## *Therapeutic Class Overview*
## *Attention Deficit/Hyperactivity Disorder (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), atomoxetine (Strattera®), clonidine extended-release (Kapvay®) and guanfacine extended-release (Intuniv®).[3-23] The cerebral stimulant agents are classified as Schedule II controlled substances due to their potential for abuse.[3-11,14-21,23] Atomoxetine, clonidine extended-release and guanfacine extended-release are not classified as controlled substances.[12,13,22] Clonidine and guanfacine, extended-release formulations, are approved as adjunctive therapy with stimulant medications as well as monotherapy.[12,13,24] 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 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).[25,26] 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.[25] 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.[27,28] Sodium oxybate (Xyrem®) is γ-hydroxybutyric acid, 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 agent is available generically.[29]

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

| Generic (Trade Name) | Food and Drug Administration- Approved Indications | Dosage Form/Strength | Generic Availability |
|---|---|---|---|
| **Anorexigenic Agents and Respiratory and Cerebral Stimulants-Amphetamines** | | | |
| Amphetamine/ dextroamphetamine salts (Adderall®*, Adderall XR®*) | Treatment of ADHD | Capsule (Adderall XR®):<br>5 mg<br>10 mg<br>15 mg<br>20 mg<br>25 mg<br>30 mg<br><br>Tablet (Adderall®):<br>5 mg<br>7.5 mg | ✔ |


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| Generic (Trade Name) | Food and Drug Administration- Approved Indications | Dosage Form/Strength | Generic Availability |
|---|---|---|---|
| | | 10 mg<br>12.5 mg<br>15 mg<br>20 mg<br>30 mg | |
| Dextroamphetamine (ProCentra®, Dexedrine Spansule®*, Zenzedi®*) | Treatment of ADHD, narcolepsy | Solution (ProCentra®):<br>5 mg/5 mL<br><br>Sustained-release capsule (Dexedrine Spansule®):<br>5 mg<br>10 mg<br>15 mg<br><br>Tablet:<br>2.5 mg<br>5 mg<br>7.5 mg<br>10 mg | ✔ |
| Lisdexamfetamine (Vyvanse®) | Treatment of ADHD | Capsule:<br>20 mg<br>30 mg<br>40 mg<br>50 mg<br>60 mg<br>70 mg | - |
| Methamphetamine (Desoxyn®*) | Exogenous obesity, treatment of ADHD | Tablet:<br>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:<br>50 mg<br>150 mg<br>250 mg | - |
| Dexmethylphenidate (Focalin®*, Focalin XR®) | Treatment of ADHD | Extended-release capsule:<br>5 mg<br>10 mg<br>15 mg<br>20 mg<br>25 mg<br>30 mg<br>35 mg<br>40 mg<br><br>Tablet:<br>2.5 mg<br>5 mg<br>10 mg | ✔ |


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| Generic (Trade Name) | Food and Drug Administration- Approved Indications | Dosage Form/Strength | Generic Availability |
|---|---|---|---|
| Methylphenidate (Concerta®*, Daytrana®, Metadate CD®*, Metadate ER®*, Methylin®, Quillivant XR®, Ritalin®*, Ritalin LA®*, Ritalin SR®*) | Treatment of ADHD, narcolepsy | Chewable tablet (Methylin®):<br>2.5 mg<br>5 mg<br>10 mg<br><br>Extended-release capsule (Metadate CD®):<br>10 mg<br>20 mg<br>30 mg<br>40 mg<br>50 mg<br>60 mg<br><br>Extended-release capsule (Ritalin LA®):<br>10 mg<br>20 mg<br>30 mg<br>40 mg<br><br>Extended-release suspension (Quillivant XR®):<br>25 mg/ 5 mL<br><br>Extended-release tablet (Concerta®):<br>18 mg<br>27 mg<br>36 mg<br>54 mg<br><br>Extended-release tablet (Metadate ER®):<br>20 mg<br><br>Solution (Methylin®):<br>5 mg/5 mL<br>10 mg/5 mL<br><br>Sustained-release tablet (Ritalin-SR®):<br>20 mg<br><br>Tablet (Ritalin®):<br>5 mg<br>10 mg<br>20 mg<br><br>Transdermal patch (Daytrana®): | ✔ |


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| Generic (Trade Name) | Food and Drug Administration- Approved Indications | Dosage Form/Strength | Generic Availability |
|---|---|---|---|
| | | 10 mg/9 hours (1.1 mg/hour)<br>15 mg/9 hours (1.6 mg/hour)<br>20 mg/9 hours (2.2 mg/hour)<br>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:<br>100 mg<br>200 mg | ✔ |
| **Central α-Agonists** | | | |
| Clonidine extended-release (Kapvay®*) | Treatment of ADHD as monotherapy and as adjunctive therapy to stimulant medications | Extended-release tablet:<br>0.1 mg<br>0.2 mg | ✔ |
| Guanfacine extended-release (Intuniv®) | Treatment of ADHD as monotherapy and as adjunctive therapy to stimulant medications | Extended-release tablet:<br>1 mg<br>2 mg<br>3 mg<br>4 mg | - |
| **Central Nervous System Agents-Miscellaneous** | | | |
| Atomoxetine (Strattera®) | Treatment of ADHD | Capsule:<br>10 mg<br>18 mg<br>25 mg<br>40 mg<br>60 mg<br>80 mg<br>100 mg | - |
| Sodium oxybate (Xyrem®) | Treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy | Solution:<br>500 mg/mL (180 mL) | - |

ADHD=attention deficit/hyperactivity disorder, OSA=obstructive sleep apnea
* Generic available in at least one dosage form or strength.

**Evidence-based Medicine**

- Data from several clinical trials demonstrate that the attention deficit/hyperactivity disorder (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. [38-125]
- 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.[43,51,68,93,94,109]


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- 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 Food and Drug Administration (FDA)-approved for use in ADHD as monotherapy and as adjunctive treatment to stimulants.[64,65,74-82]
- Armodafinil, modafinil and sodium oxybate have all been shown to be more effective compared to placebo in patients with narcolepsy, obstructive sleep apnea (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.[126-155]

**Key Points within the Medication Class**

- According to Current Clinical Guidelines:
  - Guidelines recommend the use of Food and Drug Administration (FDA)-approved agents for initial pharmacologic treatment of attention deficit/hyperactivity disorder (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.[2,24,31-33]
  - With regard to the use of non stimulant 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 extended-release are effective in reducing ADHD core symptoms; however, these agents have a smaller evidence base compared to the cerebral stimulants.[24]
  - Methylphenidate is recommended as first-line treatment of ADHD in adults, with atomoxetine and dexamphetamine recommended second line.[31-33]
  - For the treatment of narcolepsy, obstructive sleep apnea (OSA), and shift work disorder, 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.[25,139-141]
  - Even though guidelines were 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.[25,34-36]
- 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.[30]
  - 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*
# *Attention Deficit/Hyperactivity Disorder (ADHD) Agents and Stimulants*

## Overview/Summary

Attention deficit/hyperactivity disorder (ADHD) is a common psychiatric disorder 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®).[3-24] Due to the potential for abuse, the cerebral stimulant agents are classified as Schedule II controlled substances.[3-11,14-21,23] Atomoxetine, clonidine extended-release and guanfacine extended-release are not classified as controlled substances.[12,13,22] Clonidine and guanfacine extended-release formulations are approved for use as both adjunctive therapy with stimulant medications and as monotherapy.[12,13]

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 and poor concentration); and signs of disturbed sleep (e.g., snoring, restlessness or resuscitative snorts).[25,26] 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.[25] Modafinil (Provigil®) and armodafinil (Nuvigil®), the longer half-life enantiomer of modafinil, are 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.[27,28]

Sodium oxybate (Xyrem®) is γ-hydroxybutyric acid, 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.[29] Several generic ADHD agents and stimulants are currently available. Specifically, at least one short-, intermediate-, and long-acting agents is available generically.[30] The agents included in this review are listed in Table 1 categorized by medication class and by generic name, as there are multiple branded agents containing the same active ingredient.

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.[2,24,31] 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.[32] Stimulants, particularly methylphenidate, are recommended as first-line therapy in adult patients with ADHD.[24,33] Guidelines for the treatment of narcolepsy, OSA and shift work disorder 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


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due to narcolepsy. Armodafinil, the R enantiomer of modafinil, was FDA-approved in 2007; however, its role is not been address in the current guidelines.[25,34-36]

## Medications

**Table 1. Medications Included Within Class Review**[3-23,27-29]

| Generic Name (Trade name) | Medication Class | Generic Availability |
|---|---|---|
| **Anorexigenic Agents and Respiratory and Cerebral Stimulants-Amphetamines** | | |
| Amphetamine/dextroamphetamine salts (Adderall®*, Adderall XR®*) | Central nervous system stimulant | ✔ |
| Dextroamphetamine (ProCentra®, Dexedrine Spansule®*, Zenzedi®*) | 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®) | Wakefulness promoting agents | - |
| Dexmethylphenidate (Focalin®*, Focalin XR®) | Central nervous system stimulant | ✔ |
| Methylphenidate (Concerta®*, Daytrana®, Metadate CD®*, Metadate ER®*, Methylin®, Methylin ER®, Quillivant XR®, Ritalin®*, Ritalin LA®*, Ritalin SR®*) | Central nervous system stimulant | ✔ |
| Modafinil (Provigil®*) | Wakefulness promoting agents | ✔ |
| **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 | - |

*Available generically in one dosage form or strength.

**Table 2. Cerebral Stimulants/Agents Used for Attention Deficit/Hyperactivity Disorder Classified by Duration of Action**[3-23,27-29]

| 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®, Zenzedi®* | 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®, Quillivant XR®, Ritalin LA® |
| Modafinil | | | Provigil® |
| **Central α-Agonists** | | | |
| Clonidine | | | Kapvay® |


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| Generic Name(s) | Short-Acting | Intermediate-Acting | Long-Acting |
|---|---|---|---|
| Guanfacine | | | Intuniv® |
| **Central Nervous System Agents-Miscellaneous** | | | |
| Atomoxetine | | | Strattera® |
| Sodium oxybate | Xyrem® | | |

## Indications

**Table 3a. Food and Drug Administration-Approved Indication-Anorexigenic Agents and Respiratory and Cerebral Stimulants-Amphetamines**[3,4,7-9,21,23]

| Indication(s) | Amphetamine/ Dextroamphet-amine Salts | Dextroamphet-amine | Lisdex-amfetamine | Methamphet-amine |
|---|---|---|---|---|
| Exogenous obesity | | | | ✔ * |
| Narcolepsy | ✔ † | ✔ | | |
| Treatment of attention deficit/hyperactivity disorder | ✔ | ✔ | ✔ | ✔ |

*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 Food and Drug Administration-Approved Indication-Anorexigenic Agents and Respiratory and Cerebral Stimulants-Miscellaneous**[5,6,10,11,14-20,27,28]

| Indication(s) | Armodafinil | Dexmethyl-phenidate | Methyl-phenidate | Modafinil |
|---|---|---|---|---|
| Narcolepsy | | | ✔ * | |
| To improve wakefulness in patients with excessive sleepiness associated with obstructive sleep apnea, narcolepsy, and shift work disorder | ✔ | | | ✔ |
| Treatment of attention deficit/hyperactivity disorder | | ✔ | ✔ | |

*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, fatigue due to multiple sclerosis, Parkinson's disease and postpoliomyelitis syndrome.[37]

**Table 3c. Food and Drug Administration-Approved Indication-Central α-Agonists**[12,13]

| Indication | Clonidine | Guanfacine |
|---|---|---|
| Treatment of attention deficit/hyperactivity disorder 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.[37]


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**Table 3d. Food and Drug Administration-Approved Indication-Central Nervous System Agents-Miscellaneous**[22,29]

| Indication(s) | Atomoxetine | Sodium Oxybate |
|---|---|---|
| Treatment of attention deficit/hyperactivity disorder | ✔ | |
| 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.[37]

## Pharmacokinetics

**Table 4a. Pharmacokinetics-Anorexigenic Agents and Respiratory and Cerebral Stimulants-Amphetamines**[3,4,7-9,21,23]

| Drug | Absorption | Distribution | Metabolism | Elimination |
|---|---|---|---|---|
| Amphetamine/ dextro-amphetamine salts | Bioavailability: percent not reported (well-absorbed) (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: 2 to 3 hours (IR), 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: 10 to 12 hours Cl: nd |
| Lisdex-amfetamine | Bioavailability: percent not reported (rapidly absorbed) (food: increased Tmax by 1 hour) Cmax: nd Tmax: 3.5 to 3.8 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: percent not reported (rapidly absorbed) (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: Renal (62%) 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


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**Table 4b. Pharmacokinetics-Anorexigenic Agents and Respiratory and Cerebral Stimulants-Miscellaneous**[5,6,10,11,14-20,27,28]

| Drug | Absorption | Distribution | Metabolism | Elimination |
|---|---|---|---|---|
| Armodafinil | Bioavailability: percent 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: 12 to 15% | Method: Liver (extensive) (IR) Metabolites (inactive): d-ritalinic acid (IR) | Route: renal (90%) Half-life: 2.0 to 4.5 hours Cl: nd |
| Methylphenidate | Bioavailability: 10 to 52% (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), 4.7 hours (SR), 7.5 to 10.5 hours | Vd: 1.80 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 (90%) 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) |


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| Drug | Absorption | Distribution | Metabolism | Elimination |
|---|---|---|---|---|
| | (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: 15 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: 89% (food: minimal effect) Cmax: nd Tmax: 6.5 hours | Vd: nd Protein binding: 20 to 40% | Method: Liver (50%) Metabolites: nd | Route: renal (40 to 60%) Half-life: 12 to 16 hours Cl: nd |
| Guanfacine | Bioavailability: 80% (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: 16 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**[22,29]

| Drug | Absorption | Distribution | Metabolism | Elimination |
|---|---|---|---|---|
| Atomoxetine | Bioavailability: 63 to 94% (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: 88% (food: absorption delayed and decreased by high fat meals) | Vd: 0.19 to 0.58 L/kg Protein binding: <1% | Method: central nervous system, liver (extensive) Metabolites (inactive): hemisuccinic, | Route: renal (1 to 5%), fecal, expiration Half-life: 20 to 53 minutes Cl: 7 to 14 |


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| Drug | Absorption | Distribution | Metabolism | Elimination |
|---|---|---|---|---|
| | Cmax: nd<br>Tmax: 25 to 75 minutes | | succinic acid | 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 attention deficit/hyperactivity disorder (ADHD) agents and stimulants in Food and Drug Administration (FDA)-approved indications are outlined in Table 5.[38-155]

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 or 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.[38-126]

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.[43,51,69,94,95,110] 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 10 weeks, the mean ADHD rating scale (ADHD-RS) scores significantly decreased in the amphetamine/dextroamphetamine salts extended-release group compared to baseline, regardless of dose ($P<0.0001$).[43] 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 ($P<0.001$).[92] 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; $P=0.80$).[110]

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 or 0.4 mg daily significantly improved ADHD-RS from baseline at eight weeks compared to placebo ($P<0.001$).[65] 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; $P=0.80$ 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 ($P=0.001$).[75] In a study by Sallee and colleagues, adolescents randomized to receive guanfacine extended-release 1 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, 2, 3 and 4 mg groups, respectively.[76] 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 ($P<0.001$).[79] 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


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patients (six to 17 years of age).[65,75-81,84] 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.[66,82,28] 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.[64,74,113]

Armodafinil, modafinil and sodium oxybate have all been shown to be more effective compared to placebo in patients with narcolepsy, obstructive sleep apnea 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.[127-156]


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**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[38]<br><br>AMP-IR (Adderall®) 10 mg daily<br><br>vs<br><br>AMP-XR (Adderall XR®) 10 to 30 mg daily<br><br>vs<br><br>placebo | DB, PC, RCT, XO<br><br>Children six to 12 years of age diagnosed with ADHD (combined or hyperactive-impulsive subtype) | N=51<br><br>5 weeks | Primary:<br>SKAMP scales<br><br>Secondary:<br>Examination of the time course of AMP-XR | Primary:<br>AMP-IR and AMP-XR were judged to have similar efficacy, and both exceeded placebo on attention and deportment SKAMP scales (*P*<0.0001).<br><br>Secondary:<br>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[39]<br><br>AMP-IR (Adderall®) 12.5 mg daily<br><br>vs<br><br>MPH-IR 25 mg daily<br><br>vs<br><br>placebo | DB, PC, PG, RCT<br><br>Children in grades one through five diagnosed with ADHD | N=58<br><br>3 weeks | Primary:<br>CGI-S (parent and teacher)<br><br>Secondary:<br>Not reported | Primary:<br>More responders were reported with AMP-IR than MPH-IR or placebo on both CGI-S scores (*P*<0.05).<br><br>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).<br><br>Secondary:<br>Not reported |
| Pelham et al[40]<br><br>AMP-IR (Adderall®) 7.5 or 12.5 mg BID<br><br>vs<br><br>MPH-IR (Ritalin®) 10 or | DB, PC, RCT, XO<br><br>Children five to 12 years of age diagnosed with ADHD | N=25<br><br>6 weeks | Primary:<br>Time course and dose-dependent response information<br><br>Secondary: | Primary:<br>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).<br><br>Conversely, AMP-IR 7.5 mg BID and MPH-IR 17.5 mg BID produced equivalent |


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| Study and Drug Regimen | Study Design, Study Rating, and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| 17.5 mg BID<br><br>vs<br><br>placebo | | | Not reported | behavioral changes throughout the entire day.<br><br>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).<br><br>Both drugs produced low and comparable levels of clinically significant side effects.<br><br>Secondary:<br>Not reported |
| Faraone et al[41]<br><br>AMP-IR (Adderall®)<br><br>vs<br><br>MPH-IR | MA (4 trials)<br><br>Patients diagnosed with ADHD | N=216<br><br>3 to 8 weeks | Primary:<br>CGI-S (parent, teacher and investigator)<br><br>Secondary:<br>Not reported | Primary:<br>Combined results showed slightly greater efficacy with AMP-IR vs MPH-IR in clinician and parent ratings (*P*<0.05).<br><br>No statistically significant difference was found in CGI-S scores with teacher ratings (*P*≥0.26).<br><br>Secondary:<br>Not reported |
| Biederman et al[42]<br><br>AMP-XR (Adderall XR®) 10 to 30 mg daily<br><br>vs<br><br>placebo | DB, MC, PC, RCT<br><br>Children six to 12 years of age diagnosed with ADHD (hyperactive-impulsive or combined subtypes) | N=584<br><br>3 weeks | Primary:<br>CGI-S (teachers and parents)<br><br>Secondary:<br>Variation in responses based on morning and afternoon assessments | Primary:<br>Each AMP-XR treatment group had a statistically significant improvement in both CGI-S teacher and parent scales (*P*<0.001).<br><br>Secondary:<br>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.<br><br>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[43]<br><br>AMP-XR (Adderall XR®) 10 to 60 mg daily | MC, OL, PRO<br><br>Adults ≥18 years of age diagnosed with ADHD (any subtype) | N=725<br><br>10 weeks | Primary:<br>ADHD-RS, CGI-I<br><br>Secondary:<br>SF-36 | Primary:<br>At the end of the study, the mean ADHD-RS scores significantly decreased in the AMP-XR group regardless of dose compared to baseline (*P*<0.0001). Statistical analysis comparing the individual AMP-XR doses was not performed.<br><br>At the end of the study, most patients obtained CGI-I ratings of much/very much |


