargy	12 to 15	14
Fever	√	-
Hallucinations	√	√
Headache	1 to 11	5
Insomnia	≤5	-
Irritability	3 to 6	2
Malaise	√	-
Mental depression	1	-
Nervousness	1 to 3	-
Nightmares	√	√
Paresthesia	√	-
Restlessness	√	-
Seizure	-	√
Sleep terror	3	-
Somnolence	26 to 33	26
Tremor	√	-

Adverse Event(s)	Clonidine	Guanfacine
Vivid dreams	√	-
Dermatological		
Flushing	√	-
Rash	1	-
Urticaria	√	-
Gastrointestinal		
Abdominal pain	≤3	2
Anorexia	1	-
Appetite decreased	-	2
Constipation	1 to 6	3
Diarrhea	≤1	-
Dry mouth	√	3
Dyspepsia	-	√
Nausea	1 to 4	4
Stomach discomfort	-	√
Thirst	1 to 3	-
Vomiting	√	√
Weight gain	<1	√
Genitourinary		
Dysuria	√	-
Enuresis	4	√
Erectile dysfunction	2 to 3	-
Gynecomastia	1	-
Libido decreased	√	-
Nocturia	1	-
Pollakiuria	3	-
Sexual disturbances	3	-
Hepatic		
Hepatitis	√	-
Liver function test abnormalities	≤1	-
Musculoskeletal		
Arthralgia	1	-
Leg cramps	≤1	-
Myalgia	1	-
Pain in extremities	√	-
Weakness	10	-
Respiratory		
Asthma	4	√
Epistaxis	3	-
Lower respiratory tract infection	2	-
Nasal congestion	2 to 4	-
Nasal dryness	√	-
Nasopharyngitis	2	-
Upper respiratory tract infection	2 to 7	-
Special Senses		
Accommodation difficulties	√	-
Blurred vision	√	-
Dry eyes	√	-
Eye pain	√	-
Other		
Body temperature increase	≤2	-

Adverse Event(s)	Clonidine	Guanfacine
Ear infection	√	-
Ear pain	4	-
Flu-like syndrome	≤3	-
Hypersensitivity reactions	-	√
Pallor	-	√
Throat pain	3 to 5	-
Thrombocytopenic purpura	√	-
Viral infection	≤3	-

-Event not reported.
√Percent not specified.

Table 7d. Adverse Drug Events (%)-Central Nervous System Agents-Miscellaneous[21,28,36]

Adverse Event(s)	Atomoxetine	Sodium Oxybate
Cardiovascular		
Chest pain	-	√
Diastolic blood pressure increased	≤4	-
Flushing	≥2	-
Hypertension	1 to 9	6
Hypotension	<2	-
Palpitations	3	-
QT prolongation	<1	-
Reynaud's phenomenon	√	-
Stroke	√	-
Systolic blood pressure increased	4 to 5	-
Tachycardia	≤2	<1
Central Nervous System		
Abnormal dreams	4	3 to 9
Aggressive behavior	√	-
Agitation	√	√
Akathisia	√	-
Anxiety	√	3 to 6
Ataxia	-	√
Attention disturbance	-	3 to 9
Chills	3	√
Confusion	-	3 to 6
Crying	2	-
Depression	-	6
Disorientation	-	6
Dizziness	5 to 6	17
Early morning awakening	<2	-
Fatigue/lethargy	6 to 9	≤6
Fever	3	-
Headache	2 to 19	22
Hostility	√	-
Insomnia	2 to 15	5
Irritability	≤6	-
Jittery feeling	2	-
Mania	√	-
Mood swings	1 to 2	-
Nervousness	-	√
Nightmare	-	3 to 6

Adverse Event(s)	Atomoxetine	Sodium Oxybate
Panic disorder	√	-
Paresthesia	4	-
Rigors	3	-
Seizure	-	√
Sleep disorder	-	3 to 6
Sleep disturbance	3	-
Sleep paralysis	-	3 to 11
Sleep walking	-	6
Somnolence	4 to 11	8
Suicidal ideation	√	√
Syncope	√	√
Tremor	2	√
Dermatological		
Dermatitis	2 to 4	-
Diaphoresis	2	3 to 11
Flushing	2	-
Hyperhidrosis	4	3 to 6
Rash	2	√
Urticaria	√	-
Endocrine and Metabolic		
Dysmenorrhea	6	3 to 6
Hot flushes	8	-
Menstrual disturbances	2 to 3	-
Gastrointestinal		
Abdominal pain	7 to 18	3 to 11
Anorexia	<3	-
Appetite decreased	11 to 16	-
Constipation	1 to 9	√
Diarrhea	4	6 to 8
Dry mouth	4 to 21	-
Dyspepsia	4 to 6	3
Fecal incontinence	-	<1
Flatulence	2	√
Nausea	7 to 21	21
Stomach discomfort	-	-
Vomiting	3 to 11	8
Weight increase	-	√
Weight loss	2 to 3	-
Genitourinary		
Dysuria	3	-
Ejaculatory disturbance	3	-
Enuresis	-	3 to 17
Erectile disturbance	9	-
Impotence	3	-
Libido decreased	4	√
Orgasm abnormal	2	-
Prostatitis	2	-
Urinary incontinence	-	7
Urinary retention	7	-
Hepatic		
Hepatotoxicity	√	-

Adverse Event(s)	Atomoxetine	Sodium Oxybate
Jaundice	√	-
Musculoskeletal		
Hypoesthesia	-	6
Myalgia	-	√
Myasthenia	-	3 to 6
Weakness	-	6 to 8
Respiratory		
Bronchitis	-	√
Cough	11	√
Dyspnea	-	√
Nasopharyngitis	-	8
Rhinitis	-	8
Rhinorrhea	4	-
Sinus headache	3	-
Sinusitis	6	-
Upper respiratory infection	-	3
Special Senses		
Amblyopia	-	6
Blurred vision	-	3
Mydriasis	<2	-
Tinnitus	-	6
Other		
Allergic contact sensitization	√	√
Ear infection	3	-
Ear pain	-	√
Flu-like syndrome	√	√
Hypersensitivity reactions	<1	√
Influenza	3	-
Pain	-	3
Pallor	-	√
Thirst	-	√
Viral infection	-	6

-Event not reported.
√Percent not specified.

Contraindications

Table 8a. Contraindications-Anorexigenic Agents and Respiratory and Cerebral Stimulants-Amphetamines[3,4,7,8,20,22,36]

Contraindication(s)	Amphetamine/ Dextroamphetamine Salts	Dextroamphetamine	Lisdexamfetamine	Methamphetamine
Advanced arteriosclerosis	√	-	-	-
Agitated states	√	-	-	-
Glaucoma	√	-	-	-
Hypersensitivity	√	√	√	√
Hyperthyroidism	√	-	-	-
Moderate to severe hypertension	√	-	-	-
Patients receiving monoamine oxidase inhibitors	√	√	√	√

Patients with a history of drug abuse	√	-	-	-
Symptomatic cardiovascular disease	√	-	-	-

Table 8b. Contraindications-Anorexigenic Agents and Respiratory and Cerebral Stimulants-Miscellaneous[5,6,10,11,14-19,26,27,36]

Contraindication(s)	Armodafinil	Dexmethyl-phenidate	Methyl-phenidate	Modafinil
Anxiety, tension, and agitation	-	√	√	-
Family history or diagnosis of Tourette syndrome	-	√	√	-
Glaucoma	-	√	√	-
Hypersensitivity	√	√	√	√
Motor tics	-	√	√	-
Patients receiving monoamine oxidase inhibitors	-	√	√	-

Table 8c. Contraindications-Central α-Agonists[12,13,36]

Contraindication(s)	Clonidine	Guanfacine
Hypersensitivity	√	√

Table 8d. Contraindications-Central Nervous System Agents-Miscellaneous[21,28,36]

Contraindication(s)	Atomoxetine	Sodium Oxybate
Hypersensitivity	√	-
Narrow angle glaucoma	√	-
Patients receiving monoamine oxidase inhibitors	√	-
Patients receiving sedative hypnotic agents	-	√
Pheochromocytoma or a history of pheochromocytoma	√	-
Severe cardiovascular disorders whose condition would be expected to deteriorate if they experience increases in blood pressure or heart rate that could be clinically important	√	-
Succinic semialdehyde dehydrogenase deficiency	-	√

Boxed Warnings

Boxed Warning for amphetamine and dextroamphetamine[36]

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.

Boxed Warning for atomoxetine[36]

WARNING
Suicidal ideation in children and adolescents: Atomoxetine increased the risk of suicidal ideation in short-term studies in children or adolescents with 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.

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 one 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

Boxed Warning for dexmethylphenidate[36]

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

Boxed Warning for lisdexamfetamine[36]

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

Boxed Warning for methamphetamine[36]

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.

Boxed Warning for methylphenidate[36]

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 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.

Boxed Warning for sodium oxybate[36]

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,

WARNING

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 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.

Warnings/Precautions

Table 9a. Warnings and Precautions-Anorexigenic Agents and Respiratory and Cerebral Stimulants-Amphetamines[3,4,7-9,20,22,36]

Warning(s)/Precaution(s)	Amphetamine/ Dextroamphet-amine Salts	Dextro-amphetamine	Lisdex-amfetamine	Meth-amphetamine
Aggressive behavior or hostility; patients beginning therapy should be monitored for the appearance or worsening of aggressive behavior or hostility	-	√	√	-
Drug abuse and dependence; classified as a Schedule II controlled substance	√	√	√	√
Effects on growth; growth should be monitored during therapy	√	√	-	√
Emergence of new psychotic or manic symptoms; may develop with therapy	-	√	√	-
Fatigue; do not use to combat fatigue or to replace rest in healthy persons	-	-	-	√
Hazardous tasks; amphetamines may impair the ability of the patient to engage in potentially hazardous activities	-	√	√	-
Hypertension; stimulant medications cause a modest increase in blood pressure and heart rate	√	√	√	√
Preexisting psychosis; administration of stimulants may exacerbate symptoms of behavior disturbances and thought	-	√	√	-