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| Study and Drug Regimen | Study Design, Study Rating, and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | improved (522/702; 74.4%).<br><br>Secondary:<br>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[44]<br><br>Atomoxetine 1.2 to 1.8 mg/kg/day<br><br>vs<br><br>placebo | 2 DB, MC, PC, RCT<br><br>Females seven to 13 years of age diagnosed with ADHD | N=51<br><br>9 weeks | Primary:<br>ADHD-RS<br><br>Secondary:<br>CPRS-R, CGI-S (parents) | Primary:<br>Atomoxetine significantly decreased ADHD-R:S scores compared to placebo (*P*<0.05) for the entire duration of the study.<br><br>Secondary:<br>Atomoxetine statistically significantly decreased the parent-rated CPRS-R index scores compared to placebo (10.3 vs 1.0; *P*<0.001).<br><br>Atomoxetine also statistically significantly decreased the parent-rated CGI-S scores compared to placebo (1.5 vs 0.6; *P*<0.001). |
| Durell et al[45]<br><br>Atomoxetine<br><br>vs<br><br>placebo | DB, PC, RCT<br><br>Young adults 18 to 30 years of age with ADHD | N=445<br><br>12 weeks | Primary:<br>CAARS-Inv: SV total ADHD symptoms score with adult prompts<br><br>Secondary:<br>AAQoL-29, CGI-S, Patient Global Impression-Improvement, CAARS self report, BRIEF-Adult Version Self Report and asessments of depression, | Primary:<br>Compared to placebo, treatment with atomoxetine resulted in a greater improvement in CAARS: Inv: SV (-13.6±0.8 vs -9.3±0.8; 95% CI, -6.35 to -2.37; *P*<0.001).<br><br>Secondary:<br>Compared to placebo, treatment with atomoxetine resulted in a greater improvement in CGI-S (-1.1±0.1 vs -0.7±0.1; 95% CI, -0.63 to -0.24; *P*<0.001) and CAARS Self-Report (-11.9±0.8 vs -7.8±0.7; 95% CI, -5.94 to -2.15; *P*<0.001) but not on the Patient Global Impression-Improvement score. Treatment with atomoxetine was superior to placebo on the AAQoL-29 and BRIEF-Adult Version Self-Report. |


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| Study and Drug Regimen | Study Design, Study Rating, and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | anxiety, sleepiness, driving behaviors, social adaptation and substance abuse | |
| Michelson et al[46]<br><br>Atomoxetine 1.2 to 1.8 mg/kg/day<br><br>vs<br><br>placebo | MC, OL, PC, RCT<br><br>Children eight to 18 years of age diagnosed with ADHD | N=297<br><br>8 weeks | Primary:<br>ADHD-RS<br><br>Secondary:<br>CPRS-R, CHQ | Primary:<br>Significant reduction in ADHD-RS was seen in both active groups (*P*<0.001).<br><br>No difference was seen between the 1.2 and the 1.8 mg/kg/day treatment arms.<br><br>Secondary:<br>Atomoxetine 1.2 mg/kg showed significant decreases in all scales of CPRS-R (*P*<0.05).<br><br>Atomoxetine 1.8 mg/kg showed significant increase in all scales of CHQ (*P*<0.05). |
| Kratochvil et al[47]<br><br>Atomoxetine 0.5 to 1.8 mg/kg/day<br><br>vs<br><br>placebo | DB, MC, PC, RCT<br><br>Children five to six years of age diagnosed with ADHD | N=101<br><br>8 weeks | Primary:<br>ADHD-RS<br><br>Secondary:<br>CGI-S, CGI-I | Primary:<br>Atomoxetine significantly reduced mean parent (*P*<0.009) and teacher (*P*=0.02) ADHD-RS total score compared to placebo.<br><br>Secondary:<br>A total of 40% of children treated with atomoxetine and 22% of children who received placebo had CGI-I scores much too very much improved (*P*=0.1) with no significant differences between groups.<br><br>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.<br><br>Common adverse events included decreased appetite, gastrointestinal upset, and sedation. Most adverse events were considered mild or moderate by the study investigator. |


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| Study and Drug Regimen | Study Design, Study Rating, and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| Spencer et al[48]<br><br>Atomoxetine up to 90 mg daily<br><br>vs<br><br>placebo | DB, MC, PC, RCT (pooled data)<br><br>Children seven to 13 years of age diagnosed with ADHD | N=291<br><br>9 weeks | Primary:<br>ADHD-RS<br><br>Secondary:<br>CPRS-R:S, CGI-S | Primary:<br>Significant mean reductions in both active groups in all scales were reported (both studies) for ADHD-RS (*P*<0.001) and CPRS-R:S (*P*=0.023 for study one and *P*<0.001 for study two).<br><br>Secondary:<br>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).<br><br>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[49]<br><br>Atomoxetine 0.5 mg/kg/day for seven days, followed by 1.2 mg/kg/day (fast titration)<br><br>vs<br><br>atomoxetine 0.5 mg/kg/day for seven days, followed by 0.8 mg/kg/day for seven days, followed by 1.2 mg/kg/day (slow titration)<br><br>vs<br><br>placebo | DB, PC, RCT<br><br>Patients six to 17 years of age ADHD with comorbid ODD or conduct disorder | N=181<br><br>9 week | Primary:<br>SNAP-ODD, SNAP-ADHD<br><br>Secondary:<br>CGI-S | Primary:<br>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).<br><br>Comparing fast and slow titration separately, the decrease in ODD symptoms severity was significant for both individual titration groups (atomoxetine-fast: 8.6; 95% CI, 7.2 to 9.9; atomoxetine-slow: 9.0; 95% CI, 7.7 to 10.3; and placebo: 12.0; 95% CI, 10.6 to 13.5).<br><br>Atomoxetine was significantly more effective than placebo in reducing the severity of ADHD symptoms measured by SNAP-ADHD scores.<br><br>Scores reflecting severity of conduct disorder symptoms, attention-deficit and disruptive behavior, were significantly reduced after nine weeks of atomoxetine treatment.<br><br>Secondary:<br>CGI-S and individual treatment behaviors showed were significantly reduced after treatment with atomoxetine.<br><br>The most common adverse events included fatigue, sleep disorders, nausea, and gastrointestinal complaints and were reported the first three weeks of treatment in |


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| Study and Drug Regimen | Study Design, Study Rating, and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | 60.0% of atomoxetine-fast, 44.3% of atomoxetine-slow, and 18.6% of placebo group study patients. |
| Hammerness et al[50]<br><br>Atomoxetine 0.5 to 1.4 mg/kg/day | OL, PRO<br><br>Children six to 17 years of age diagnosed with ADHD who had a prior trial of stimulant treatment | N=34<br><br>6 weeks | Primary:<br>ADHD-RS, CGI<br><br>Secondary:<br>Not reported | Primary:<br>There was a significant reduction in ADHD RS symptoms compared to baseline.<br><br>There was a significant reduction in ADHD-RS symptoms score from baseline to the second week of atomoxetine treatment.<br><br>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.<br><br>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.<br><br>Commonly reported adverse events (>10%) included gastrointestinal problems, headache and sedation.<br><br>Secondary:<br>Not reported |
| Adler et al[51]<br><br>Atomoxetine 60 to 120 mg/day | MC, OL<br><br>Adults diagnosed with ADHD | N=384<br><br>4 years | Primary:<br>CAARS-Inv:SV total ADHD symptom score<br><br>Secondary:<br>CAARS-Self:SV, CGI-ADHD-S, HAM-D-17, HAMA, WRAADDS, SDS | Primary:<br>The mean CAARS-Inv:SV total ADHD symptom scores decreased 30.2% from baseline to endpoint (-8.8; *P*<0.001).<br><br>Secondary:<br>Significant decreases were found on the CAARS-Inv:SV subscales, and the CAARS-Self:SV total and subscales (*P*<0.001).<br><br>CGI-ADHD-S and WRAADDS scores improved significantly from baseline (-1.1 and -5.0, respectively; *P*<0.001 for both).<br><br>SDS total and subscale scores improved 25.3% (-3.8; *P*<0.001).<br><br>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). |


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| | | | | HR, DBP, SBP increased. Weight loss over the course of the study was statistically significant (-0.94 kg; *P*<0.001). |
| Wietecha et al[52]<br><br>Atomoxetine 40 mg daily titrated to 100 mg daily after two weeks<br><br>vs<br><br>placebo | DB, PC, RCT<br><br>Adults with ADHD having both a spouse/partner and child | N=502<br><br>24 weeks | Primary:<br>CAARS-Inv: SV and CGI-S<br><br>Secondary:<br>Not reported | Primary:<br>Treatment with atomoxetine resulted in a greater improvement in CAARS-Inv: SV (-16.43 vs -8.65; *P*<0.001) and CGI-S compared to placebo at week 24 (*P*<0.001).<br><br>Secondary:<br>Not reported. |
| Biederman et al[53]<br><br>Atomoxetine 0.5 to 1.2 mg/kg/day<br><br>vs<br><br>AMP-XR (Adderall XR®) 10 to 30 mg daily | DB, FD, MC, RCT<br><br>Females six to 12 years of age diagnosed with ADHD | N=57<br><br>18 days | Primary:<br>SKAMP-A<br>SKAMP-D<br>Academic testing<br><br>Secondary:<br>Adverse events | Primary:<br>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).<br><br>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).<br><br>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).<br><br>Secondary:<br>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[54]<br><br>Atomoxetine 0.5 mg/kg once daily<br><br>vs | MC, OL, PRO, RCT<br><br>Children six to 12 years of age diagnosed with ADHD | N=1,323<br><br>3 weeks | Primary:<br>Investigator-related ADHD-RS and CGI-I, performed at weeks one, two, and three; PSQ | Primary:<br>The ADHD-RS change from baseline measured at each time point showed that both treatments were effective.<br><br>MPH-ER produced significantly greater improvements in ADHD-RS scores at weeks, one, two, and three (*P*<0.001). |


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| MPH-ER (Concerta®)<br>18 mg once daily | | | Secondary:<br>Not reported | 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).<br><br>Significantly more children treated with MPH ER than with atomoxetine achieved a CGI-I score ≤2 after week three (*P*<0.001).<br><br>Parent-rated PSQ scores revealed statistically significantly greater improvements with MPH-ER than with atomoxetine.<br><br>Secondary:<br>Not reported |
| Newcorn al[55]<br><br>Acute Comparison Trial:<br>Atomoxetine 0.8 to 1.8 mg/kg/day administered BID<br><br>vs<br><br>MPH-ER (Concerta®)<br>18 to 54 mg once daily<br><br>vs<br><br>placebo<br><br>XO Trial:<br>Atomoxetine 0.8 to 1.8 mg/kg/day administered BID<br><br>Patients on MPH-ER were switched to atomoxetine during the | DB, PC, RCT, XO<br><br>Children six to 16 years of age diagnosed with ADHD (any subtype) | Acute Comparison Trial:<br>N=516<br><br>6 weeks<br><br>XO Trial:<br>N=178<br><br>6 weeks | Primary:<br>ADHD-RS<br><br>Secondary:<br>CGI-S, CPRS, CHQ, and Daily Parent Ratings of Evening and Morning Behavior-Revised | *Acute Comparison Trial*<br>Primary:<br>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).<br><br>Secondary:<br>Atomoxetine and MPH-ER produced greater improvements in CGI-S, CPRS and CHQ compared to placebo. MPH-ER also produced greater improvements compared to atomoxetine on CGI-S, CPRS and CHQ (*P*=0.004, *P*=0.003, *P*=0.02, respectively).<br><br>*XO Trial*<br>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 XO trial. Of the 69 patients who did not respond to atomoxetine in the second trial, 42% had previously responded to MPH-ER.<br><br>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 |


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| XO trial. | | | | response, 51% showed significantly better response, and 39% showed roughly the same response to treatment with atomoxetine. |
| Starr et al[56]<br><br>Atomoxetine 0.5 mg/kg once daily<br><br>vs<br><br>MPH-ER (Concerta®) 18 mg once daily | OL, RCT<br><br>African-American children six to 12 years of age diagnosed with ADHD | N=183<br><br>3 weeks | Primary:<br>Investigator-related ADHD-RS and CGI-I, performed at weeks one, two, and three; PSQ<br><br>Secondary:<br>Not reported | Primary:<br>For the ADHD-RS scores, both treatment groups achieved significant improvements from baseline at all time points (*P*<0.001).<br><br>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).<br><br>Significantly more children treated with MPH ER than atomoxetine achieved a CGI-I score ≤2 after week three (*P*<0.01).<br><br>Parent-rated PSQ scores revealed statistically significantly greater improvements with MPH ER than with atomoxetine.<br><br>Secondary:<br>Not reported |
| Wang et al[57]<br><br>Atomoxetine 0.8 to 1.8 mg/kg/day<br><br>vs<br><br>MPH-IR 0.2 to 0.6 mg/kg/day administered BID | DB, MC, RCT<br><br>Children six to 16 years of age diagnosed with ADHD | N=330<br><br>8 weeks | Primary:<br>ADHD-RS<br><br>Secondary:<br>CPRS-R:S, CGI-S, treatment-emergent adverse events, weight | Primary:<br>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).<br><br>Secondary:<br>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).<br><br>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.<br><br>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 - |


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| | | | | 0.4 kg; *P*<0.001). |
| Kratochvil et al[58]<br><br>Atomoxetine titrated up to 2 mg/kg/day<br><br>vs<br><br>MPH-IR titrated up to 60 mg/day | MC, OL<br><br>Males seven to 15 years of age and females seven to nine year of age diagnosed with ADHD | N=228<br><br>10 weeks | Primary:<br>ADHD-RS<br><br>Secondary:<br>CPRS-R, CGI-S, safety | Primary:<br>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).<br><br>Secondary:<br>There were no statistically significant differences between treatment groups on all of the CPRS-R and CGI-S outcome measures (*P*<0.001).<br><br>Tolerability was also similar between the two drugs with no statistical differences in discontinuations (*P*=0.18).<br><br>Statistically significant increases in pulse and BFI were seen with both atomoxetine and MPH-IR (*P*<0.05). |
| Sutherland et al[59]<br><br>Atomoxetine<br>40 to 100 mg/day<br><br>vs<br><br>atomoxetine 40 to 100 mg/day and buspirone 15 to 45 mg/day<br><br>vs<br><br>placebo | DB, MC, PC, RCT<br><br>Men and women 18 to 60 years of age diagnosed with ADHD | N=241<br><br>8 weeks | Primary:<br>AISRS<br><br>Secondary:<br>Not reported | Primary:<br>There was a significantly greater decrease in the AISRS total score for atomoxetine plus buspirone than placebo at weeks one to seven, with an estimated mean difference of -4.80 (*P*=0.001).<br><br>There was a greater decrease in the AISRS total score for atomoxetine plus buspirone than for atomoxetine at weeks one to seven, but only statistically significant at week four (*P*<0.09).<br><br>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.<br><br>Discontinuations due to treatment-related adverse events were 15.5% for atomoxetine plus buspirone, 11.3% for atomoxetine and 14.9% for placebo.<br><br>Secondary:<br>Not reported |


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| Ni et al[60]<br><br>Atomoxetine titrated up to 1.2 mg/kg/day<br><br>vs<br><br>MPH-IR titrated up to 60 mg/day | OL, RCT<br><br>Patients 18 to 50 years of age diagnosed with ADHD | N=63<br><br>8 to 10 weeks | Primary:<br>ASRS, CGI-ADHD-S, AAQoL, WFIRS-S and safety<br><br>Secondary:<br>Not reported | Primary:<br>At visit one (weeks four and five), both the MPH-IR and atomoxetine treatment groups experienced statistically significant reductions from baseline in ASRS scores for inattention (-5.77 and -8.93, respectively; *P*<0.001 for both) and hyperactivity-impulsivity (-3.69 and -8.11, respectively; *P*<0.001). The differences between the treatment groups was significant, favoring treatment with atomoxetine (*P*<0.05).<br><br>Significant reductions from baseline in ASRS scores were apparent at visit two (eight to 10 weeks) for both the inattention (-9.25 and -10.20, respectively; *P*<0.001) and hyperactivity-impulsivity subtypes (-6.21 and -7.80, respectively; *P*<0.001); however, differences between treatment groups were not statistically significant.<br><br>Both treatment groups experienced improved CGI-ADHD-S scores at all time points compared to baseline values (*P*<0.001 for all); however, differences between groups were not statistically significant.<br><br>The mean AAQoL scores significantly increased from baseline to visit one (weeks four and five) and visit two (weeks eight to 10) for both treatment groups. The effect sizes as assessed by Cohen's *d* ranged from 0.59 to 1.63 (*P*<0.01).<br><br>Both treatment groups experienced significant improvements in the severity of functional impairment (WFIRS-S) from baseline to visit one (weeks four to five) or (weeks eight to 10). Cohen's *d* ranged from 0.49 to 1.70 for the MPH-IR group and 0.42 to 1.11 for the atomoxetine group. Differences between the treatment groups were not statistically significant.<br><br>Decreased appetite, vomiting and palpitation were frequently reported in both treatment groups. There was no significant difference in the occurrence of adverse events between treatment groups. Moreover, there was no significant change in body weight, BP, or HR during the study period (*P*>0.05 for all).<br><br>Secondary:<br>Not reported |
| Sutherland et al[61]<br><br>Atomoxetine 40 to 100 | DB, MC, PC, RCT | N=241<br><br>8 weeks | Primary:<br>AISRS | Primary:<br>There was a significantly greater decrease in the AISRS total score for atomoxetine plus buspirone than placebo at weeks one to seven, with an estimated mean |