Warning(s)/Precaution(s)	Amphetamine/ Dextroamphet-amine Salts	Dextro-amphetamine	Lisdex-amfetamine	Meth-amphetamine
disorder in patient with preexisting psychotic disorder				
Prescribing/dispensing; prescribe or dispense the least amount feasible at one time in order to minimize the possibility of overdosage	√	√	√	√
Screening patients for bipolar disorder; prior to initiating therapy, patients with comorbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder	-	√	√	-
Seizures; stimulants may lower the convulsive threshold in patients with a history of seizures, discontinue therapy in the presence of seizures	-	√	√	-
Serious cardiovascular events; sudden death, stroke, and myocardial infarction have been reported with therapy and patients should have a careful history and physical exam to assess for the presence of cardiac disease before initiating therapy	-	√	√	-
Tartrazine sensitivity; some products may contain tartrazine which may cause allergic-like reactions	-	√	-	-
Tics; amphetamines have been reported to exacerbate motor and phonic tics and Tourette syndrome	-	-	√	-
Tolerance; tolerance to the anorectic effect usually develops within a few weeks and when it occurs, the recommended dose should not be exceeded in an attempt to increase the effect	-	-	-	√
Visual disturbances; difficulties with accommodation and blurring have been reported with stimulant treatment	-	√	√	-

Table 9b. Warnings and Precautions-Anorexigenic Agents and Respiratory and Cerebral Stimulants-Miscellaneous[5,6,10,11,14-19,26,27,36]

Warning(s)/Precaution(s)	Armodafinil	Dexmethyl-phenidate	Methyl-phenidate	Modafinil

Warning(s)/Precaution(s)	Armodafinil	Dexmethyl-phenidate	Methyl-phenidate	Modafinil
Aggressive behavior or hostility; patients beginning therapy should be monitored for the appearance or worsening of aggressive behavior or hostility	-	√	-	-
Angioedema and anaphylactoid reactions; discontinue therapy and immediately report any signs or symptoms suggesting angioedema or anaphylaxis	√	√	-	√
Cardiovascular system; therapy has not been evaluated in patients with a recent history of myocardial infarction or unstable angina, and such patients should be treated with caution	√	-	-	√
Contact sensitization; use of transdermal patch may lead to contact sensitization	-	-	√	-
Continuous positive airway pressure use in patients with OSA; indicated as an adjunct to standard treatment(s) for the underlying obstruction	√	-	-	√
Depression; do not use transdermal patch to treat severe depression	-	-	√	-
Diagnosis of sleep disorders; therapy should be used only in patients who have had a complete evaluation of their excessive sleepiness, and in whom a diagnosis of either narcolepsy, OSA, and/or shift-work disorder has been made in accordance with International Classification of Sleep Disorders or Diagnostic and Statistical Manual of Mental Disorders diagnostic criteria	√	-	-	√
Drug abuse and dependence; classified as a Schedule II controlled substance	-	√	√	-
Drugs affecting the central nervous system; may alter judgment, thinking, or motor skills	√	-	-	√
Effects on growth; growth should be monitored during therapy	-	√	√	-
Emergence of new psychotic or manic symptoms; may develop with therapy	-	√	-	-
External heat; avoid exposing	-	-	√	-

Warning(s)/Precaution(s)	Armodafinil	Dexmethyl-phenidate	Methyl-phenidate	Modafinil
transdermal patch application site to direct external heat sources while wearing the patch				
Fatigue; do not use transdermal patch for the prevention or treatment of normal fatigue states	-	-	√	-
Hypertension; stimulant medications cause a modest increase in blood pressure and heart rate	-	√	√	-
Multi-organ hypersensitivity reactions; discontinue therapy if suspected	√	-	-	√
Patients using cyclosporine; blood levels of cyclosporine may be reduced with therapy	√	-	-	√
Patients using steroidal contraceptives; effectiveness of steroidal contraceptives may be reduced with therapy, alternative or concomitant methods of contraception are recommended	√	-	-	√
Persistent sleepiness; patients with excessive sleepiness should be frequently reassessed for their degree of sleepiness and, if appropriate, advised to avoid driving or other potentially dangerous activity	√	-	-	√
Psychiatric symptoms have been reported	√	√	√	√
Screening patients for bipolar disorder; prior to initiating therapy, patients with comorbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder	-	√	-	-
Seizures; stimulants may lower the convulsive threshold in patients with a history of seizures, discontinue therapy in the presence of seizures	-	√	√	-
Serious cardiovascular events; sudden death, stroke, and myocardial infarction have been reported with therapy and patients should have a careful history and physical exam to assess for the presence of cardiac disease before initiating therapy	-	√	√	-
Serious rash, including Stevens-	√	-	-	√

Warning(s)/Precaution(s)	Armodafinil	Dexmethyl-phenidate	Methyl-phenidate	Modafinil
Johnson Syndrome; serious rash requiring hospitalization and discontinuation of treatment has been reported in adults and children				
Visual disturbances; difficulties with accommodation and blurring have been reported with stimulant treatment	-	√	√	-

Table 9c. Warnings and Precautions-Central α-Agonists[12,13,36]

Warning(s)/Precaution(s)	Clonidine	Guanfacine
Abrupt discontinuation; do not discontinue therapy without consulting a healthcare professional due to the potential risk of withdrawal effects	√	-
Allergic reactions; substitution of oral therapy may elicit an allergic reaction in patients who developed allergic reactions from therapy with the transdermal system	√	-
Hypotension/bradycardia/syncope; treatment can cause dose-related decreases in blood pressure and heart rate	√	√
Other clonidine-containing products; do not use concomitantly	√	-
Other guanfacine-containing products; do not use concomitantly	-	√
Patients with vascular disease, cardiac conduction disease, or renal disease; use with caution	√	-
Sedation and somnolence; caution against operating heavy equipment or driving until response to treatment is known	√	√

Table 9d. Warnings and Precautions-Central Nervous System Agents-Miscellaneous[21,28,36]

Warning(s)/Precaution(s)	Atomoxetine	Sodium Oxybate
Aggressive behavior or hostility; patients beginning therapy should be monitored for the appearance or worsening of aggressive behavior or hostility	√	-
Allergic events; although uncommon, allergic reactions have been reported	√	-
Central nervous system depression/respiratory depression; potential to impair respiratory drive, especially in patients with already-compromised respiratory function	-	√
Confusion/neuropsychiatric adverse events; emergence requires careful and immediate evaluation	-	√
Depression; emergence requires careful and immediate evaluation	-	√
Effects on blood pressure and heart rate; use with caution in patients whose underlying medical conditions could be worsened by increases in blood pressure or heart rate	√	-
Effects on growth; growth should be monitored during therapy	√	-
Effects on urine outflow from the bladder; rates of urinary retention and hesitation have been reported in adults	√	-
Emergence of new psychotic or manic symptoms; may develop with therapy	√	-
Incontinence; if urinary or fecal incontinence is reported, consider pursuing investigations to rule out underlying etiologies	-	√
Priapism; rare postmarketing cases have been reported	√	-
Rapid onset of central nervous system depressant effects; only administer	-	√

Warning(s)/Precaution(s)	Atomoxetine	Sodium Oxybate
at bedtime and while in bed		
Screening patients for bipolar disorder; prior to initiating therapy, patients with comorbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder	√	-
Serious cardiovascular events; sudden death, stroke, and myocardial infarction have been reported with therapy and patients should have a careful history and physical exam to assess for the presence of cardiac disease before initiating therapy	√	-
Severe liver injury; postmarketing reports indicate therapy can cause severe liver injury and therapy should be discontinued in patients with jaundice or laboratory evidence of liver injury, and should not be restarted	√	-
Sleepwalking; episodes should be fully evaluated and appropriate interventions considered	-	√
Sodium intake; appropriate daily intake of sodium should be reviewed in patients with heart failure, hypertension, or compromised renal function (see approved package labeling)	-	√
Suicidal ideation; increased risk of suicidal ideation was observed in short-term trials in children and adolescents with ADHD	√	-

Drug Interactions

Table 10a. Drug Interactions-Anorexigenic Agents and Respiratory and Cerebral Stimulants-Amphetamines[3,4,7-9,20,22,36]

Description	Amphetamine/ Dextroamphetamine Salts	Dextroamphetamine	Lisdexamfetamine	Methamphetamine
Furazolidone: increased sensitivity to central nervous system stimulants. If an interaction is suspected, monitor patients for signs and symptoms of toxicity, and reduce the dose of the central nervous system stimulant accordingly.	√	√	√	√
Guanethidine: central nervous system stimulants can reverse the hypotensive effects of guanethidine. Monitor patients. If there is a loss of blood pressure control, discontinue the central nervous system stimulant or switch to alternative hypotensive therapy.	√	√	√	√
Monoamine oxidase inhibitor: exaggerated pharmacologic effects caused by central nervous system stimulants. Avoid coadministration.	√	√	√	√
Serotonin Reuptake Inhibitors: increased sensitivity to sympathomimetic effects and increased risk of serotonin syndrome. If these agents must be used concurrently, monitor for increased central nervous system. Adjust therapy as needed.	√	√	√	√
Urinary alkalinizers: alkalinized urine may prolong the effects of central nervous system stimulants. Avoid agents that may alkalinize the urine, particularly in overdose situations.	√	√	√	√

Table 10b. Drug Interactions-Anorexigenic Agents and Respiratory and Cerebral Stimulants-Miscellaneous[5,6,10,11,14-19,26,27,36]