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| mg/day<br><br>vs<br><br>atomoxetine 40 to 100 mg/day plus buspirone 15 to 45 mg/day<br><br>vs<br><br>placebo | Patients 18 to 60 years of age diagnosed with ADHD | | Secondary:<br>Not reported | difference -4.80 (*P*=0.001).<br><br>There was a greater decrease in the AISRS total score for atomoxetine plus buspirone than for atomoxetine at weeks one to seven, but only statistically significant at week four (*P*<0.09).<br><br>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.<br><br>Discontinuations due to treatment-related adverse events were 15.5% for atomoxetine plus buspirone, 11.3% for atomoxetine, and 14.9% for placebo.<br><br>Secondary:<br>Not reported |
| Prasad et al[62]<br><br>Atomoxetine 0.5 to 1.8 mg/kg/day<br><br>vs<br><br>standard current therapy | MC, OL, RCT<br><br>Children seven to 15 years of age diagnosed with ADHD | N=201<br><br>10 weeks | Primary:<br>CHIP-CE<br><br>Secondary:<br>ADHD-RS, CGI-S, CGI-I, HSPP, FBIM | Primary:<br>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).<br><br>Secondary:<br>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).<br><br>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).<br><br>There was not a statistically significant difference between groups in reduction in FBIM scores (*P*>0.05). |
| Cheng et al[63]<br><br>Atomoxetine<br><br>vs | MA (9 trials)<br><br>Patients diagnosed with ADHD | N=1,828<br><br>Variable duration | Primary:<br>ADHD-RS<br><br>Secondary:<br>CTRS-RS, | Primary:<br>Atomoxetine significantly improved ADHD-RS scores compared to placebo (*P*<0.01 for all).<br><br>Secondary: |


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| placebo | | | CPRS-R:S, CGI-S, CHQ | Atomoxetine significantly improved CTRS-RS, CPRS-R:S, and CGI-S scores compared to placebo (*P*<0.01 for all).<br><br>Atomoxetine significantly improved quality of life as measured by the CHQ compared to placebo (*P*<0.01). |
| Hazell et al[64]<br><br>Clonidine 0.1 to 0.2 mg/day<br><br>vs<br><br>placebo | PC, RCT, TB<br><br>Children six to 14 years of age with ADHD and co-morbid ODD or conduct disorder | N=67<br><br>6 weeks | Primary:<br>CBC (subscales conduct and hyperactive index)<br><br>Secondary:<br>Not reported | Primary:<br>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).<br><br>Compared to placebo, clonidine was associated with a greater reduction in standing SBP measured and with transient sedation and dizziness.<br><br>Study patients treated with clonidine have a greater reduction in a number of unwanted effects associated with psychostimulant treatment compared to placebo.<br><br>Secondary:<br>Not reported |
| Jain et al[65]<br><br>Clonidine ER 0.2 mg/day<br><br>vs<br><br>Clonidine ER 0.4 mg/day<br><br>vs<br><br>placebo | DB, PC, RCT<br><br>Patients six to 17 years of age diagnosed with ADHD | N=236<br><br>8 weeks | Primary:<br>ADHD-RS (total score)<br><br>Secondary:<br>ADHD-RS (inattention and hyperactivity), CPRS-R:S, CGI-S, CGI-I, PGA, treatment-emergent adverse events | Primary:<br>Improvement from baseline to week five in ADHD-RS total score was significantly greater in both clonidine ER groups vs placebo (*P*<0.001).<br><br>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.<br><br>Secondary:<br>A significant improvement in mean change in ADHD-RS inattention score at week five vs baseline was -7.7 for both clonidine ER groups vs -3.4 for the placebo group (*P*<0.001 for clonidine ER 0.2 mg/day; *P*<0.006 for clonidine ER 0.4 mg/day).<br><br>Improvements from baseline to week five in ADHD-RS hyperactivity score were -4.1 in the placebo group, -7.9 in the clonidine ER 0.2-mg/day group, and -8.8 in the clonidine ER 0.4-mg/day group (*P*<0.0012). |


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| | | | | 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.<br><br>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).<br><br>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).<br><br>The most common treatment-emergent adverse event was mild-to-moderate somnolence. Changes on ECG were minor and due to the pharmacology of clonidine. |
| Kollins et al[66]<br><br>Clonidine ER 0.1 to 0.4 mg/day plus psychostimulant<br><br>vs<br><br>placebo plus psycho-stimulant | DB, MC, PC, RCT<br><br>Children and adolescents diagnosed with hyperactive or combined subtype ADHD who had inadequate response to their psychostimulant therapy | N=198<br><br>8 weeks | Primary:<br>ADHD-RS (total score)<br><br>Secondary:<br>ADHD-RS (hyperactivity and inattention), CPRS, CGI-S, CGI-I, PGA | Primary:<br>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).<br><br>Secondary:<br>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.<br><br>The most commonly treatment-emergent adverse event reported were mild to moderate in severity and included somnolence, headache, fatigue, upper abdominal pain, and nasal congestion. |
| Wigal et al[67]<br><br>DXM (Focalin®) 2.5 to 10 mg BID<br><br>vs | DB, MC, PC, RCT<br><br>Children six to 17 years of age diagnosed with | N=132<br><br>4 weeks | Primary:<br>SNAP-T<br><br>Secondary:<br>SNAP-P, CGI-I<br>Math test | Primary:<br>Both DXM and MPH-IR significantly improved SNAP-T scores compared to placebo (*P*=0.004 and *P*=0.0042, respectively)<br><br>Secondary:<br>The DXM group decreased SNAP-P scores at both 3 and 6 PM assessments |


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| MPH-IR 5 to 20 mg BID<br><br>vs<br><br>placebo | ADHD (any subtype) | | performance (clinic and home) | 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).<br><br>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).<br><br>Both DXM and MPH-IR significantly improved clinic-based math test scores compared to placebo (*P*=0.001 and *P*=0.0041 respectively).<br><br>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[68]<br><br>DXM-XR (Focalin XR®) 5 to 30 mg/day<br><br>vs<br><br>placebo | DB, MC, PC, RCT<br><br>Children six to 17 years of age diagnosed with ADHD (any subtype) | N=97<br><br>7 weeks | Primary: CADS-T<br><br>Secondary: CADS-P, CGI-I, CGI-S, CHQ (physical and psychosocial) | Primary:<br>DXM-XR significantly increased CADS-T scores from baseline compared to placebo (16.3 vs 5.7; *P*<0.001).<br><br>Secondary:<br>DXM-XR significantly increased CADS-P scores from baseline compared to placebo (17.6 vs 6.5; *P*<0.001).<br><br>DXM-XR improved overall CGI-I scores in a greater percent of patients compared to placebo (67.3 vs 13.3%; *P*<0.001).<br><br>DXM-XR significantly improved CGI-S scores in a greater percent of patients than placebo (64.0 vs 11.9%; *P*<0.001).<br><br>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[69]<br><br>DXM-XR (Focalin XR®) 20 to 40 mg/day | DB, MC, PC, RCT<br><br>Adults 18 to 60 | N=184<br><br>5 weeks | Primary: ADHD-RS<br><br>Secondary: | Primary:<br>All doses of DXM-XR significantly improved ADHD-RS scores from baseline compared to placebo (*P*<0.05). |


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| vs<br><br>placebo | years of age diagnosed with ADHD (any subtype), childhood onset of symptoms, and a baseline ADHD-RS score ≥24 | | ADHD-RS, CGI-I, CGI-S, CAARS, Q-LES-Q | Secondary:<br>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%.<br><br>All doses DXM-XR significantly improved CGI-I scores over placebo (*P*<0.05 for all).<br><br>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%.<br><br>All doses of DXM-XR significantly improved CAARS scores compared to placebo (*P*<0.05 for all).<br><br>None of the groups improved Q-LES-Q scores from baseline nor were there significant differences between groups. |
| Adler et al[70]<br><br>DXM-XR (Focalin XR®) 20 to 40 mg/day<br><br>vs<br><br>placebo<br><br>After completion of DB phase, patients could enter an OL extension phase with flexible dosing 20 to 40 mg/day for six months. | DB, MC, RCT<br><br>Patients 18 to 60 years of age diagnosed with ADHD | N=103<br><br>6 months | Primary:<br>Long-term safety and tolerability<br><br>Secondary:<br>ADHD-RS, CGI-I | Primary:<br>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.<br><br>Secondary:<br>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.<br><br>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. |


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| Brams et al[71]<br><br>DXM-XR 20 mg/day<br><br>vs<br><br>DXM-XR 30 mg/day<br><br>vs<br><br>placebo | DB, RCT, XO<br><br>Children 6 to 12 years of age with ADHD previously stabilized on MPH (40 mg to 60 mg/day) or DXM (20 mg to 30 mg/day) | N=165<br><br>3 weeks | Primary:<br>Change in average SKAMP-combined score from pre-dose to 10, 11 and 12 hours post-dose<br><br>Secondary:<br>Not reported | Primary:<br>The mean change from pre-dose in SKAMP-combined score was significantly greater in the DXM-XR 30 mg group compared to the DXM-XR 20 mg group (-4.47 vs -2.02; P=0.002). Significantly greater improvement in ADHD symptoms was observed in the DXM-XR 30 mg group compared to the DXM-XR 20 mg group at hours 10 through 12.<br><br>Secondary:<br>Not reported |
| Stein et al[72]<br><br>DXM-XR (Focalin XR®) 10 to 30 mg/day<br><br>vs<br><br>AMP-XR (Adderall XR®) 10 to 30 mg/day | DB, PC, RCT<br><br>Patients nine to 17 years of age with ADHD | N=56<br><br>8 weeks | Primary:<br>ADHD-RS, CGI-I, CGI-S, WFIS, SERS<br><br>Secondary:<br>Not reported | Primary:<br>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.<br><br>There were significant dose-related decreases for Inattention symptoms ($P$<0.001) that were more modest and did not differ by type of stimulant.<br><br>There were significant dose-related decreases in CGI-S scores ($P$<0.001) that did not differ by type of stimulant.<br><br>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.<br><br>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.<br><br>Secondary:<br>Not reported |
| Muniz et al[73]<br><br>DXM-XR (Focalin XR®) | DB, MC, RCT<br><br>Children six to 12 | N=84<br><br>10 weeks | Primary:<br>SKAMP | Primary:<br>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). |


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| 20 mg/day<br><br>vs<br><br>DXM-XR (Focalin XR®) 30 mg/day<br><br>vs<br><br>MPH-ER (Concerta®) 36 mg/day<br><br>vs<br><br>MPH-ER (Concerta®) 54 mg/day<br><br>vs<br><br>placebo | years of age diagnosed with ADHD and stabilized on MPH ≥2 weeks | | Secondary:<br>Not reported | 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.<br><br>All active treatments provided a significant benefit over placebo at most time points to 12 hours post-dosing.<br><br>Secondary:<br>Not reported |
| Scahill et al[74]<br><br>Guanfacine 0.5 mg at bedtime, day four added 0.5 mg in the morning, day eight added 0.5 mg afternoon dose<br><br>vs<br><br>placebo | DB, PC, PG, RCT<br><br>Children seven to 15 years of age diagnosed with ADHD and tic disorder | N=34<br><br>8 weeks | Primary:<br>ADHD-RS, CGI-I, CPRS-R (hyperactivity index), YGTSS, CPT<br><br>Secondary:<br>Not reported | Primary:<br>Guanfacine was associated with a mean improvement of 37% in the teacher-rated ADHD-RS total score compared to 8% improvement for placebo ($P<0.01$).<br><br>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.<br><br>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.<br><br>Tic severity decreased by 31% in the guanfacine group, compared to 0% in the placebo group ($P=0.05$).<br><br>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% |


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| | | | | in omission errors in the placebo group.<br><br>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.<br><br>Secondary:<br>Not reported |
| Kollins et al[75]<br><br>Guanfacine ER 1 to 3 mg once daily<br><br>vs<br><br>placebo | DB, MC, PC, RCT<br><br>Patients six to 17 years of age diagnosed with ADHD | N=182<br><br>6 weeks | Primary:<br>CANTAB-CRT<br><br>Secondary:<br>CANTAB-SWM, DSST, PERMP | Primary:<br>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).<br><br>Secondary:<br>Guanfacine ER treatment was associated with significant improvement in ADHD symptoms (*P*=0.001)<br><br>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[76]<br><br>Guanfacine ER 1 to 4 mg once daily<br><br>vs<br><br>placebo | DB, MC, PC, RCT<br><br>Patients six to 17 years of age with ADHD and a baseline score of 24 on the ADHD-RS-IV | N=324<br><br>9 weeks | Primary:<br>ADHD-RS-IV total score<br><br>Secondary:<br>CPRS-R, CGI-I, PGA | Primary:<br>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.<br><br>Placebo-adjusted mean baseline-to-endpoint changes for symptoms of inattentiveness were: -4.2 (*P*=0.002), -3.0 *P*=0.02), -3.5 (*P*=0.007), and -4.0 (*P*=0.002) for guanfacine ER 1, 2, 3, and 4 mg, respectively. Placebo-adjusted mean baseline-to-endpoint changes for symptoms of hyperactivity/impulsivity were: -2.7 (*P*=0.028), -2.5 (*P*=0.03), -3.9 (*P*=0.001), and -4.0 (*P*=0.0008) for guanfacine ER 1, 2, 3, and 4 mg, respectively.<br><br>Secondary: |


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| | | | | Using placebo-adjusted LSMD in change from baseline at endpoint in CPRS-R total scores, the 4 mg guanfacine ER dose demonstrated significant efficacy at eight hours (-10.2; *P*=0.004) and 12 hours (-7.5; *P*=0.04). The 3 mg guanfacine ER dosage group demonstrated significant improvements in CPRS-R results at eight (-11.8; *P*=0.002), 12 (-9.6; *P*=0.01), and 14 hours (-9.8; *P*=0.0156) postdose. The 2 mg guanfacine ER dosage group demonstrated significant improvements in CPRS-R scores at eight hours (-9.0; *P*=0.01) postdose. For the 1 mg guanfacine ER dosage group, the placebo-adjusted LSMD in CPRS-R at eight, 12, 14, and 24 hours were -12.8 (*P*=0.0004), -11.4 (*P*=0.002), -10.4 (*P*=0.0077), and -8.9 (*P*=0.02), respectively.<br><br>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).<br><br>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).<br><br>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 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[77]<br><br>Guanfacine ER 1 to 4 mg once daily | ES, OL<br><br>Patients six to 17 years of age with ADHD and a baseline score of 24 on the ADHD- | N=257<br><br>24 months | Primary:<br>ADHD-RS-IV, CPRS-R, CGI-I, CHQ-PF50, CTRS-R, PGA<br><br>Secondary: | Primary:<br>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. |


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| | RS-IV | | Not reported | 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.<br><br>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.<br><br>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).<br><br>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 ($P<0.001$).<br><br>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%).<br><br>For the PGA, 59.7% of patients were rated as very much or much improved at end point.<br><br>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 ($P<0.001$).<br><br>Secondary:<br>Not reported |
| Sallee et al[78]<br><br>Guanfacine ER 1 to 4 mg/day | DB, PC, RCT (Post-hoc analysis)<br><br>Patients 6 to 17 | N=631<br><br>Variable duration | Primary:<br>Change in ADHD-RS total scores | Primary:<br>For patients with the predominantly inattentive subtype of ADHD, patients treated with guanfacine ER achieved significantly greater mean reductions from baseline in ADHD-RS total scores compared to placebo ($P\leq0.020$). For patients with combined-type ADHD, patients treated with guanfacine ER achieved significantly greater |


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| vs<br><br>placebo | years of age with ADHD | | Secondary:<br>Not reported | reductions in ADHD-RS total score from baseline compared to placebo at treatment weeks one through five and at study end ($P \leq 0.011$).<br><br>Secondary:<br>Not reported |
| Connor et al[79]<br><br>Guanfacine ER 1 to 4 mg once daily<br><br>vs<br><br>placebo | DB, MC, PC, RCT<br><br>Patients six to 12 years of age with a diagnosis of ADHD and the presence of oppositional symptoms | N=217<br><br>9 weeks | Primary:<br>Change from baseline to endpoint in the oppositional subscale of the CPRS-R:L<br><br>Secondary:<br>Change in ADHD-RS-IV total score and safety | Primary:<br>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 ($P<0.001$).<br><br>Secondary:<br>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 ($P<0.001$).<br><br>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[80]<br><br>Guanfacine ER 2 to 4 mg once daily<br><br>vs<br><br>placebo | DB, MC, PC, RCT<br><br>Patients six to 17 years of age with ADHD combined subtype, predominantly inattentive subtype, or predominantly hyperactive- | N=345<br><br>8 weeks | Primary:<br>ADHD-RS-IV total score observed during the last treatment week of the dosage escalation period (weeks one to five)<br><br>Secondary: | Primary:<br>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.<br><br>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. |


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| | impulsive subtype | | 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) | Secondary:<br>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).<br><br>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.<br><br>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).<br><br>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.<br><br>The most commonly reported treatment-emergent adverse events were somnolence, fatigue, upper abdominal pain and sedation. The incidence of somnolence in patients who were receiving guanfacine ER 1, 2, 3, and 4 mg doses was 12.7, 11.4, 20.9, and 17.5%, respectively. SBP, DBP, and pulse rate decreased as guanfacine ER dosages increased, then increased as dosages stabilized and tapered down. The greatest mean changes from baseline in SBP and DBP for patients who were receiving guanfacine ER 2, 3, and 4 mg doses were -7.0 mm Hg (week 3) and -3.8 mm Hg (week 2), -7.0 mm Hg (week 3) and -4.7 mm Hg (weeks three and five), and -10.1 mm Hg (week four) and -7.1 mm Hg (week four), respectively. The greatest mean changes from baseline in pulse rate for patients who were receiving guanfacine ER 2, 3, and 4 mg doses were -5.7 beats per minute (week three), -8.1 beats per minute (week three), and -8.0 beats per minute (week four), respectively. Mean changes in height and weight from baseline to end point were not significant across the treatment groups. |
| Biederman et al[81]<br><br>Guanfacine ER 2 to 4 | ES, OL<br><br>Patients six to 17 | N=240<br><br>24 months | Primary:<br>Safety | Primary:<br>Somnolence (30.4%), headache (26.3%), fatigue (14.2%), and sedation (13.3%) were the most frequently reported adverse events. |