Description	Armodafinil	Dexmethylphenidate	Methylphenidate	Modafinil
Benzodiazepine: benzodiazepine plasma levels may be reduced, decreasing the pharmacologic effects. Closely observe the patient's clinical response to benzodiazepines when armodafinil or modafinil is started or stopped. Adjust benzodiazepine dose as needed.	√	-	-	√
Monoamine oxidase inhibitors: hypertensive crisis. Dexmethylphenidate is contraindicated with monoamine oxidase inhibitors.	-	√	-	-
Monoamine oxidase inhibitors: hypertensive crisis. Monitor blood pressure during combination therapy.	-	-	√	-

Table 10c. Drug Interactions-Central α-Agonists[12,13,36]

Description	Clonidine	Guanfacine
β-blockers: potentially life-threatening increases in blood pressure. Closely monitor blood pressure after initiation or discontinuation of therapy or a β-blocker when they are given concurrently.	√	-
Tricyclic antidepressants: antihypertensive effect of guanfacine may be decreased. Monitor blood pressure in patients receiving guanfacine when starting, stopping, or charging the dose of the tricyclic antidepressant or using an antihypertensive agent with a different mechanism of action.	-	√
Tricyclic antidepressants: loss of blood pressure control and possible life-threatening increases in blood pressure. Avoid combination if possible by using other agents.	√	-

Table 10d. Drug Interactions-Central Nervous System Agents-Miscellaneous[21,28,36]

Description	Atomoxetine	Sodium Oxybate
Monoamine oxidase inhibitors: increased risk of serious or fatal reactions. Coadministration is contraindicated.	√	-
Serotonin reuptake inhibitors: atomoxetine plasma concentrations may be relaxed, increasing the pharmacologic effects and adverse reactions. Closely monitor the patient when the dose of certain serotonin reuptake inhibitors is started, stopped, or changed. Adjust the dose of atomoxetine as needed.	√	-

Table 11. Dosing and Administration[3-22,26-28,36]

Generic Name	Adult Dose	Pediatric Dose	Availability
Single-Entity Products			
Anorexigenic Agents and Respiratory and Cerebral Stimulants-Amphetamines			
Amphetamine/ dextro-amphetamine salts	Treatment of ADHD: Capsule (adults): 20 mg once daily in the morning Tablet: 2.5 to 5 mg once or twice daily; maintenance, up to 40 mg/day	Treatment of ADHD: Capsule: 10 mg once daily in the morning; maximum, 30 mg/day Tablet: 2.5 to 5 mg once or twice daily; maintenance, up to 40 mg/day	Capsule (Adderall XR®): 5 mg 10 mg 15 mg 20 mg 25 mg 30 mg Tablet (Adderall®): 5 mg 7.5 mg 10 mg 12.5 mg 15 mg 20 mg 30 mg
Dextro-amphetamine	Treatment of ADHD: Solution, tablet: initial, 2.5 to 5 mg once or twice daily; maintenance, up to 40 mg/day Sustained-release capsule: initial, 5 mg once or twice daily; maintenance, up to 40 mg/day Narcolepsy: Solution, sustained-release capsule, tablet: 5 to 60 mg/day administered in divided doses	Treatment of ADHD in children 6 years of age and older: Solution, tablet: initial, 2.5 to 5 mg once or twice daily; maintenance, up to 40 mg/day Sustained-release capsule: initial, 5 mg once or twice daily; maintenance, up to 40 mg/day Narcolepsy in adolescents 12 years of age and older: Solution, sustained-release capsule, tablet: 5 to 60 mg/day administered in divided doses	Solution (Procentra®): 5 mg/5 mL Sustained-release capsule (Dexedrine® Spansule®): 5 mg 10 mg 15 mg Tablet: 5 mg 10 mg
Lisdexamfetamine	Treatment of ADHD: Capsule: initial, 30 mg once daily in the morning; maximum, 70 mg/day	Treatment of ADHD in children 6 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 Treatment of 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 Treatment of ADHD in children 6 years of age and older:	Tablet: 5 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
		Tablet: initial, 5 mg once or twice daily; maintenance, 20 to 25 mg/day	
Anorexigenic Agents and Respiratory and Cerebral Stimulants-Miscellaneous			
Armodafinil	Improve wakefulness in patients with excessive sleepiness associated with OSA and narcolepsy: Tablet: 150 or 250 mg once daily in the morning Improve wakefulness in patients with excessive sleepiness associated with shift work disorder: Tablet: 150 mg/day administered approximately one hour prior to the start of their work shift	Not approved for use in patients less than 17 years of age	Tablet: 50 mg 150 mg 250 mg
Dexmethyl-phenidate	Treatment of ADHD: Extended-release capsule (new starts): initial, 5 to 10 mg once daily in the morning; maximum, 40 mg/day Extended-release capsule (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	Treatment of ADHD in children 6 years of age and older: Extended-release capsule (new starts): initial, 5 to 10 mg once daily in the morning; maximum, 30 mg/day Extended-release capsule (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	Extended-release capsule: 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 Extended-release capsule (Metadate CD®, Ritalin LA®	Treatment of ADHD: Chewable tablet, solution, tablet: initial, 5 mg twice daily; maintenance, increase dose gradually Extended-release tablet (Concerta®; new starts):	Chewable tablet (Methylin®): 2.5 mg 5 mg 10 mg Extended-release capsule (Metadate CD®):