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| mg once daily | years of age with ADHD combined subtype, predominantly inattentive subtype, or predominantly hyperactive-impulsive subtype | | Secondary: ADHD-RS-IV, PGA, CHQ-PF50 | 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.<br><br>Hypotension was reported in 2.9% of patients and bradycardia was reported in 2.1% of patients.<br><br>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.<br><br>Secondary:<br>The mean ADHD-RS-IV total score was significantly reduced from baseline to endpoint (-18.1; *P*<0.001 vs baseline).<br><br>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.<br><br>For PGA scores, 58.6% of patients were 'improved' at endpoint compared to baseline of the preceding study.<br><br>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[82]<br><br>Guanfacine ER 1 to 4 mg once daily, added to existing stimulant therapy | MC, OL<br><br>Patients six to 17 years of age with ADHD (combined, predominantly inattentive, or predominantly hyperactive- | N=75<br><br>9 weeks | Primary: ADHD-RS-IV, CPRS-R, CGI-I, CGI-S, CHQ-PF50, and PGA<br><br>Secondary: Not reported | Primary:<br>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.<br><br>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% |


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| | impulsive subtype) and who were on a stable regimen of either MPH or AMP ≥1 month with suboptimal control of ADHD symptoms | | | in the guanfacine ER plus AMP subgroup).<br><br>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.<br><br>At baseline, the mean PDSS score was 15.0. Decreases were observed at visit six (-4.8) and end point (-3.1).<br><br>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.<br><br>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%.<br><br>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).<br><br>The percentage of patients showing improvement at end point on the CGI was 73.0%. On the PGA, 84.1% of patients showed improvement.<br><br>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).<br><br>Secondary:<br>Not reported |


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| Wilens et al[83]<br><br>Guanfacine ER 1 to 4 mg/day in the morning plus placebo at bedtime<br><br>vs<br><br>placebo in the morning and guanfacine ER 1 to 4 mg/day in the afternoon<br><br>vs<br><br>placebo<br><br>Patients continued stable dose of psycho-stimulant given in the morning. | DB, MC, PC, RCT<br><br>Children and adolescents six to 17 years of age diagnosed with ADHD | N=461<br><br>9 weeks | Primary:<br>ADHD-RS<br><br>Secondary:<br>CGI-S, CGI-I | Primary:<br>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).<br><br>Secondary:<br>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).<br><br>At study endpoint, small mean decreases in pulse, SBD, and DBP were observed in guanfacine ER treatment groups compared to placebo plus psychostimulant group.<br><br>The most common treatment-emergent adverse events were mild to moderate in severity and included headache, somnolence and upper respiratory infections. |
| Faraone et al[84]<br><br>Guanfacine ER 1 to 4 mg once daily | MA<br><br>Patients six to 17 years of age with ADHD (combined subtype, predominantly inattentive subtype, or predominantly hyperactive-impulsive subtype) | N=813<br><br>6 to 9 weeks | Primary:<br>Predictors of efficacy and sedation using various models<br><br>Secondary:<br>Not reported | Primary:<br>*Actual Dose Model*<br>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).<br><br>The only significant influence on the frequency of sedation-related adverse events was treatment duration (*P*=0.034).<br><br>*mg/kg Dose Model:*<br>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). |


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| | | | | Treatment duration (*P*<0.001) and baseline total ADHD-RS symptom scores (*P*<0.001) were predictors of weekly total ADHD-RS symptom scores.<br><br>The only significant influence on the frequency of sedation-related adverse events was treatment duration (*P*=0.034).<br><br>*Titration Rate Dose Model:*<br>The presence or absence of ADHD symptoms was significantly influenced by the titrated dose of medication received by the participant (*P*=0.005).<br><br>The number of symptoms was significantly influenced by treatment duration (*P*<0.001) and baseline total ADHD-RS scores (*P*<0.001).<br><br>The only significant influence on the frequency of sedation-related adverse events was treatment duration (*P*=0.034).<br><br>Secondary:<br>Not reported |
| Adler et al[85]<br><br>LDX 30 to 70 mg/day<br><br>vs<br><br>placebo | DB, PC, RCT<br><br>Adults 18 to 55 years of age with a primary diagnosis of ADHD and executive function deficits (assessed by baseline BRIEF-A GEC T-scores ≥65) | N=161<br><br>10 weeks | Primary:<br>BRIEF-A scales (GEC, index and clinical subscales)<br><br>Secondary:<br>Not reported | Primary:<br>At week 10 or early termination, treatment with LDX was associated with significantly greater reductions from baseline in mean BRIEF-A GEC T-scores compared to placebo (*P*<0.0001) and significantly greater reductions from baseline in mean T-scores for both BRIEF-A index scales (metacognition scale) and all nine clinical subscales (*P*≤0.0056 for all). At week 10 or early termination, patients treated with LDX had mean T-scores for BRIEF-A indices and clinical subscales that were below levels of clinically significant deficits in executive function. The mean GEC T-scores were 57.2 and 68.3 for the LDX and placebo groups, respectively.<br><br>Secondary:<br>Not reported |
| Babcock et al[86]<br><br>LDX 30 to 70 mg/day | DB, MC, RCT (Post-hoc analysis) | N=36<br><br>4 weeks | Primary:<br>Mean change in ADHD-RS score from baseline | Primary:<br>At study end, the change from baseline in mean ADHD-RS scores for LDX -treated patients was similar in the AMP group and the overall study group. The prior AMP non-responders in the placebo group had a change from baseline in ADHD-RS total |


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| vs<br><br>placebo | Adults with ADHD who remained symptomatic on AMP therapy prior to enrollment in a four-week trial | | Secondary:<br>Change in CGI-S, CGI-I | score of -13.5. In the overall efficacy population, the placebo group experienced a change from baseline of -7.8.<br><br>Secondary:<br>Mean CGI scores were similar between the prior AMP subgroup and overall efficacy population in the LDX groups. In addition, the percentage of clinical responders and symptomatic remitters was comparable at all time points assessed in both LDX groups. |
| Biederman et al[87]<br><br>LDX 30 to 70 mg/day<br><br>vs<br><br>placebo | DB, MC, PC, RCT<br><br>Children six to 12 years of age diagnosed with ADHD and with an ADHD-RS score ≥28 | N=209<br><br>4 weeks | Primary:<br>ADHD-RS<br><br>Secondary:<br>CPRS-R, CGI-S, CGI-I | Primary:<br>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).<br><br>Secondary:<br>Each LDX group significantly improved CPRS-R scores throughout the day compared to the placebo group (*P*<0.01 for all).<br><br>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).<br><br>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[88]<br><br>LDX 30 to 70 mg/day<br><br>vs<br><br>placebo<br><br>AMP-XR 10 to 30 mg was used as a control arm. | DB, MC, PC, RCT, XO<br><br>Children six to 12 years of age diagnosed with ADHD | N=52<br><br>12 weeks | Primary:<br>SKAMP scale<br><br>Secondary:<br>PERMP, CGI-I | Primary:<br>SKAMP scores significantly improved in both the LDX and AMP-XR groups compared to the placebo group (*P*<0.0001 for both).<br><br>Secondary:<br>PERMP scores for both the LDX and AMP-XR groups significantly decreased compared to the placebo group (*P*<0.0001 for both).<br><br>The CGI-I scores significantly improved in the both LDX and AMP-XR groups compared to the placebo group (*P*<0.0001). |


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| Brams et al[89]<br><br>LDX 30 to 70 mg/day<br><br>vs<br><br>placebo | DB, RCT<br>Withdrawal study<br><br>Adults 18 to 55 years of age with baseline ADHD-RS with adult prompt total scores <22 and CGI-S ratings of 1, 2 or 3 | N=116<br><br>6 weeks | Primary:<br>Proportion of patients with symptom relapse (≥50% increase in ADHD-RS score and ≥2 rating-point increase in CGI-S score)<br><br>Secondary:<br>Not reported | Primary:<br>At study end, 8.9% of patients in the LDX group and 75.0% of patients in the placebo group experienced symptom relapse (*P*<0.0001), with most patients showing relapse after one and two weeks of the randomized withdrawal period.<br><br>Secondary:<br>Not reported |
| Coghill et al[90]<br><br>LDX 30 to 70 mg/day<br><br>vs<br><br>MPH-ER (Concerta®) 18 to 54 mg/day<br><br>vs<br><br>placebo | DB, MC, PC, PG, RCT<br><br>Children and adolescents six to 17 years of age diagnosed with ADHD | N=336<br><br>7 weeks | Primary:<br>ADHD-RS<br><br>Secondary:<br>CGI-I | Primary:<br>The LS mean change from baseline in ADHD-RS total score was significantly greater for patients treated with LDX (-24.3±1.2) and MPH-ER (-18.7±1.1) compared to placebo (-5.7±1.1; *P*<0.001 for both).<br><br>The LS mean change from baseline in ADHD-RS total score was significantly greater with LDX or MPH-ER compared to placebo at every time point evaluated (*P*<0.001 for all visits). Effect sizes based on the difference in LS mean change in ADHD-RS total score from baseline to endpoint were 1.80 and 1.26 for LDX and MPH-ER, respectively.<br><br>The decreases in both the ADHD-RS hyperactivity/impulsivity and inattention subscale scores from baseline were also significantly greater for patients treated with LDX or MPH-ER compared to placebo. The LS mean change from baseline to endpoint in hyperactivity/impulsivity was significantly greater with LDX compared to placebo (-8.7; 95% CI -10.3 to -7.2; *P*<0.001) as was the change in inattention score (-9.9; 95% CI, -11.5 to -8.3; *P*<0.001). The LS mean change from baseline to endpoint significantly favored MPH-ER compared to placebo for hyperactivity/impulsivity (-6.0; 95% CI, -7.5 to -4.5; *P*<0.001) and inattention (-7.0; 95% CI, -8.6 to -5.4; *P*<0.001) scores.<br><br>Secondary:<br>The proportions of patients with a CGI-I rating of 'very much improved' or 'much |


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| | | | | improved' after seven weeks of treatment were 78 and 61% for patients treated with LDX or MPH-ER, respectively, compared to 14% of patients treated with placebo (*P*<0.001 for both). |
| Findling et al[91]<br><br>LDX 30 to 70 mg/day<br><br>vs<br><br>placebo | DB, PC, RCT<br><br>Adolescents 13 to 17 years of age diagnosed with ADHD | N=314<br><br>4 weeks | Primary:<br>ADHD-RS<br><br>Secondary:<br>CGI-I, YQOL-R, treatment-emergent adverse events | Primary:<br>Differences in ADHD-RS total scores favored all LDX doses compared to placebo at all weeks (*P*<0.0076).<br><br>Secondary:<br>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).<br><br>YQOL-R scores at the end of the study indicated improvement with LDX treatment, but did not result in significant differences compared to placebo.<br><br>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[92]<br><br>LDX 30 to 70 mg/day | MC, OL, SA<br><br>Children six to 12 years of age diagnosed with ADHD | N=274<br><br>12 months | Primary:<br>ADHD-RS<br><br>Secondary:<br>CGI-S | Primary:<br>Mean ADHD-RS total score improved by 27.2 points (*P*<0.001).<br><br>Mean ADHD-RS inattentive subscale score improved by 13.4 points (*P*<0.001).<br><br>Mean ADHD-RS hyperactivity score improved by 13.8 points (*P*<0.001).<br><br>After improvements during the first four weeks, improvements in ADHD-RS scores were maintained throughout eleven months of treatment.<br><br>Secondary:<br>Improvement in scale scores seen in >80% of study patients at endpoint and >95% of completers at 12 months were rated as improved.<br><br>Adverse event included insomnia and vomiting and considered mild or moderate by the study investigator. There were no clinical meaningful changes in BP or |


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| | | | | electrocardiographic parameters. |
| Jain et al[93]<br><br>LDX 20 to 70 mg/day<br><br>vs<br><br>placebo | OL, PC, RCT, SA, XO (Post-hoc analysis)<br><br>Children 6 to 12 years of age with ADHD and baseline ADHD-RS IV total score ≥28 who had received MPH within six months of study enrollment | N=150<br><br>Variable duration | Primary:<br>*Study 1*<br>Change in ADHD-RS total score from baseline<br>*Study 2*<br>Mean SKAMP-D subscore over the course of a laboratory school day<br><br>Secondary:<br>*Study 1*<br>CGI-S, EESC, BRIEF-Parent form<br>*Study 2*<br>SKAMP-A, PERMP math scores, ADHD-RS and CGI scores | *Study 1*<br>Primary:<br>Of patients treated with LDX, the mean change from baseline in ADHD-RS total score was similar for the overall study population and the prior MPH group, with a 64.9% improvement observed in the prior MPH group.<br><br>Secondary:<br>Of patients treated with LDX, the mean change in BRIEF scores from baseline were similar for the overall study population and the prior MPH group. The mean change in CGI-I scores, EESC total scores and the BRIEF index subscale scores from baseline were similar between the overall study population and the prior MPH group. In addition, the BRIEF index subscale scores were normalized at endpoint. The rates of symptomatic remission were similar between the overall study population and the prior MPH group; however, the prior MPH group had numerically lower remission rates compared to the overall group. A clinical response was achieved in 89.6% and 86.7% of the overall population and the prior MPH group, respectively.<br><br>*Study 2*<br>Primary:<br>Improvements in SKAMP-D subscores were similar for both the overall study population and the prior MPH group. For both groups, SKAMP-D scores were improved at all post-dose time points from 1.5 hours to 13 hours with LDX vs placebo ($P \leq 0.0046$ and $P \leq 0.0284$ for all time points in the overall study population and prior MPH group, respectively).<br><br>Secondary:<br>Improvements in SKAMP-A scores were similar in the overall study population and prior MPH group from 1.5 hours to 13 hours post-dose with LDX vs placebo ($P<0.0001$ and $P \leq 0.0114$ for all time points in the overall study population and prior MPH group, respectively). The PERMP-A and PERMP-C scores were improved to a similar degree in both the overall study population and the prior MPH group at all post-dose time points from 1.5 to 13.0 hours with LDX vs placebo ($P<0.0001$ for all time points in the overall study population and prior MPH group, respectively, for both PERMP-A and PERMP-C). |


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| | | | | The change from baseline in mean ADHD-RS total scores for the overall study population and the prior MPH groups were similar when taking LDX and placebo during the XO phase (57.1 and 18.1% for patients who had previously received MPH in the LDX group and the placebo group, respectively). At visit five during the XO period, mean CGI-I scores were 1.7 and 3.5 for patients taking LDX and placebo, respectively, for the overall study population and 1.7 and 3.7, respectively, for the prior MPH group who had received ≥1 mg/kg/day of MPH. |
| Weisler et al[94]<br><br>LDX 30 to 70 mg/day | DB, PC, RCT, SA<br><br>Adults aged 18 to 55 years of age diagnosed with ADHD | N=349<br><br>12 months | Primary:<br>ADHD-RS<br><br>Secondary:<br>CGI-S, CGI-I | Primary:<br>Mean ADHD-RS total scores improved at week one of treatment and sustained throughout the eleven month treatment period (*P*<0.001).<br><br>Mean ADHD-RS total scores improved by 24.8 points from baseline to study endpoint (*P*<0.001).<br><br>Secondary:<br>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.<br><br>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.<br><br>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[95]<br><br>LDX 30 to 70 mg/day | Post-hoc analysis of Weisler et al[82]<br><br>Adults aged 18 to 55 years of age diagnosed with ADHD who had completed ≥2 weeks of | N=345<br><br>12 months | Primary:<br>ADHD-RS-IV<br><br>Secondary:<br>Not reported | Primary:<br>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.<br><br>At trial end, 285/345 patients were classified as clinical responders (ADHD-RS-IV |


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| | treatment with LDX | | | total score decrease of ≥30% from baseline and CGI-I score of one or two). Of the 93 patients with predominantly inattention symptom cluster at baseline, 74 were classified as clinical responders at trial end. All 13 patients who had predominantly hyperactivity/impulsivity symptom cluster at baseline were classified as clinical responders at endpoint. At endpoint, 236 of patients who had combined type ADHD at baseline, 196 were classified as clinical responders.<br><br>Secondary:<br>Not reported |
| Wigal et al[96]<br><br>MPH-ER (Concerta®) 18 to 54 mg/day<br><br>vs<br><br>placebo | DB, PC, RCT<br><br>Children nine to 12 years of age diagnosed with ADHD | N=78<br><br>5 months | Primary:<br>PERMP, SKAMP, TOVA, Finger Windows forward and backward subtest<br><br>Secondary:<br>Not reported | Primary:<br>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).<br><br>MPH-ER significantly improved performance on inattention, deportment, and total ratings of the SKAMP measure (*P*<0.001) as compared to placebo.<br><br>Children taking MPH-ER had statistically significantly better scores than children taking placebo on response time (*P*<0.000).<br><br>MPH-ER significantly improved performance on memory as compared to placebo.<br><br>Most common adverse effects included decreased appetite, upper abdominal pain, headache and irritability. Most adverse events were considered mild or moderate by the study investigator.<br><br>Secondary:<br>Not reported |
| Casas et al[97]<br><br>MPH-ER (Concerta®) 54 to 72 mg/day<br><br>vs | DB, MC, PC, RCT<br><br>Men and women 18 to 65 years of age diagnosed with ADHD | N=279<br><br>13 weeks | Primary:<br>CAARS-Inv: SV<br><br>Secondary:<br>CGI-S, CGI-C, CAARS-Self: SV, SDS, AIMA- | Primary:<br>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.<br><br>Secondary:<br>Mean improvement in CGI-S score was significantly greater with MPH-ER 72 mg |