Generic Name	Adult Dose	Pediatric Dose	Availability
	new starts): initial, 20 mg once daily in the morning; maximum, 60 mg/day Extended-release capsule (Ritalin LA®; patients currently receiving methylphenidate): administer equivalent total daily doses Extended-release tablet (Concerta®; new starts): initial, 18 to 36 mg/day; maximum, 72 mg/day Extended-release tablet (Concerta®; patients currently receiving methylphenidate): dosing is based on current dose regimen and clinical judgment Extended-release tablet (Metadate ER®): may be used in place of tablets when the eight hour dosage of the sustained-release tablet corresponds to the titrated eight hour dosage with the tablets Sustained-release tablet: may be used in place of tablets when the eight hour dosage of the sustained-release tablet corresponds to the titrated eight hour dosage with the tablets Transdermal patch: initial, 10 mg; maintenance, titrate to effect <u>Narcolepsy:</u> Chewable tablet, solution, tablet (adults): 20 to 30 mg/day administered in two or three divided doses Extended-release tablet (Metadate ER®): may be used in place of tablets	initial, 18 mg once daily in the morning; maximum, 54 (children) and 72 mg/day (adolescents) Extended-release tablet (Concerta®; patients currently receiving methylphenidate): dosing is based on current dose regimen and clinical judgment Extended-release tablet (Metadate ER®): may be used in place of tablets when the eight hour dosage of the sustained-release tablet corresponds to the titrated eight hour dosage with the tablets Sustained-release tablet: may be used in place of tablets when the eight hour dosage of the sustained-release tablet corresponds to the titrated eight hour dosage with the tablets Transdermal patch: initial, 10 mg; maintenance, titrate to effect <u>Narcolepsy:</u> Chewable tablet, solution, tablet: initial, 5 mg twice daily; maintenance, increase dose gradually Extended-release tablet (Metadate ER®): may be used in place of tablets when the eight hour dosage of the sustained-release tablet corresponds to the titrated eight hour dosage with the tablets Sustained-release tablet: may be used in place of tablets when the eight hour dosage of the sustained-	10 mg 20 mg 30 mg 40 mg 50 mg 60 mg Extended-release capsule (Ritalin LA®): 10 mg 20 mg 30 mg 40 mg Extended-release tablet (Concerta®): 18 mg 27 mg 36 mg 54 mg Extended-release tablet (Metadate ER®): 20 mg Solution (Methylin®): 5 mg/5 mL 10 mg/5 mL Sustained-release tablet (Ritalin-SR®): 20 mg Tablet (Ritalin®): 5 mg 10 mg 20 mg Transdermal patch (Daytrana®): 10 mg/9 hours (1.1. mg/hour) 15 mg/9 hours (1.6 mg/hour) 20 mg/9 hours (2.2 mg/hour) 30 mg/9 hours (3.3 mg/hour)

Generic Name	Adult Dose	Pediatric Dose	Availability
	when the eight hour dosage of the sustained-release tablet corresponds to the titrated eight hour dosage with the tablets Sustained-release tablet: may be used in place of tablets when the eight hour dosage of the sustained-release tablet corresponds to the titrated eight hour dosage with the tablets	release tablet corresponds to the titrated eight hour dosage with the tablets	
Modafinil	Improve wakefulness in patients with excessive sleepiness associated with OSA and narcolepsy: Tablet: 200 mg once daily in the morning Improve wakefulness in patients with excessive sleepiness associated with shift work disorder: Tablet: 200 mg/day administered approximately one hour prior to the start of their work shift	Not approved for use in patients less than 17 years of age	Tablet: 100 mg 200 mg
Central α-Agonists			
Clonidine	Treatment of ADHD as monotherapy and as adjunctive therapy to stimulant medications: Extended-release tablet: initial, 0.1 mg at bedtime; maintenance, 0.1 to 0.4 mg/day administered in two divided doses	Treatment of ADHD as monotherapy and as adjunctive therapy to stimulant medications in children 6 years of age and older: Extended-release tablet: initial, 0.1 mg at bedtime; maintenance, 0.1 to 0.4 mg/day administered in two divided doses	Extended-release tablet: 0.1 mg 0.2 mg
Guanfacine	Treatment of ADHD as monotherapy and as adjunctive therapy to stimulant medications: Extended-release tablet: initial, 1 mg once daily; maintenance, 1 to 4 mg/day	Treatment of ADHD as monotherapy and as adjunctive therapy to stimulant medications in children 6 years of age and older: Extended-release tablet: initial, 1 mg once daily; maintenance, 1 to 4 mg/day	Extended-release tablet: 1 mg 2 mg 3 mg 4 mg
Central Nervous System Agents-Miscellaneous			
Atomoxetine	Treatment of ADHD: Capsule (>70 kg and adults): initial, 40 mg/day;	Treatment of ADHD: Capsule (≤70 kg): initial, 0.5 mg/kg/day; maintenance,	Capsule: 10 mg 18 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	maintenance, 80 mg/day; maximum, 100 mg/day	1.2 mg/kg/day; maximum, 1.4 mg/kg/day	25 mg 40 mg 60 mg 80 mg 100 mg
Sodium oxybate	Treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy: Solution: initial, 4.5 g/night divided into two equal doses of 2.25 g; maintenance, increase to 6 to 9 g/night	Safety and efficacy in patients younger than 16 years of age have not been established.	Solution: 500 mg/mL (180 mL)