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| placebo | | | A | than placebo (*P*<0.001); however, there was no significant difference with MPH-ER 54 mg compared to placebo.<br><br>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.<br><br>CAARS-Self:SV scores decreased significantly compared to placebo in both MPH-ER treatment groups (*P*<0.05).<br><br>There was no significant change in SDS score from baseline in either treatment group.<br><br>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.<br><br>The most common adverse events with MPH-ER were mild to moderate in severity and included headache, decreased appetite, dry mouth and nausea. |
| Wigal et al[98]<br><br>MPH-ER suspension (Quillivant XR®)<br>20 to 60 mg/day<br><br>vs<br><br>placebo | DB, MC, PC, RCT, XO<br><br>Children six to 12 years of age diagnosed with ADHD | N=45<br><br>2 weeks | Primary:<br>SKAMP combined score<br><br>Secondary:<br>Onset of action and duration of clinical effect, subscale scores for SKAMP, PERMP, CGI-S and CGI-I | Primary:<br>Children treated with MPH-ER suspension experienced a statistically significant improvement in SKAMP combined score at four hours post-dose compared to children treated with placebo. The LS mean SKAMP combined score was 7.12 in children receiving MPH-ER suspension compared to 19.58 in children receiving placebo (LS mean difference, -12.46; *P*<0.0001).<br><br>Secondary:<br>There were statistically significant improvements from baseline with MPH-ER suspension compared to placebo at each time point tested (45 minutes, two, four, eight, 10 and 12 hours), with the onset of action at 45 minutes post-dose and a duration of effect continuing to be significant compared to placebo at 12 hours post-dose.<br><br>The results of the remaining secondary endpoints were not presented in this study. |


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| Wilens et al[99]<br><br>MPH-ER (Concerta®)<br>18 to 54 mg/day | MC, OS, PRO<br><br>Children six to 13 years of age diagnosed with ADHD | N=432<br><br>1 year | Primary:<br>HR and BP after one year<br><br>Secondary:<br>Not reported | Primary:<br>Compared to baseline, MPH-ER was associated with minor clinical, although statistically significant, DBP elevations (1.5 mm Hg; *P*<0.001), SBP elevations (3.3 mm Hg; *P*<0.001) and HR (3.9 beats per minute; *P*<0.0001) at the 12-month end point.<br><br>Secondary:<br>Not reported |
| Mattos et al[100]<br><br>MPH-ER (Concerta®)<br>18 to 72 mg/day | MC, OL<br><br>Men and women 18 to 65 years of age diagnosed with ADHD | N=60<br><br>12 weeks | Primary:<br>ASRS, AAQoL, STAI, HAMD, CGI-I<br><br>Secondary:<br>Not reported | Primary:<br>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).<br><br>AAQoL subscales (*P*<0.001), as well as AAQoL total score (*P*<0.001), significantly improved from baseline to week 12.<br><br>A significant reduction in STAI, CGI-I, and HAMD, scores were observed (*P*<0.0001).<br><br>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.<br><br>Secondary:<br>Not reported |
| Cox et al[101]<br><br>MPH-ER (Concerta®)<br>36 mg once daily on days one to five, followed by 72 mg once daily on days six to 17<br><br>vs | DB, PC, RCT, XO<br><br>Adolescents 16 to 19 years of age diagnosed with ADHD and licensed to drive | N=35<br><br>21 to 38 days | Primary:<br>IDS, assessed using an Atari Research Driving Simulator on days 10 and 17; subjective ratings of driving performance by | Primary:<br>Overall IDS values were significantly better than with placebo with MPH-ER (*P*<0.001), but not with AMP-ER (*P*=0.24).<br><br>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).<br><br>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 |


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| AMP-XR (Adderall XR®) 15 mg once daily on days one to five, followed by 30 mg once daily on days six to 17<br><br>vs<br><br>placebo | | | participants and investigators<br><br>Secondary:<br>Not reported | category of inappropriate braking (*P*=0.04).<br><br>Subjective ratings of driving performance by participants and investigators rated MPH-ER as better for driving performance (*P*=0.008).<br><br>Secondary:<br>Not reported |
| Yang et al[102]<br><br>MPH-ER 18 to 54 mg/day<br><br>vs<br><br>atomoxetine 0.5 to 1.4 mg/kg/day | RCT, SB<br><br>Children and adolescents seven to 14 years of age diagnosed with ADHD | N=142<br><br>4 to 6 weeks | Primary:<br>RCFT, Digit span, Stroop color word test<br><br>Secondary:<br>Not reported | Primary:<br>Both MPH-ER and atomoxetine significantly improved visual memory, verbal memory, and word inference time.<br><br>Visual and verbal memory was not significantly different from the control group at post-treatment assessment (*P*>0.05).<br><br>Although word interference time was more improved than the control group, there was no statistically significant difference (*P*>0.05).<br><br>Secondary:<br>Not reported |
| Wolraich et al[103]<br><br>MPH-ER (Concerta®) 18 to 54 mg/day<br><br>vs<br><br>MPH-IR 5 to 15 mg TID<br><br>vs<br><br>placebo | DB, PC, PG, RCT<br><br>Children six to 12 years of age diagnosed with ADHD (any subtype) | N=282<br><br>28 days | Primary:<br>Iowa Conners I/O and O/D rating scale (parents and teachers)<br><br>Secondary:<br>SNAP-IV scores (teachers and parents), CGI-I scores (investigators), global | Primary:<br>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).<br><br>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).<br><br>Secondary:<br>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).<br><br>There was not a significant difference in SNAP-IV scores between the MPH-ER and |


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| | | | assessment of efficacy (parents and teachers) | MPH-IR groups.<br><br>CGI-I scores significantly improved in the MPH-ER and MPH-IR groups compared to the placebo group (*P*<0.001).<br><br>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[104]<br><br>MPH-ER (Concerta®) 18 to 54 mg/day<br><br>vs<br><br>MPH-IR 5 to 15 mg TID<br><br>vs<br><br>placebo | DB, PC, RCT, XO<br><br>Children six to 12 years of age diagnosed with ADHD (any subtype) who were taking MPH prior to study entry | N=68<br><br>1 week | Primary:<br>Iowa Conners I/O and O/D rating scales (teacher and parents), SKAMP scale (teacher)<br><br>Secondary:<br>Not reported | Primary:<br>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).<br><br>MPH-ER scored significantly better than MPH-IR in the parent Iowa Conners I/O rating scales (*P*<0.05).<br><br>In the SKAMP scales, MPH-ER and MPH-IR were similar in efficacy, but both were significantly better than placebo.<br><br>Secondary:<br>Not reported |
| Gau et al[105]<br><br>MPH-ER (Concerta®) 18 to 36 mg/day<br><br>vs<br><br>MPH-IR 5 to 10 mg TID | OL, RCT<br><br>Children six to 15 years of age diagnosed with ADHD (any subtype) who were taking MPH (10 to 40 mg/day) | N=64<br><br>28 days | Primary:<br>CTRS-RS, CPRS-RS, SKAMP-A, SKAMP-D<br><br>Secondary:<br>SAICA, CGI | Primary:<br>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).<br><br>Secondary:<br>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).<br><br>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).<br><br>The MPH-XR group had a significantly greater number of patients being very much |


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| | | | | or much improved (84.4%) than the MPH-IR group (56.3%) (*P*=0.014) based on the CGI score. |
| Lopez et al[106]<br><br>MPH-ER (Concerta®) 18 to 36 mg/day<br><br>vs<br><br>MPH-XR (Ritalin LA®) 20 mg/day<br><br>vs<br><br>placebo | DB, PC, RCT<br><br>Children six to 12 years of age diagnosed with ADHD who were previously stabilize on MPH (equivalent dose of 10 mg BID) | N=36<br><br>28 days | Primary:<br>SKAMP scales<br><br>Secondary:<br>Not reported | Primary:<br>Both MPH-ER and MPH-XR statistically improved SKAMP scale scores compared to placebo (*P*<0.001).<br><br>Secondary:<br>Not reported |
| Swanson et al[107]<br><br>MPH-ER (Concerta®) 18 to 54 mg/day<br><br>vs<br><br>MPH-XR (Metadate CD®) 20 to 60 mg/day<br><br>vs<br><br>placebo | DB, MC, PC, RCT, XO<br><br>Children six to 12 years of age diagnosed with ADHD (inattentive type, hyperactive-impulsive type, or combined type) being treated with MPH in doses of 10 to 60 mg/day | N=184<br><br>7 weeks | Primary:<br>SKAMP scales, PERMP<br><br>Secondary:<br>Not reported | Primary:<br>MPH-ER and MPH-XR demonstrated similar efficacy, and both were better than placebo in SKAMP and PERMP scores (*P*<0.016).<br><br>Secondary:<br>Not reported |
| Silva et al[108]<br><br>MPH-ER (Concerta®) 18 mg | MC, RCT, SB, XO<br><br>Children six to 12 years of age | N=54<br><br>6 weeks | Primary:<br>SKAMP-A rating subscale<br><br>Secondary: | Primary:<br>All doses of the study medications significantly improved SKAMP-A scores from baseline at all time points, compared to placebo (*P*<0.038).<br><br>ER-MPH 20 and 40 mg showed significantly greater differences from predose on the |


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| vs<br><br>MPH-ER (Concerta®) 36 mg<br><br>vs<br><br>MPH-ER (ER-MPH) 20 mg<br><br>vs<br><br>MPH-ER 40 mg<br><br>vs<br><br>placebo<br><br>All medications were dosed once per study day (6 consecutive Saturdays).<br><br>Patients continued their regular ADHD medications on Sunday through Thursday of the study weeks, with no medications allowed on Friday. | diagnosed with ADHD and stabilized on MPH (20 to 40 mg/day) | | SKAMP-D and SKAMP-C rating subscales and written math tests | 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.<br><br>Secondary:<br>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[109]<br><br>MPH-IR 0.125 mg/kg/ dose BID for one week (low dose) | DB, RCT, XO<br><br>Children five to 13 years of age with PDD and hyperactivity | N=33<br><br>4 weeks | Primary:<br>JAMES, Caregiver-Child Interaction measure (competing | Primary:<br>Significant positive effect of MPH was seen on social communication (*P*<0.05); comparing each of the three MPH doses of MPH compared to placebo, the low dose showed significant improvement compared to placebo (*P*<0.05); no significant differences found between placebo and the medium or high doses. |


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| vs<br><br>MPH-IR 0.25 mg/kg/ dose BID for one week (medium dose)<br><br>vs<br><br>MPH-IR 0.50 mg/kg/ dose BID for one week (high dose)<br><br>vs<br><br>placebo for one week | | | demands and clean-up task) captured social communication, self-regulation and affective behavior<br><br>Secondary:<br>Not reported | 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.<br><br>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).<br><br>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).<br><br>No significant improvement on affective behavior for the clean-up task and any MPH dose (*P*>0.05).<br><br>Secondary:<br>Not reported |
| Spencer et al[110]<br><br>MPH-IR TID<br><br>vs<br><br>MPH-ER once daily (Concerta®) | PG, RCT, SB<br><br>Patients 19 to 60 years of age diagnosed with ADHD who were on stable therapy with MPH-IR | N=61<br><br>6 weeks | Primary:<br>AISRS<br><br>Secondary:<br>Not reported | Primary:<br>MPH-IR responders randomized to MPH-IR or MPH-ER had no effect on AISRS score at the study endpoint (11.2 vs 10.7; *P*=0.80).<br><br>Study patients stabilized on MPH-IR and switched to MPH-ER remained satisfied over 71% of the time.<br><br>MPH-IR treatment group missed significantly more doses than the MPH-ER treatment group (7.3 vs 3.3; *P*=0.02).<br><br>Secondary:<br>Not reported |
| Efron et al[111]<br><br>MPH-IR 0.3 mg/kg/ | DB, RCT, XO<br><br>Children five to | N=125<br><br>4 weeks | Primary:<br>SERS | Primary:<br>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 |


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| dose BID<br><br>vs<br><br>DEX-IR 0.15 mg/kg/ dose BID<br><br>Patients received one drug for two weeks then XO to the other stimulant for two weeks. | 15 years of age diagnosed with ADHD | | Secondary:<br>Not reported | of the SERS questionnaire which assess the 17 most common side effects of stimulants including trouble sleeping, decreased appetite and anxiousness.<br><br>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).<br><br>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).<br><br>Secondary:<br>Not reported |
| Pelham et al[112]<br><br>MPH-IR 10 mg BID<br><br>vs<br><br>MPH-SR (Ritalin SR®) 20 mg/day<br><br>vs<br><br>DEX-SR (Dexedrine®) 10 mg/day<br><br>vs<br><br>pemoline 56.25 mg/day<br><br>vs<br><br>placebo | DB, PC, RCT, XO<br><br>Males eight to 13 years of age diagnosed with ADHD | N=22<br><br>8 weeks | Primary:<br>Evaluated social behavior during activities, classroom performance, and performance on a continuous performance task<br><br>Secondary:<br>Not reported | Primary:<br>Each of the active treatment groups were more effective than placebo on most measures of social behavior from the medication assessment (*P*<0.05).<br><br>DEX-SR and pemoline tended to produce the most consistent effects.<br><br>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).<br><br>Secondary:<br>Not reported |


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| Palumbo et al[113]<br><br>MPH-IR 5 to 60 mg/day<br><br>vs<br><br>clonidine 0.05 to 0.6 mg/day<br><br>vs<br><br>MPH-IR plus clonidine<br><br>vs<br><br>placebo | DB, MC, PC, RCT<br><br>Children seven to 12 years of age diagnosed with ADHD | N=122<br><br>16 weeks | Primary:<br>CASQ-T<br><br>Secondary:<br>CASQ-P, CGAS | Primary:<br>For CASQ-T, clonidine did not improve ADHD symptoms. Study patients treated with MPH showed significant improvement compared to those not treated with MPH.<br><br>Secondary:<br>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[114]<br><br>MPH-XR (Metadate CD®) 20 to 60 mg/day<br><br>vs<br><br>placebo | DB, MC, PC, RCT<br><br>Children six to 16 years of age diagnosed with ADHD | N=321<br><br>3 weeks | Primary:<br>CGI-S (teacher)<br><br>Secondary:<br>CGI-S (parents), CGI-I scores, adverse events | Primary:<br>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).<br><br>Secondary:<br>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).<br><br>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).<br><br>In the MPH-XR group, 52% of children reported at least one adverse event vs 38% from the placebo group (*P*=0.014). The rate of anorexia was more significant in the MPH-XR group vs the placebo group (9.7 vs 2.5%; *P*=0.007). |
| McGough et al[115]<br><br>MPH transdermal patch 10 to 27 mg/day | OL, RCT (first five weeks) then DB, PC | N=80<br><br>7 weeks | Primary:<br>Evaluate time course effects of MPH | Primary:<br>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). |


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| vs<br><br>placebo | Children six to 12 years of age diagnosed with ADHD | | transdermal patch vs placebo transdermal patch via SKAMP-A, SKAMP-D, PERMP, ADHD-RS-IV, CPRS-R, CGI-I, and PGA rating scales<br><br>Secondary: Acute efficacy and tolerability of MPH transdermal patch | 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).<br><br>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).<br><br>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).<br><br>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).<br><br>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).<br><br>Secondary:<br>More treatment-emergent adverse events were recorded with MPH transdermal patch therapy (39 events, 24 participants) vs placebo therapy (25 events, 18 participants).<br><br>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[116]<br><br>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 | DB, DR, MC, RCT<br><br>Children seven to 12 years of age diagnosed with ADHD | N=36<br><br>8 days | Primary: MPH transdermal patch efficacy and influence of exposure time on morning effects | Primary:<br>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).<br><br>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). |


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| 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 or 7 AM). | | | Secondary:<br>Not reported | Incidence of skin rash was reported as 40 to 50%.<br><br>Secondary:<br>Not reported |
| Pelham et al[117]<br><br>MPH transdermal patch: 12.5 $cm^2$, 25 $cm^2$, and 37.5 $cm^2$ plus behavior modification<br><br>Each participant had two days on each treatment without concomitant behavior modification and four days on each treatment with behavior modification. | DR, RCT<br><br>Children aged six to 12 years diagnosed with ADHD | N=27<br><br>6 weeks | Primary:<br>Proportion that reached individual target goals in Daily Report Card scores<br><br>Secondary:<br>Not reported | Primary:<br>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).<br><br>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.<br><br>Secondary:<br>Not reported |
| Faraone et al[118]<br><br>MPH transdermal patch 10 to 30 mg/day worn for nine hours per day<br><br>or<br><br>MPH-ER (Concerta®) 18 to 54 mg/day | DB, MC, PC, RCT<br><br>Children six to 12 years of age diagnosed with ADHD (predominantly hyperactive-impulsive, | N=268<br><br>5 weeks | Primary:<br>CSHQ<br><br>Secondary:<br>Not reported | Primary:<br>No significant difference in the severity of sleep problems was observed among the treatment and placebo groups ($P$≥0.233).<br><br>No significant differences in the numbers of sleep problems were observed between MPH transdermal patch/MPH-ER and placebo ($P$≥0.554).<br><br>There was no significant effect of MPH dosage on sleep problems ($P$=0.135).<br><br>The effects of each MPH treatment and the various doses of these treatments on |


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| vs<br><br>placebo | predominantly inattentive, or combined type) | | | each CSHQ subscale were identical to the effects observed for the total CSHQ scale.<br><br>Secondary:<br>Not reported |
| Findling et al[119]<br><br>MPH transdermal patch 10 to 30 mg/day<br><br>or<br><br>MPH-ER (Concerta®) 18 to 54 mg/day<br><br>vs<br><br>placebo | DB, PC, RCT<br><br>Children six to 12 years of age diagnosed with ADHD | N=282<br><br>7 weeks | Primary:<br>ADHD-RS<br><br>Secondary:<br>CTRS-R, CPRS-R, CGI-S, CGI-I | Primary:<br>Mean total ADHD-RS scores were similar between MPH transdermal patch, MPH-ER, and placebo at baseline (43.0, 43.8, and 41.9, respectively), but not at endpoint (18.8, 21.8, and 32.1, respectively). Mean change from baseline in ADHD-RS scores was greater in study patients receiving MPH transdermal patch and MPH-ER compared to patients receiving placebo (*P*<0.001).<br><br>There was a two-fold improvement of ADHD symptoms in active treatments compared to placebo from baseline to study endpoint.<br><br>Secondary:<br>MPH transdermal patch and MPH-ER showed improvements over placebo in mean total parent and teacher scores from baseline to endpoint.<br><br>More study patients receiving MPH transdermal patch and MPH-ER compared to placebo were rated as improved by clinicians and parents (*P*<0.001).<br><br>Adverse events included decreased appetite, nausea, vomiting and insomnia. Most adverse events were considered mild or moderate by the study investigator. |
| Chou et al[120]<br><br>MPH-ER (Concerta®) 18, 36, or 54 mg once daily | OS<br><br>Children six to 19 years of age with ADHD who have received MPH-IR for ≥1 month | N=521<br><br>10 weeks (six weeks forced-titration phase to achieve remission, followed by a four week | Primary:<br>Symptomatic remission<br><br>Secondary:<br>Changes in efficacy and satisfaction, safety | Primary:<br>Using the forced-titration of MPH-ER dosage to increase the dosage during the first six weeks, the remission rate significantly increased with time from 4.8% (at baseline), 25% (week two), 44.2% (week four), 58.8% (week six), up to 59.6% (week 10) among 507 ITT patients. Among 439 patients who completed the 10 week follow-up assessments, 290 (66.1%) patients achieved symptomatic remission (95% CI, 61.6 to 70.5). The non-remission group had higher mean daily doses compared to the remission group from visit two to trial end.<br><br>Secondary:<br>Among the 439 patients who completed the treatment, there was a significant |


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| | | main-tenance phase) | | 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.<br><br>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.<br><br>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).<br><br>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. |
| Faraone et al[121]<br><br>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)<br><br>Patients diagnosed with ADHD | N=2,988<br><br>Variable duration | Primary:<br>Effect sizes<br><br>Secondary:<br>Not reported | Primary:<br>All of the drugs groups produced a significant measure of effect compared to the placebo group (*P*<0.0001).<br><br>The effect sizes for non stimulant medications were significantly less than those for immediate-release stimulants (*P*<0.0001) or long-acting stimulants (*P*=0.0008).<br><br>The two classes of stimulant medications (short acting and long acting) did not differ significantly from one another (*P*=0.14).<br><br>Secondary:<br>Not reported |
| Schelleman et al[122]<br><br>ADHD medications<br><br>vs | RETRO<br><br>Children three to 17 years of age who were dispensed a | N=241,417<br><br>Variable duration | Primary:<br>Sudden cardiac death, or ventricular arrhythmia, stroke, MI | Primary and Secondary:<br>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).<br><br>None of the strokes identified during exposed time to ADHD medications were |


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| nonusers | prescription for an AMP, atomoxetine, or MPH | | Secondary:<br>All-cause death | validated. No MIs were identified in study patients who used ADHD medication.<br><br>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[123]<br><br>AMP and MPH<br><br>vs<br><br>nonusers | RETRO<br><br>Patients six to 21 years of age diagnosed with ADHD who were prescribed AMP or MPH | N=171,126<br><br>Variable duration | Primary:<br>Cardiac events (inpatient diagnosis of chest pain, cardiac dysrhythmia or transient cerebral ischemia) and cardiac symptoms (tachycardia, palpitations, or syncope)<br><br>Secondary:<br>Not reported | Primary:<br>There were 0.92 new cardiac events and 3.08 new cardiac symptoms per 1,000,000 days of current stimulant use.<br><br>Current stimulant use compared to no stimulant use was not associated with less severe cardiovascular event (adjusted OR, 0.69; 95% CI, 0.42 to 1.12).<br><br>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).<br><br>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.<br><br>No significant differences were observed in risks of cardiovascular events (adjusted OR, 2.14; 95% CI, 0.82 to 5.63) or symptoms (adjusted OR, 1.08; 95% CI, 0.66 to 1.79) for current MPH use compared to AMP use.<br><br>Secondary:<br>Not reported |
| Schelleman et al[124]<br><br>AMP, atomoxetine, MPH | RETRO<br><br>Patients three to 17 years of age with a prescription for an AMP, atomoxetine, or | N=219,954<br><br>Variable duration | Primary:<br>Sudden death, ventricular arrhythmia, stroke, MI<br><br>Secondary:<br>Not reported | Primary:<br>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).<br><br>None of the strokes identified during exposed time to ADHD medications were validated. |


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| | MPH | | | No MIs were identified in ADHD medication users.<br><br>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).<br><br>Secondary:<br>Not reported |
| Hanwella et al[125]<br><br>Atomoxetine<br><br>vs<br><br>MPH | MA (five trials)<br><br>Children and adolescents six to 16 years of age diagnosed with ADHD | N=2,762<br><br>Variable duration | Primary:<br>ADHD-RS<br><br>Secondary:<br>Not reported | Primary:<br>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).<br><br>There was no significant difference in response rates between the two medications (RR, 0.93; 95% CI, 0.76 to 1.14).<br><br>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).<br><br>Secondary:<br>Not reported |
| Bloch et al[126]<br><br>ADHD medications | MA (11 trials)<br><br>Children diagnosed with ADHD and Tourette's | N=77<br><br>Variable duration | Primary:<br>ADHD severity (ADHD-RS, CADS-P, CADS-T, CTRS-R) and tic severity (YGTSS, STSSS, HMVTS, and | Primary:<br>MPH, α-2 agonists, desipramine, and atomoxetine demonstrated efficacy in improving ADHD symptoms in children with co-morbid tics.<br><br>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.<br><br>Secondary:<br>Not reported |


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| | | | GTSS)<br><br>Secondary:<br>Not reported | |
| **Narcolepsy** | | | | |
| Harsh et al[127]<br><br>Armodafinil 150 to 250 mg once daily<br><br>vs<br><br>placebo | DB, MC, PC, RCT<br><br>Patients 18 to 65 years of age diagnosed with narcolepsy | N=196<br><br>12 weeks | Primary:<br>MWT 0900-1500 sleep latency, CGI-C<br><br>Secondary:<br>MWT 1500-1900 sleep latency, CGI-C, CDR, ESS, BFI | Primary:<br>Mean MWT 0900–1500 sleep latency increased 1.3, 2.6, and 1.9 minutes from baseline in the 150 mg, 250 mg, and armodafinil combined groups, respectively, and decreased 1.9 minutes from baseline in the placebo group (*P*<0.01 for all comparisons).<br><br>Secondary:<br>Mean MWT 1500–1900 sleep latency increased 1.5, 1.6, and 1.6 minutes in the 150 mg, 250 mg, and armodafinil combined groups, respectively, and decreased 1.2 minutes from baseline in the placebo group. The differences for the armodafinil combined group vs placebo and the 150 mg group vs the placebo group were significant (*P*<0.05 for both comparisons).<br><br>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.<br><br>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).<br><br>There were not significant effects on mean continuity of attention between the treatment groups.<br><br>Armodafinil demonstrated significantly greater improvements in quality of episodic secondary memory compared to placebo at the final visit (*P*<0.05). |


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| | | | | 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).<br><br>Differences in the change from baseline on the ESS were statistically significant in favor of each armodafinil group compared to placebo at weeks eight (*P*<0.01 for all comparisons) and 12 (*P*<0.01) and at the final visit (150 mg/day, -4.1; *P*=0.0044, 250 mg/day, -3.8; *P*=0.0015, and combined group, -3.9; *P*=0.0006).<br><br>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.<br><br>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).<br><br>Headache, nausea, dizziness, and decreased appetite were the most commonly reported adverse events with armodafinil. |
| No authors listed<br>US Modafinil in Narcolepsy Group[128]<br><br>Modafinil 200 to 400 mg/day<br><br>vs<br><br>placebo | DB, MC, PC, RCT<br><br>Adults 18 to 68 years of age diagnosed with narcolepsy | N=283<br><br>9 weeks | Primary:<br>ESS<br><br>Secondary:<br>MSLT, MWT, CGI-C | Primary:<br>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.<br><br>Secondary:<br>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.<br><br>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.<br><br>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. |


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| No authors listed<br>US Modafinil in Narcolepsy Group[129]<br><br>Modafinil 200 to 400 mg/day<br><br>vs<br><br>placebo | DB, MC, PC, RCT<br><br>Adults 17 to 67 years of age diagnosed with narcolepsy | N=271<br><br>9 weeks | Primary:<br>MWT, CGI-C<br><br>Secondary:<br>MSLT, ESS | Primary:<br>MWT improved for both modafinil groups vs the placebo group (*P*<0.001) at each follow-up visit (weeks three, six, nine).<br><br>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).<br><br>Secondary:<br>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.<br><br>Mean ESS scores were reduced by both treatment groups (*P*<0.001) vs the placebo group. |
| Broughton et al[130]<br><br>Modafinil 200 to 400 mg/day<br><br>vs<br><br>placebo | MC, PC, RCT, XO<br><br>Patients 27 to 59 years of age diagnosed with narcolepsy | N=75<br><br>6 weeks | Primary:<br>MWT results, patient assessed sleepiness<br><br>Secondary:<br>ESS | Primary:<br>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.<br><br>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).<br><br>Secondary:<br>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[131]<br><br>Modafinil 100 mg in the morning and 200 mg at noon (or vice versa)<br><br>vs<br><br>placebo | DB, MC, PC, RCT, XO<br><br>Patients 27 to 54 years of age diagnosed with narcolepsy | N=50<br><br>12 weeks | Primary:<br>Results of sleep logs, CGI<br><br>Secondary:<br>MWT | Primary:<br>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).<br><br>The CGI scores were not statistically significantly different between the modafinil group and the placebo group (*P*=0.19).<br><br>Secondary:<br>MWT scores were significantly improved in the modafinil group compared to the |


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| | | | | placebo group (*P*<0.05). |
| Boivin et al[132]<br><br>Modafinil 200 mg in morning and 100 mg at noon<br><br>vs<br><br>placebo | DB, PC, RCT, XO<br><br>Patients 31 to 61 years of age with a history of EDS, cataplexy, at least two sleep onset REM periods and MSLT less than five minutes | N=10<br><br>12 weeks | Primary:<br>Subjectively assessed sleepiness, FCRTT, PLM, nocturnal sleep organization<br><br>Secondary:<br>Not reported | Primary:<br>Subjective sleepiness was significantly reduced in the modafinil group compared to the placebo group (*P*<0.05) based on home questionnaires.<br><br>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).<br><br>Modafinil did not statistically significantly decrease PLMs over placebo (*P*=0.06).<br><br>Modafinil did not display negative effects on any of the nocturnal sleep parameters measured (*P* value not significant).<br><br>Secondary:<br>Not reported |
| Thorpy et al[133]<br><br>Modafinil 200 to 400 mg/day | OL, RCT<br><br>Adults 17 to 65 years of age diagnosed with narcolepsy who had been receiving MPH for EDS for a month | N=40<br><br>5 weeks | Primary:<br>ESS, tolerability<br><br>Secondary:<br>Not reported | Primary:<br>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.<br><br>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.<br><br>Secondary:<br>Not reported |
| No authors listed<br>US Xyrem MC Study Group[134]<br><br>Phase I (two weeks): Continue sodium oxybate at the dose previously prescribed. | DB treatment withdrawal study design (alternative to conventional DB, PC, RCT)<br><br>Patients ≥16 | N=55<br><br>4 weeks | Primary:<br>Cataplexy attacks, treatment-emergent adverse events<br><br>Secondary: | Primary:<br>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).<br><br>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. |


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| Phase II (two weeks): Continue sodium oxybate treatment at previously prescribed dose<br><br>vs<br><br>conversion to placebo | years of age with narcolepsy or symptoms of narcolepsy who were previously stabilized on sodium oxybate 3 to 9 g/day | | Not reported | There were no symptoms of withdrawal reported by the study investigators.<br><br>Secondary:<br>Not reported |
| No authors listed Xyrem International Study Group[135]<br><br>Sodium oxybate 4.5 to 9 g/day administered at bedtime<br><br>vs<br><br>placebo | DB, MC, PC, RCT<br><br>Patients ≥16 years of age with narcolepsy or symptoms of narcolepsy | N=228<br><br>8 weeks | Primary:<br>ESS, MWT, CGI-C<br><br>Secondary:<br>Not reported | Primary:<br>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).<br><br>Study patients treated with 9 g of sodium oxybate nightly displayed a significant median increase of >10 minutes in the MWT (*P*<0.001).<br><br>Improvements in EDS were incremental in those study patients who received concomitant stimulants alone.<br><br>Significant improvements in the CGI-C were observed for each group treated with sodium oxybate (*P*≤0.001).<br><br>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.<br><br>Secondary:<br>Not reported |
| No authors listed Xyrem International Study Group[136] | DB, MC, PC, RCT | N=228<br><br>8 weeks | Primary:<br>Narcolepsy symptoms, | Primary:<br>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 |


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| Sodium oxybate 4.5 to 9 g/day administered at bedtime<br><br>vs<br><br>placebo | Patients ≥16 years of age with narcolepsy or symptoms of narcolepsy | | medication use, adverse events<br><br>Secondary:<br>Not reported | (*P*=0.003), 65.0 (*P*=0.002), and 84.7% (*P*<0.001), respectively.<br><br>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.<br><br>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.<br><br>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.<br><br>Secondary:<br>Not reported |
| Black et al[137]<br><br>Sodium oxybate 4.5 to 9 g/day administered at bedtime<br><br>vs<br><br>placebo | DB, PC, PG, RCT<br><br>Patients ≥16 years of age with narcolepsy or symptoms of narcolepsy | N=228<br><br>8 weeks | Primary:<br>Sleep architecture, narcolepsy symptoms and adverse events<br><br>Secondary:<br>Not reported | Primary:<br>Following four (*P*<0.001) and eight weeks (*P*<0.001) of sodium oxybate treatment, study patients demonstrated significant dose-related increases in the duration of stage three and four sleep, reaching a median increase of 52.5 minutes in patients receiving 9 g nightly.<br><br>Compared to placebo-treated patients, delta power was significantly increased in all treatment dose groups.<br><br>Stage one sleep and the frequency of nocturnal awakenings were each significantly decreased at the 6 and 9 g/night doses.<br><br>The changes in nocturnal sleep coincided with significant decreases in the severity and frequency of narcolepsy symptoms.<br><br>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 |


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| | | | | and appeared to be dose-related as documented by study investigators.<br><br>Secondary:<br>Not reported |
| Weaver et al[138]<br><br>Sodium oxybate 4.5 to 9 g/day in two divided doses taken at bedtime and again 2.5 to four hours later<br><br>vs<br><br>placebo | DB, MC, RCT<br><br>Patients 16 to 75 years of age with narcolepsy who were experiencing cataplexy and EDS with recurrent episodes for ≥3 months | N=285<br><br>4 weeks | Primary:<br>FOSQ<br><br>Secondary:<br>Not reported | Primary:<br>The nightly administration of sodium oxybate showed statistically significant dose-related improvements in functional status and quality of life as evidenced by the total FOSQ ($P$<0.001), as well as in the activity level ($P$<0.001), vigilance ($P$<0.001), general productivity ($P$=0.002), and social outcomes ($P$<0.001) subscales.<br><br>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.<br><br>Secondary:<br>Not reported |
| Wang et al[139]<br><br>Sodium oxybate | RETRO<br><br>Patients receiving sodium oxybate | N=~26,000<br><br>68 months | Primary:<br>Occurrence of abuse/misuse of sodium oxybate<br><br>Secondary:<br>Not reported | Primary:<br>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.<br><br>Of those 26,000 patients, 0.2% reported ≥1 of the events studied. These included 10 cases (0.039%) meeting DSM-IV abuse criteria, four cases (0.016%) meeting DSM-IV dependence criteria, eight cases (0.031%, including three of the previous four) with withdrawal symptoms reported after discontinuation of sodium oxybate, two confirmed cases (0.008%) of sodium oxybate–facilitated sexual assault, eight cases (0.031%) of overdose with suicidal intent, 21 deaths (0.08%) in patients receiving sodium oxybate treatment with one death known to be related to sodium oxybate, and three cases (0.01%) of traffic accidents involving drivers taking sodium oxybate.<br><br>During the study period, approximately 600,000 bottles of sodium oxybate were distributed, and five incidents (0.0009%) of diversion were reported.<br><br>Secondary: |


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| Black et al[140]<br><br>Sodium oxybate 6 to 9 g/day<br><br>vs<br><br>modafinil 200 to 600 mg/day<br><br>vs<br><br>sodium oxybate 6 to 9 g/day plus modafinil 200 to 600 mg/day<br><br>vs<br><br>placebo | DB, MC, PC, RCT<br><br>Patients ≥18 years of age with narcolepsy taking 200 to 600 mg of modafinil daily for the treatment of EDS | N=270<br><br>8 weeks | Primary: MWT<br><br>Secondary: ESS, CGI-C | Primary:<br>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).<br><br>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.<br><br>In the sodium oxybate plus modafinil group, there was an increase in daytime sleep latency from 10.43 to 13.15 minutes (*P*<0.001), suggesting that this combination of drugs produced an additive effect.<br><br>Secondary:<br>The sodium oxybate group showed a decrease in median average EES scores, from 15 to 12 (*P*<0.001).<br><br>The sodium oxybate plus modafinil group showed a decreased in median average EES scores from 15 to 11 (*P*<0.001).<br><br>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.<br><br>The placebo and the modafinil-treated study patients demonstrated no significant change in symptoms. |
| Black et al[141]<br><br>Sodium oxybate 6 g/day<br><br>vs<br><br>modafinil 200 to 600 | DB, PC, RCT<br><br>Patients ≥18 years of age with narcolepsy taking modafinil 200 to 600 mg/day for the treatment of | N=278<br><br>8 weeks | Primary: Sleep architecture, MWT<br><br>Secondary: Not reported | Primary:<br>Following eight weeks of treatment, there was no significant change in total sleep time for any group.<br><br>Significant changes in total non-REM sleep among patients receiving sodium oxybate and sodium oxybate plus modafinil included a median increase in Stage three and four sleep (43.5 and 24.25 minutes, respectively; *P*<0.001 for each) and delta power (*P*<0.001 for each) and significant decrease in the number of nocturnal |


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| mg/day<br><br>vs<br><br>sodium oxybate<br>6 g/day plus modafinil<br>200 to 600 mg/day<br><br>vs<br><br>placebo | EDS | | | awakenings in sodium oxybate (*P*=0.008) and sodium plus modafinil (*P*=0.014) treated study patients.<br><br>No significant changes in PSG parameters were noted in patients treated with placebo or modafinil alone.<br><br>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.<br><br>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.<br><br>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.<br><br>Secondary:<br>Not reported |
| **Obstructive Sleep Apnea** | | | | |
| Hirshkowitz et al[142]<br><br>Armodafinil 150 mg/day<br><br>vs<br><br>placebo | DB, MC, PC, RCT<br><br>Patients 18 to 65 years of age with a diagnosis of OSA/hypopnea syndrome who complained of residual excessive sleepiness during | N=263<br><br>12 weeks | Primary:<br>MWT, CGI-C<br><br>Secondary:<br>CDR, ESS, BFI | Primary:<br>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).<br><br>Armodafinil significantly improved MWT sleep latency compared to placebo at each visit (*P*<0.01 for all).<br><br>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).<br><br>Secondary: |