Clinical Guidelines

Table 12. Clinical Guidelines

Clinical Guideline	Recommendations
American Academy of Pediatrics: **Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit Hyperactivity Disorder in Children and Adolescents (2011)**[23]	Preschool-aged children (four to five years of age) • The primary care clinician should prescribe evidence-based parent- and/or teacher-administered behavior therapy as the first-line of treatment. • Methylphenidate may be prescribed if the behavior interventions do not provide significant improvement and there is moderate-to-severe continuing disturbance in the child's function. Elementary school-aged children (six to 11 years of age) • The primary care clinician should prescribe FDA-approved medications for ADHD and/or evidence-based parent and/or teacher-administered behavior therapy as treatment for ADHD, preferably both. • The evidence is particularly strong for stimulant medications and sufficient but less strong for atomoxetine, extended-release guanfacine, and extended-release clonidine (in that order). Adolescents (12 to 18 years of age) • The primary care clinician should prescribe FDA-approved medications for ADHD with the assent of the adolescent and may prescribe behavior therapy as treatment for ADHD, preferably both. General considerations • Stimulant medications are highly effective for most children in reduction 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

Clinical Guideline	Recommendations
	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)**[30]	Medication trials • 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. • 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. • 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 and atomoxetine trials are unsuccessful (due to either poor response or side effects in spite of adjustment), or if associated comorbidity is present, alternative medication trials may be considered. • Second-line medications for ADHD therapy include tricyclic antidepressants (imipramine, desipramine), alpha adrenergic agonist (clonidine) a non-tricyclic antidepressant (bupropion), or immediate-release guanfacine.
National Institute for Health and Clinical Excellence: **Attention Deficit Hyperactivity Disorder: Diagnosis and Management of Attention Deficit Hyperactivity Disorder in Children, Young People, and Adults (2008)**[31]	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

Clinical Guideline	Recommendations
	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. 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)**[2]	• 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,

Clinical Guideline	Recommendations
	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 Transition to Adult Services and in Adults (2006)**[32]	<u>Treatment recommendations for children</u> • Proven first-line treatments in children include psychostimulants and atomoxetine. • Second-line treatment options include imipramine and bupropion. • Clonidine and guanfacine may be used as adjunctive treatments. • Qualitative assessments suggest that all agents are more effective than placebo and have similar efficacy; however, there have been few head-to-head comparisons. • The agents are not equivalent in terms of adverse events. • The response to different agents varies between individuals and with different doses. <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)**[33]	• Most of the agents used to treat excessive sleepiness have little effect on cataplexy or other REM sleep associated symptoms. Most antidepressants and anti-cataplectics have little effect on alertness. However, some compounds act on both symptoms. Compounds should be selected depending on the diagnosis and the targeted symptoms. Coadministration of two or more classes of compounds may be needed in some patients to adequately address their symptoms. • Modafinil is effective for treatment of daytime sleepiness due to narcolepsy. • Sodium oxybate is effective for treatment of cataplexy, daytime sleepiness,

Clinical Guideline	Recommendations
	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 (2006)**[34]	• Modafinil 100 to 400 mg/day is recommended as the first-line pharmacological treatment of excessive daytime sleepiness and irresistible episodes of sleep. • Methylphenidate 10 to 60 mg/day is recommended as the second line pharmacological treatment of excessive daytime sleepiness and irresistible episodes of sleep. • Nonpharmacological treatment recommendations include taking planned naps throughout the day scheduled on a patient-by-patient basis.
American Academy of Sleep Medicine: **Clinical Guideline for the Evaluation, Management and Long-term Care of Obstructive Sleep Apnea in Adults (2009)**[24]	<u>Weight reduction</u> • Successful dietary weight loss may improve the apnea-hypopnea index in obese OSA patients. • Dietary weight loss should be combined with a primary treatment for OSA. • Bariatric surgery may be adjunctive in the treatment of OSA in obese patients. <u>Pharmacologic agents</u> • Modafinil is recommended for the treatment of residual excessive daytime sleepiness in OSA patients who have sleepiness despite effective 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 OSA. <u>Supplemental oxygen</u> • Oxygen supplementation is not recommended as a primary treatment for OSA. <u>Medical therapies intended to improve nasal patency</u> • Short-acting nasal decongestants are not recommended for treatment of OSA. • Topical nasal corticosteroids may improve the apnea-hypopnea index in patients with OSA and concurrent rhinitis, and thus may be a useful adjunct to primary therapies for OSA. <u>Positional Therapies</u> • Positional therapy is an effective secondary therapy or can be a supplement to primary therapies for OSA in patients who have a low apnea-hypopnea index in the non-supine vs that in the supine position.
American Academy of Sleep Medicine:	<u>Shift work disorder</u> • Planned napping before or during the night shift is indicated to improve

Clinical Guideline	Recommendations
Practice Parameters for the Clinical Evaluation and Treatment of Circadian Rhythm Sleep Disorders (2007)[35]	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.