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| | CPAP therapy | | | 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).<br><br>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).<br><br>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[143]<br><br>Armodafinil 150 to 250 mg/day<br><br>vs<br><br>placebo | DB, MC, PC, RCT<br><br>Patients 18 to 65 years of age with a diagnosis of moderate OSA/ hypopnea syndrome and residual excessive sleepiness despite effective, regular, and stable use of CPAP treatment | N=395<br><br>12 weeks | Primary:<br>MWT, CGI-C<br><br>Secondary:<br>ESS, CDR, BFI | Primary:<br>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.<br><br>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.<br><br>Secondary:<br>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).<br><br>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).<br><br>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).<br><br>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). |


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| | | | | 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.<br><br>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).<br><br>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[144]<br><br>Armodafinil 200 mg/day<br><br>vs<br><br>placebo | DB, PC, PG, RCT<br><br>Patients 18 to 65 years of age diagnosed with obstructive sleep apnea | N=249<br><br>18 months | Primary:<br>CGI-C as related to sleepiness, mean change from baseline in MWT to mean sleep latency at final visit<br><br>Secondary:<br>ESS | Primary:<br>The proportion of patients with least minimal improvement on CGI-C was significantly greater in the armodafinil group compared to the placebo group (69 vs 53%; *P*=0.012).<br><br>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).<br><br>Secondary:<br>Mean ESS scores were significantly reduced in study patients treated with armodafinil compared to patients treated with placebo (-6.3 vs -4.8; *P*=0.003).<br><br>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[145]<br><br>Modafinil 200 to 400 mg/day<br><br>vs<br><br>placebo | DB, MC, PC, RCT<br><br>Adults 18 to 70 years of age with OSA/ hypopnea syndrome and | N=305<br><br>12 weeks | Primary:<br>MWT, ESS<br><br>Secondary:<br>CGI-C, FOSQ | Primary:<br>Modafinil significantly improved mean sleep latency on the MWT compared to placebo (*P*<0.001).<br><br>Modafinil significantly decreased the ESS scores compared to placebo (*P*<0.001).<br><br>There were no significant differences in MWT or ESS scores seen between the two modafinil treatment groups (*P*>0.15 for each). |


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| | having residual excessive sleepiness during CPAP therapy | | | Secondary:<br>At the end of the study, modafinil had significant improvements in CGI-C compared to placebo (*P*<0.001).<br><br>Modafinil improved mean FOSQ scores compared to placebo (*P*<0.02) for vigilance, general productivity, and activity level. |
| Weaver et al[146]<br><br>Modafinil 200 to 400 mg/day<br><br>vs<br><br>placebo | 2 DB, MC, PC, RCT (Pooled analysis)<br><br>Patients 24 to 76 years of age diagnosed with OSA and residual excessive sleepiness associated with CPAP | N=480<br><br>4 to 12 weeks | Primary:<br>FOSQ<br><br>Secondary:<br>Not reported | Primary:<br>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.<br><br>A greater proportion of patients who received modafinil were considered responders compared to patients who received placebo (45 vs 25%; *P*<0.001).<br><br>Analysis based on the individual FOSQ questions demonstrated that 18 of the 30 questions increased at least one point for significantly more patients who received modafinil (*P*<0.05).<br><br>Secondary:<br>Not reported |
| Williams et al[147]<br><br>Modafinil 200 mg/day<br><br>vs<br><br>placebo | DB, RCT, XO<br><br>Men diagnosed with OSA who were modafinil-naïve | N=21<br><br>2 days | Primary:<br>Driving simulation, subjective sleepiness<br><br>Secondary:<br>Not reported | Primary:<br>During CPAP withdrawal, severe sleep-disordered breathing was evident and administration of modafinil improved simulated driving performance (steering variability; *P*<0.0001, mean reaction time; *P*<0.0002, lapses on a current task; *P*<0.01), psychomotor vigilance task (mean one/reaction time and lapses, both *P*<0.0002), and subjective sleepiness (*P*<0.01).<br><br>Secondary:<br>Not reported |
| **Shift Work Disorder** | | | | |
| Czeisler et al[148]<br><br>Armodafinil 150 mg/day | DB, MC, PC, RCT | N=254<br><br>12 weeks | Primary:<br>MSLT, CGI-C | Primary:<br>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 |


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| Study and Drug Regimen | Study Design, Study Rating, and Demographics | Sample Size and Study Duration | End Points | Results |
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| administered 30 to 60 minutes before the start of work shift<br><br>vs<br><br>placebo | 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 four or higher for sleepiness on work nights, including the commute to and from work | | Secondary:<br>KSS, CDR | final visit (*P*<0.001).<br><br>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).<br><br>Secondary:<br>Patient-reported levels of sleepiness during the night shift on the KSS were reduced with armodafinil compared to placebo at all visits.<br><br>Armodafinil improved most items assessed in the electronic diaries, including the maximum level of sleepiness during the night shift and commute home, and mean number of mistakes, accidents, or near misses compared to placebo.<br><br>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).<br><br>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).<br><br>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).<br><br>Continuity of attention improved at the final visit in patients who received armodafinil compared to those who received placebo (*P*<0.001).<br><br>Adverse events included headache, nausea, nasopharyngitis and anxiety. Most |


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| Study and Drug Regimen | Study Design, Study Rating, and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | adverse events were considered mild or moderate by the investigator. |
| Tembe et al[149]<br><br>Armodafinil 150 mg administered one hour prior to night shift<br><br>vs<br><br>modafinil 200 mg administered one hour prior to night shift | DB, MC, RCT<br><br>Patients 18 to 60 years of age suffering from excessive sleepiness associated with SWD | N=211<br><br>12 weeks | Primary:<br>Proportion of patients showing ≥2 grades of improvement (responder) based on SSS in both groups<br><br>Secondary:<br>Improvement in mean SSS grades, compliance, patients' as well as physicians' global assessment for efficacy and safety | Primary:<br>Responder rates with armodafinil (72.12%) and modafinil (74.29%) were comparable (*P*=0.76).<br><br>Secondary:<br>Armodafinil and modafinil significantly improved mean sleepiness grades as compared to baseline (*P*<0.0001).<br><br>At the end of therapy, compliance in both modafinil group (99.31%) and armodafinil group (99.13%) was found to be comparable (*P*=0.63).<br><br>Both physicians' and patients' assessment of efficacy was comparable among the treatment groups.<br><br>Adverse events were similar with modafinil (40.57%) and armodafinil (42.87%; *P*=0.78). The most commonly treatment-emergent adverse events reported were mild to moderate in severity and included headache, nausea, and dry mouth. |
| Erman et al (abstract)[150]<br><br>Armodafinil 150 mg administered one hour prior to night shift<br><br>vs<br><br>placebo | DB, MC, PC, PG, RCT<br><br>Patients 18 to 65 years of age suffering from excessive sleepiness associated with SWD | N=383<br><br>6 weeks | Primary:<br>SDS-M and FOSQ-10<br><br>Secondary:<br>Not reported | Primary:<br>Patients treated with armodafinil experienced significantly greater improvements in SDS-M composite scores at final visit compared to patients treated with placebo (-6.8 vs -4.5, respectively; *P*=0.0027).<br><br>Patients in the armodafinil treatment group demonstrated a greater improvement in total FOSQ-10 score from baseline to six weeks compared to placebo (3.6 vs 2.7; *P*=0.0351); however, there was no difference between treatments at the final visit (3.4 vs 2.7; *P*=0.0775).<br><br>Secondary:<br>Not reported |


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| Study and Drug Regimen | Study Design, Study Rating, and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| Erman et al[151]<br><br>Armodafinil 150 mg administered one hour prior to night shift<br><br>vs<br><br>placebo | DB, MC, PC, RCT<br><br>Patients 18 to 65 years of age suffering from excessive sleepiness associated with SWD | N=383<br><br>6 weeks | Primary:<br>CGI-C<br><br>Secondary:<br>GAF and KSS | Primary:<br>Significantly more patients treated with armodafinil experienced an improvement in CGI-C compared to placebo at three weeks (78 vs 51%; *P*<0.0001) and at six weeks (80 vs 56%; *P*<0.0001). Similarly, more patients treated with armodafinil experienced an improvement in late-in-shift CGI-C at the final visit compared to placebo (77 vs 57%; *P*<0.0001).<br><br>At the final visit, most patients in the armodafinil group were categorized as 'much improved' (33%) or 'very much improved' (24%) on the late-in-shift CGI-C rating scale. For patients treated with placebo, 38% had 'no change' in their condition compared to only 19% of patients in the armodafinil group.<br><br>Secondary:<br>The mean (±SD) improvement from baseline in GAF score at the final visit was significantly greater in the armodafinil group compared to the placebo group (9.4 vs 5.0; *P*<0.0001). Improvements in GAF scores were also significantly greater for armodafinil-treated patients at three weeks (6.9 vs 3.7; *P*<0.0001) and six weeks (9.8 vs 4.9; *P*<0.0001) compared to patients treated with placebo. A higher proportion of patients treated with armodafinil had GAF scores greater than 70 ("normal function") at each visit, with almost twice as many patients receiving armodafinil reaching GAF scores greater than 70 at final visit compared to placebo (51 vs 28%; *P* value not reported).<br><br>The improvements in KSS scores from baseline to the final visit were significantly greater for armodafinil-treated patients compared to patients receiving placebo (-2.8 vs -1.8; *P*<0.0001). The KSS scores were also significantly improved in the armodafinil group compared to the placebo group at three weeks (-2.6 vs -1.6; *P*<0.0001) and six weeks (-2.9 vs -1.8; *P*<0.0001). |
| Czeisler et al[152]<br><br>Modafinil 200 mg/ day administered 30 to 60 minutes before the start of work shift<br><br>vs | DB, MC, PC, RCT<br><br>Adults 18 to 60 years of age diagnosed with SWD and worked each month at | N=204<br><br>3 months | Primary:<br>MSLT, CGI-C, Psychomotor Vigilance Test<br><br>Secondary:<br>Not reported | Primary:<br>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).<br><br>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). |


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| Study and Drug Regimen | Study Design, Study Rating, and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| placebo | 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 | | | 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).<br><br>Secondary:<br>Not reported |
| **Miscellaneous** | | | | |
| Black et al[153]<br><br>Armodafinil<br>100 to 250 mg/day (OSA) or 100 to 250 mg/night 30 minutes to one hour before night shift but no later than 23:00 (SWD) | DB, MC, OL<br><br>Men and women 18 to 65 years of age with a diagnosis of OSA, SWD, or narcolepsy | N=743<br><br>≥12 months | Primary:<br>Tolerability and efficacy (CGI-C, ESS, BFI)<br><br>Secondary:<br>Not reported | Primary:<br>Discontinuations due to adverse events occurred in 13% of study patients during the initial study period.<br><br>Most adverse events were mild to moderate in severity and included headache (25%), nasopharyngitis (17%), and insomnia (14%).<br><br>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.<br><br>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.<br><br>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).<br><br>Armodafinil improved wakefulness, measured by the ESS, in the treated OSA and narcolepsy groups, at all follow-up visits compared to baseline.<br><br>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.<br><br>Secondary: |


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| Study and Drug Regimen | Study Design, Study Rating, and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | Not reported |
| Schwartz et al[154]<br><br>Armodafinil 100 to 250 mg/day (OSA and narcolepsy) or 100 to 250 mg/day 30 minutes to one hour before the start of night shift but no later than 23:00 (SWD) | MC, OL<br><br>Patients 18 to 65 years of age who had a complaint of excessive sleepiness associated with OSA, SWD, or narcolepsy | N=328<br><br>12 months | Primary:<br>CGI, ESS, adverse events<br><br>Secondary:<br>Not reported | Primary:<br>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.<br><br>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).<br><br>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.<br><br>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.<br><br>Secondary:<br>Not reported |
| Jean-Pierre et al[155]<br><br>Modafinil 200 mg/ day<br><br>vs<br><br>placebo | DB, MC, PC, RCT<br><br>Patients ≥18 years of age diagnosed with cancer with a survival expectancy >6 months | N=877<br><br>4.5 years | Primary:<br>BFI question 3, ESS, POMS-DD<br><br>Secondary:<br>Not reported | Primary:<br>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.<br><br>Daytime sleepiness improved significantly in the modafinil group ($P$=0.002).<br><br>Modafinil had no statistically significant effect on depression ($P$>0.05).<br><br>Secondary:<br>Not reported |
| Orlikowski et al[156]<br><br>Modafinil 300 mg/ day<br><br>vs | DB, MC, PC, RCT<br><br>Patients ≥18 years of age | N=28<br><br>2.5 years | Primary:<br>MWT<br><br>Secondary:<br>MLST, ESS, | Primary:<br>At four weeks, the mean MWT score was 16.4 minutes in the modafinil group and 15.8 minutes in the placebo group ($P$=0.71).<br><br>Secondary: |


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| Study and Drug Regimen | Study Design, Study Rating, and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| placebo | diagnosed with myotonic muscular dystrophy type one experiencing hypersomnia | | global assessment (patient and physician), HAMD, SF-36 | 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.<br><br>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. |

Drug regimen abbreviations: AMP=mixed amphetamine salts, BID=twice a day, DEX=dextroamphetamine, DXM=dexmethylphenidate, ER=extended release, 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, DR=dose ranging, ES=extension study, FD=forced dose, HR=hazard ratio, LS=least squares, LSMD=least squares mean difference, 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, RETRO=retrospective, RR=relative risk, SA=single arm, SB=single blind, SD=standard deviation, SMD=standardized mean difference, 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, BRIEF=Behavior Rating Inventory of Executive Function, BRIEF-A=Behavior Rating Inventory of Executive Function-Adult Version, CAARS=Conners adult ADHD rating scale, CAARS-Inv:SV=Conner's 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, CHQ-PF50=Child Health Questionnaire-Parent Form, 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, DSM-IV=Diagnostic and Statistical Manual of Mental Disorders Fourth Edition, DSST=Digit Symbol Substitution Task/Coding Test, EDS=excessive daytime sleepiness, ECG=electrocardiogram, EESC=Expression and Emotion Scale for Children, ESS=Epworth sleep scale, FCRTT=four-choice reaction time test, FBIM=Family Burden of Illness Module, FOSQ=functional outcomes of sleep questionnaire, FOSQ-10=functional outcomes of sleep questionnaire short version, GAF=global assessment of functioning, GTSS=Global tic severity scale, HAMA=Hamilton Anxiety Rating Scale, HAMD=Hamilton Depression Rating 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, MI=myocardial infarction, mm Hg=millimeters per mercury, MSLT=multiple sleep latency test, MWT=maintenance of wakefulness test, O/D=oppositional/defiance, ODD=oppositional defiant disorder, OSA=obstructive sleep apnea, 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, SBP=systolic blood pressure, REM=rapid eye movement, RCFT=Rey Complex Figure Test, SAICA=Social Adjustment Scale for Children and Adolescents, SDS=Sheehan disability scale, SDS-M= modified 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, 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, STSS=Shapiro Tourette syndrome severity scale, SWD=Shift Work Disorder, TOVA=test of variables of attention, WFIS=Weiss Functional Impairment Scale, WFIRS-S=Weiss Functional Impairment Rating Scale Self-Report, WRAADDS=Wender-Reimherr Adult Attention-Deficit Disorder Scale, YGTSS=Yale global tic severity scale, YQOL-R=Youth quality of life-research version.


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**Table 6. Special Populations**[3-23,27-29]

| Drug | Population and Precaution | | | | |
|---|---|---|---|---|---|
| | Elderly/ Children | Renal Dysfunction | Hepatic Dysfunction | Pregnancy Category | Excreted in Breast Milk |
| **Anorexigenic Agents and Respiratory and Cerebral Stimulants-Amphetamines** | | | | | |
| Amphetamine/ dextro-amphetamine salts | Not studied in elderly patients (IR).<br><br>Safety and efficacy in children <3 years of age have not been established (IR).<br><br>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.<br><br>Safety and efficacy in children <3 years of age have not been established (IR, solution).<br><br>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 | Safety and efficacy in elderly patients have not been established.<br><br>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 established. | No dosage adjustment required. | No dosage adjustment required. | C | Yes; advise to refrain from nursing. |


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| Drug | Population and Precaution | | | | |
|---|---|---|---|---|---|
| | Elderly/ Children | Renal Dysfunction | Hepatic Dysfunction | Pregnancy Category | Excreted in Breast Milk |
| | 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.<br><br>Safety and efficacy in children <17 years of age have not been established. | No dosage adjustment required.<br><br>A safe and effective dose for patients with severe renal impairment (CrCl <20 mL/minute) has not been established. | 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.<br><br>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.<br><br>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-ation should be given to the use of a lower dose in elderly patients. | No dosage adjustment required. | Hepatic dosage adjustment required; with severe hepatic dysfunction, reduce the | C† | Unknown; use with caution. |


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| Drug | Population and Precaution | | | | |
|---|---|---|---|---|---|
| | Elderly/ Children | Renal Dysfunction | Hepatic Dysfunction | Pregnancy Category | Excreted in Breast Milk |
| | Safety and efficacy in children <16 years of age have not been established. | | dose by one half of that recom-mended for healthy patients. | | |
| **Central α-Agonists** | | | | | |
| Clonidine | Safety and efficacy have not been established.<br><br>Safety and efficacy in children <6 years of age have not been established. | Dose adjustment based on degree of impairment is recommended; monitor patients. | Not studied in hepatic dysfunction. | C | Yes; use with caution. |
| Guanfacine | Safety and efficacy have not been established.<br><br>Safety and efficacy in children <6 years of age have not been established. | Dose adjustment may be required in patients with significant renal impairment; monitor patients. | Not studied in hepatic dysfunction. | B | Unknown; use with caution. |
| **Central Nervous Agents-Miscellaneous** | | | | | |
| Atomoxetine | Safety and efficacy have not been established.<br><br>Safety and efficacy in children <6 years of age have not been established; 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. |
| Sodium oxybate | Limited experience in the elderly; monitor elderly patients closely for | Not studied with renal dysfunction. | Hepatic dosage adjustment required; with comp- | C | Unknown; use with caution. |


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| Drug | Population and Precaution | | | | |
|---|---|---|---|---|---|
| | Elderly/ Children | Renal Dysfunction | Hepatic Dysfunction | Pregnancy Category | Excreted in Breast Milk |
| | impaired motor and/or cognitive function.<br><br>Safety and efficacy in children have not been established. | | romised liver function, the starting dose should be decreased by one half. | | |