Conclusions

There are several central nervous system agents that are Food and Drug Administration (FDA)-approved for the treatment of attention deficit hyperactivity disorder (ADHD), including the cerebral stimulants (amphetamines and methylphenidate derivatives), as well as atomoxetine (Strattera®), clonidine extended-release (Kapvay®) and guanfacine extended-release (Intuniv®).[3-22] The cerebral stimulants are classified as Schedule II controlled substances, and are associated with Boxed Warnings regarding risk of abuse.[3-20,22,36] Atomoxetine, clonidine extended-release, and guanfacine extended-release are not classified as controlled substances.[12,13,21] Clonidine and guanfacine, extended-release formulations, are the first ADHD medications to achieve FDA-approval as adjunctive therapy with stimulant medications, but are also indicated for use as monotherapy.[12,13,23] Both agents are available generically in immediate-release formulations, though these formulations are not FDA-approval for use in ADHD. Furthermore, extended-release formulations of these agents cannot be substituted for immediate-release formulations on a mg-per-mg basis due to differences in pharmacokinetics.[12,13,29] Atomoxetine is associated with a Boxed Warning regarding an increased risk of suicidal ideation observed in short-term trials in children and adolescents with.[36]

Some cerebral stimulant agents are also FDA-approved for the treatment of a variety of sleep disorders, including narcolepsy, obstructive sleep apnea (OSA), and shift work disorder. Modafinil (Nuvigil®) and armodafinil (Provigil®) (the longer half-life enantiomer of modafinil) are both FDA-approved to improve wakefulness in adult patients with excessive sleepiness associated with narcolepsy, OSA, and shift work sleep disorder. These agents have been shown to produce psychoactive and euphoric effects similar to stimulants, as well as alterations in mood, perception, thinking and feelings. As a result, these agents are classified as Schedule IV controlled substances.[26,27] Sodium oxybate (Xyrem®) is γ-hydroxybutyric acid (GHB), a known drug of abuse. It is approved for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy. It is classified as a Schedule III controlled substance. Non-medical uses of sodium oxybate are classified under Schedule I. Sodium oxybate is associated with a Boxed Warning regarding associated important central nervous system adverse reactions. Furthermore, this agent is available though the Xyrem® Success Program.[28,36]

There are currently several generic ADHD agents and stimulants. At least one short-, intermediate-, and long-acting agents are available generically.[29] Several clinical trials have demonstrated the effectiveness of the ADHD agents and stimulants in their respective FDA-approved indications. Evidence consistently demonstrates that these agents significantly improve ADHD and sleepiness rating scales compared to placebo, respectively. There is insufficient evidence to suggest that one ADHD agent and stimulant is more efficacious than another. In addition, there is limited efficacy data regarding the treatment of ADHD in the adult population.[37-141] Guidelines recommend the use of FDA-approved agents for initial pharmacologic treatment of ADHD, and preference of one agent over another is not stated. Stimulant medications are still recognized as the most effective treatment option for most children with ADHD, and

response to one stimulant dose not predict response to another. Other factors associated with treatment decisions include presence of comorbid conditions, patient/family preference, storage/administration issues at school, history and/or presence of substance abuse, pharmacokinetics, and anticipated adverse events.[2,23,30-32] With regard to the use of nonstimulant medications in the treatment of ADHD, atomoxetine is recognized as a good option for patients with comorbid anxiety, sleep initiation disorder, substance abuse, or tics, or if initially preferred by parents and/or the physician. Overall, atomoxetine, clonidine extended-release, and guanfacine are effective in reducing ADHD core symptoms; however, these agents have a smaller evidence base compared to the cerebral stimulants.[23] With regard to the treatment of ADHD in adults, methylphenidate is recommended first-line, with atomoxetine and dexamphetamine recommended second line.[31,32]

Guidelines for the treatment of narcolepsy, OSA, and shift work disorder have not been updated since FDA-approval of sodium oxybate. Guidelines recommend the use of FDA-approved agents for the treatment of such sleep disorders, with modafinil recommended first-line for the treatment of narcolepsy. Even though guidelines are published prior to FDA-approval of sodium oxybate, the agent is the only one to be recognized as being an effective option for the treatment of cataplexy due to narcolepsy. Of note, armodafinil, the R enantiomer of modafinil, was FDA-approved in 2007; however, is not addressed in guidelines published after its approval.[24,33-35]

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