ADHD=attention deficit hyperactivity disorder, CrCl=creatinine clearance, ER=extended-release, IR=immediate-release
†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**[3,4,7-9,21,23]

| 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† | ✔ | ✔ | ✔ |
| Peripheral vascular disease | - | ✔ | - | - |
| Raynaud's disease | - | ✔ | - | ✔ |
| 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 | ✔ */2† | ✔ | 12 | ✔ |
| Insomnia | 12 to 27† | ✔ | 13 to 27 | ✔ |
| Irritability | ✔ *† | - | 10 | - |
| Labile affect | - | - | 3 | - |
| Mania | - | ✔ | ✔ | ✔ |
| Nervousness | 6 to 13† | - | - | - |
| Overstimulation | ✔ * | ✔ | ✔ | ✔ |
| Psychotic episodes | ✔ * | ✔ | ✔ | ✔ |


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| Adverse Events | Amphetamine/ Dextroam-phetamine Salts | Dextro-amphetamine | Lisdex-amfetamine | Meth-amphetamine |
|---|---|---|---|---|
| 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 | ✔ † | - | ✔ | - |
| Blurred vision | ✔ *† | ✔ | ✔ | - |
| Dysmenorrhea | 2 to 4† | - | - | - |
| Dyspnea | 2 to 4† | - | 2 | - |
| Growth suppression | - | ✔ | ✔ | ✔ |
| Hypersensitivity reactions | - | - | ✔ | - |
| Infection | 2 to 4† | - | - | - |
| Tolerance | - | - | - | ✔ |
| Weakness | 2 to 6† | - | - | - |

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


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**Table 7b. Adverse Drug Events (%)-Anorexigenic Agents and Respiratory and Cerebral Stimulants-Miscellaneous**[5,6,10,11,14-20,27,28]

| 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 to 21 |
| Attention disturbance | 1 | - | - | - |
| Cerebral arteritis | - | ✔ | ✔ | - |
| Cerebral occlusion | - | ✔ | ✔ | - |
| Depression | 1 to 3 | ✔ | ✔ | 2 |
| Dizziness | 3 to 8 | 6 | ✔ | 5 |
| Drowsiness | - | ✔ | ✔ | - |
| Dyskinesia | - | ✔ | ✔ | 1 |
| Emotional instability | - | - | 6† | - |
| Fatigue/lethargy | 2 | - | - | - |
| Fever | 1 | 5 | ✔ | - |
| Hallucinations | - | - | ✔† | - |
| Headache | 14 to 28 | 25 to 39 | ✔/28† | 34 |
| Hyperkinesia | - | - | - | 1 |
| Hypertonia | - | - | - | 1 |
| Insomnia | 4 to 6 | ✔ | ✔/13 to 30† | 3 to 21 |
| Jittery feeling | - | 12 | ✔ | - |
| Labile affect | - | - | ✔ | - |
| Mania | - | - | ✔ | ✔ |
| Migraine | 1 | - | - | - |
| Nervousness | 1 | ✔ | ✔ | 7 |
| Neuroleptic malignant syndrome | - | ✔ | ✔ | - |
| Overstimulation | - | - | - | 1 |
| Paresthesia | 1 | - | ✔ | 2 |
| Psychotic episodes | - | - | - | ✔ |
| Restlessness | - | 12 | - | - |
| Seizures | - | - | ✔† | - |
| Somnolence | - | - | - | 2 |
| Tic | - | - | ✔/7† | - |
| Tourette's exacerbation | - | ✔ | ✔ | - |


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| Adverse Event(s) | Armodafinil | Dexmethyl-phenidate | Methyl-phenidate | Modafinil |
|---|---|---|---|---|
| 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 | 3 to 5 | - | ✔ | 6 |
| Dry mouth | 2 to 7 | 7 to 20 | ✔ | 4 |
| Dyspepsia | 2 | 5 to 9 | ✔ | 5 |
| Flatulence | - | - | - | 1 |
| Mouth ulceration | - | - | - | 1 |
| Nausea | 7 to 14 | 9 | ✔ /12† | 11 |
| Stomach cramps | - | ✔ | - | - |
| Thirst | 1 | - | - | 1 |
| Vomiting | 1 | - | ✔ /10† | - |
| Weight loss | - | ✔ | ✔ / 9† | - |
| **Genitourinary** | | | | |
| Abnormal urine | - | - | - | 1 |
| Erectile disturbance | - | - | ✔ | - |
| Hematuria | - | - | - | 1 |
| Libido decreased | - | - | ✔ | - |
| Polyuria | 1 | - | - | - |
| **Hematologic** | | | | |
| Agranulocytosis | - | - | - | ✔ |
| Anemia | - | ✔ | ✔ | - |
| Eosinophilia | - | - | - | 1 |
| Leukopenia | - | ✔ | ✔ | - |
| Pancytopenia | ✔ | - | ✔ | - |
| Thrombocytopenic purpura | - | ✔ | ✔ | - |
| **Hepatic** | | | | |
| Hepatic coma | - | ✔ | ✔ | - |


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

†Transdermal formulation.
-Event not reported.
✔ Percent not specified.

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

| Adverse Event(s) | Clonidine | Guanfacine |
|---|---|---|
| **Cardiovascular** | | |
| Atrioventricular block | ✔ | ✔ |
| Bradycardia | ≤4 | - |
| Cardiac arrhythmia | ✔ | - |
| Chest pain | ✔ | - |
| Congestive heart failure | ✔ | - |
| Electrocardiogram abnormalities | ✔ | - |
| Hypertension | - | ✔ |


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| Adverse Event(s) | Clonidine | Guanfacine |
|---|---|---|
| Hypotension | - | 4 |
| Orthostatic hypotension | ✔ | - |
| Pallor | ✔ | - |
| Palpitations | 1 | - |
| Raynaud'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 | 6 to 8 |
| Emotional disorder | 3 to 4 | - |
| Fatigue/lethargy | 12 to 15 | 14 |
| Fever | ✔ | - |
| Hallucinations | ✔ | ✔ |
| Headache | 1 to 11 | 21 to 24 |
| Insomnia | ≤5 | 12 |
| Irritability | 3 to 6 | 2 |
| Malaise | ✔ | - |
| Mental depression | 1 | - |
| Nervousness | 1 to 3 | - |
| Nightmares | ✔ | ✔ |
| Paresthesia | ✔ | - |
| Restlessness | ✔ | - |
| Seizure | - | ✔ |
| Sleep terror | 3 | - |
| Somnolence | 26 to 33 | 18 to 38 |
| Tremor | ✔ | - |
| Vivid dreams | ✔ | - |
| **Dermatological** | | |
| Flushing | ✔ | - |
| Rash | 1 | - |
| Urticaria | ✔ | - |
| **Gastrointestinal** | | |
| Abdominal pain | ≤3 | 10 to 11 |
| 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 | ✔ | ✔ |


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| Adverse Event(s) | Clonidine | Guanfacine |
|---|---|---|
| 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 | - |
| 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**[22,29]

| Adverse Event(s) | Atomoxetine | Sodium Oxybate |
|---|---|---|
| **Cardiovascular** | | |
| Chest pain | - | ✔ |
| Diastolic blood pressure increased | 4 to 22 | - |
| Flushing | ≥2 | - |
| Hypertension | 1 to 9 | 6 |
| Hypotension | <2 | - |


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| Adverse Event(s) | Atomoxetine | Sodium Oxybate |
|---|---|---|
| Palpitations | 3 | - |
| QT prolongation | <1 | - |
| Raynaud's phenomenon | ✔ | - |
| Stroke | ✔ | - |
| Systolic blood pressure increased | 4 to 13 | - |
| Tachycardia | 2 to 24 | <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 | - |
| Nightmare | - | 3 to 6 |
| 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 |


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| Adverse Event(s) | Atomoxetine | Sodium Oxybate |
|---|---|---|
| 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 26 | 21 |
| Stomach discomfort | - | - |
| Vomiting | 3 to 11 | 8 |
| Weight loss | 2 to 30 | - |
| **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 | ✔ | - |
| 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 | ✔ | ✔ |


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| Adverse Event(s) | Atomoxetine | Sodium Oxybate |
|---|---|---|
| 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**[3,4,7-9,21,23]

| Contraindication(s) | Amphetamine/ Dextroam-phetamine Salts | Dextro-amphetamine | Lisdex-amfetamine | Meth-amphetamine |
|---|---|---|---|---|
| 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**[5,6,10,11,14-20,27,28]

| 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]

| Contraindication(s) | Clonidine | Guanfacine |
|---|---|---|
| Hypersensitivity | ✔ | ✔ |


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**Table 8d. Contraindications-Central Nervous System Agents-Miscellaneous**[22,29]

| Contraindication(s) | Atomoxetine | Sodium Oxybate |
|---|---|---|
| Concurrent use of alcohol | - | ✔ |
| 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**[37]

**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**[37]

**WARNING**

Suicidal ideation in children and adolescents: Atomoxetine increased the risk of suicidal ideation in short-term studies in children or adolescents with attention deficit hyperactivity disorder. 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 attention deficit hyperactivity disorder 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 attention deficit hyperactivity disorder 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**[37]

**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.


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**Boxed Warning for lisdexamfetamine**[37]

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

**Boxed Warning for methamphetamine**[37]

| 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**[37]

| 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**[37]

| WARNING |
| --- |
| Sodium oxybate is a gamma hydroxybutyrate, a known drug of abuse. Abuse has been associated with some important central nervous system adverse reactions, including death. Even at recommended doses, use has been associated with confusion, depression, and other neuropsychiatric reactions. Reports of respiratory depression occurred in clinical trials. Almost all of the patients who received sodium oxybate during clinical trials were receiving central nervous system stimulants.<br><br>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).<br><br>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. |


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## Warnings/Precautions

**Table 9a. Warnings and Precautions-Anorexigenic Agents and Respiratory and Cerebral Stimulants-Amphetamines**[3,4,7-9,21,23]

| Warning(s)/Precaution(s) | Amphetamine/ Dextroamphet-amine Salts | Dextro-amphetamine | Lisdex-amfetamine | Meth-amphet-amine |
|---|---|---|---|---|
| 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 | ✔ | ✔ | ✔ | ✔ |
| Peripheral vasculopathy has been reported and may result in digital ulceration and/or soft tissue breakdown; monitoring is recommended and discontinuation may be necessary | ✔ | ✔ | ✔ | ✔ |
| Preexisting psychosis; administration of stimulants may exacerbate symptoms of behavior disturbances and thought 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 | ✔ | ✔ | ✔ | ✔ |


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| Warning(s)/Precaution(s) | Amphetamine/ Dextroamphet-amine Salts | Dextro-amphetamine | Lisdex-amfetamine | Meth-amphet-amine |
|---|---|---|---|---|
| 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**[5,6,10,11,14-20,27,28]

| 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 | ✔ | - | - | ✔ |


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| Warning(s)/Precaution(s) | Armodafinil | Dexmethyl-phenidate | Methyl-phenidate | Modafinil |
|---|---|---|---|---|
| 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 obstructive sleep apnea; 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, obstructive sleep apnea, 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 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 | ✔ | - | - | ✔ |


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| Warning(s)/Precaution(s) | Armodafinil | Dexmethyl-phenidate | Methyl-phenidate | Modafinil |
|---|---|---|---|---|
| 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 | ✔ | - | - | ✔ |
| Peripheral vasculopathy has been reported and digital ulceration and/or soft tissue breakdown may result, monitoring is recommended and dosage adjustment or discontinuation may be necessary. | - | ✔ | ✔ | - |
| 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 | ✔ | - | - | ✔ |
| Priapism has been reported with methylphenidate products in both pediatric and adult patients | - | ✔ | ✔ | - |
| 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-Johnson Syndrome; serious rash | ✔ | - | - | ✔ |


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

| 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**[22,29]

| 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 at bedtime and while in bed | - | ✔ |


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| Warning(s)/Precaution(s) | Atomoxetine | Sodium Oxybate |
|---|---|---|
| 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 attention deficit hyperactivity disorder | ✔ | - |

## Drug Interactions

**Table 10a. Drug Interactions-Anorexigenic Agents and Respiratory and Cerebral Stimulants-Amphetamines**[3,4,7-9,21,23]

| 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. | ✔ | ✔ | ✔ | ✔ |


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**Table 10b. Drug Interactions-Anorexigenic Agents and Respiratory and Cerebral Stimulants-Miscellaneous**[5,6,10,11,14-20,27,28]

| 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. | - | - | ✔ | - |
| Oral contraceptives: may reduce efficacy of oral contraceptives. | ✔ | - | - | ✔ |

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

| 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. | ✔ | - |
| Tizanidine: potentially symptomatic additive hypotension. | ✔ | - |
| 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**[22,29]

| Description | Atomoxetine | Sodium Oxybate |
|---|---|---|
| Barbiturates: increased sleep duration and central nervous system depression. | - | ✔ |
| Benzodiazepines: increased sleep duration and central nervous system depression. | - | ✔ |
| Buspirone: increased sleep duration and central nervous system depression. | - | ✔ |
| Central nervous system depressants: increased sleep duration and central nervous system depression. | - | ✔ |
| Monoamine oxidase inhibitors: increased risk of serious or fatal reactions. Coadministration is contraindicated. | ✔ | - |


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| Description | Atomoxetine | Sodium Oxybate |
|---|---|---|
| Quinidine: increased plasma concentrations and pharmacologic effects. | ✔ | - |
| 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. | ✔ | - |
| Yohimbine: increased risk of new or worsened preexisting supine hypertension in patients with autonomic failure. | ✔ | - |
| Zolpidem: increased sleep duration and central nervous system depression. | - | ✔ |

**Table 11. Dosing and Administration**[3-23,27-29]

| Generic Name | Adult Dose | Pediatric Dose | Availability |
|---|---|---|---|
| **Anorexigenic Agents and Respiratory and Cerebral Stimulants-Amphetamines** | | | |
| Amphetamine/ dextro-amphetamine salts | Treatment of ADHD:<br>Capsule (adults): 20 mg once daily in the morning<br><br>Tablet: 2.5 to 5 mg once or twice daily; maintenance, up to 40 mg/day<br><br>Narcolepsy:<br>Capsule, tablet (adults): 5 to 60 mg daily in divided doses | Treatment of ADHD:<br>Capsule: 10 mg once daily in the morning; maximum, 30 mg/day<br><br>Tablet: 2.5 to 5 mg once or twice daily; maintenance, up to 40 mg/day<br><br>Narcolepsy in children six to 12 years of age:<br>Capsule, tablet: 5 mg once daily; may increase by 5 mg weekly until optimal response<br><br>Narcolepsy in children 12 years of age and older:<br>Capsule, tablet: 10 mg once daily; may increase by 10 mg weekly until optimal response | Capsule:<br>5 mg<br>10 mg<br>15 mg<br>20 mg<br>25 mg<br>30 mg<br><br>Tablet:<br>5 mg<br>7.5 mg<br>10 mg<br>12.5 mg<br>15 mg<br>20 mg<br>30 mg |
| Dextro-amphetamine | Treatment of ADHD:<br>Solution, tablet: initial, 2.5 to 5 mg once or twice daily; maintenance, up to 40 mg/day<br><br>Sustained-release capsule: initial, 5 mg once or twice daily; maintenance, up to 40 mg/day<br><br>Narcolepsy: | Treatment of ADHD in children six years of age and older:<br>Solution, tablet: initial, 2.5 to 5 mg once or twice daily; maintenance, up to 40 mg/day<br><br>Sustained-release capsule: initial, 5 mg once or twice daily; maintenance, up to 40 mg/day<br><br>Narcolepsy in adolescents | Solution:<br>5 mg/5 mL<br><br>Sustained-release capsule:<br>5 mg<br>10 mg<br>15 mg<br><br>Tablet:<br>2.5 mg<br>5 mg<br>7.5 mg<br>10 mg |


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| Generic Name | Adult Dose | Pediatric Dose | Availability |
|---|---|---|---|
| | Solution, sustained-release capsule, tablet: 5 to 60 mg/day administered in divided doses | 12 years of age and older: Solution, sustained-release capsule, tablet: 5 to 60 mg/day administered in divided doses | |
| Lisdex-amfetamine | Treatment of ADHD: Capsule: initial, 30 mg once daily in the morning; maximum, 70 mg/day | Treatment of ADHD in children six years of age and older: Capsule: initial, 30 mg once daily in the morning; maximum, 70 mg/day | Capsule: 20 mg 30 mg 40 mg 50 mg 60 mg 70 mg |
| Meth-amphetamine | Exogenous obesity: Tablet: 5 mg taken one half hour before each meal<br><br>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<br><br>Treatment of ADHD in children six years of age and older: Tablet: initial, 5 mg once or twice daily; maintenance, 20 to 25 mg/day | Tablet: 5 mg |
| **Anorexigenic Agents and Respiratory and Cerebral Stimulants-Miscellaneous** | | | |
| Armodafinil | Improve wakefulness in patients with excessive sleepiness associated with obstructive sleep apnea and narcolepsy: Tablet: 150 or 250 mg once daily in the morning<br><br>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 | Safety and efficacy in children <17 years of age have not been established. | 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<br><br>Extended-release capsule (patients currently receiving methylphenidate): initial, | Treatment of ADHD in children six years of age and older: Extended-release capsule (new starts): initial, 5 to 10 mg once daily in the morning; maximum, 30 mg/day<br><br>Extended-release capsule (patients currently receiving | Extended-release capsule: 5 mg 10 mg 15 mg 20 mg 25 mg 30 mg 35 mg 40 mg<br><br>Tablet: |


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| Generic Name | Adult Dose | Pediatric Dose | Availability |
|---|---|---|---|
| | half the dose of racemic methylphenidate<br><br>Tablet (new starts): initial, 2.5 mg twice daily; maximum, 10 mg twice daily<br><br>Tablet (patients currently receiving methylphenidate): initial, half the dose of racemic methylphenidate; maximum, 10 mg twice daily | methylphenidate): initial, half the dose of racemic methylphenidate<br><br>Tablet (new starts): initial, 2.5 mg twice daily; maximum, 10 mg twice daily<br><br>Tablet (patients currently receiving methylphenidate): initial, half the dose of racemic methylphenidate; maximum, 10 mg twice daily | 2.5 mg<br>5 mg<br>10 mg |
| Methylphenidate | Treatment of ADHD:<br>Chewable tablet, solution, tablet: 20 to 30 mg/day administered in two or three divided doses<br><br>Extended-release capsule (new starts): initial, 20 mg once daily in the morning; maximum, 60 mg/day<br><br>Extended-release capsule (patients currently receiving methylphenidate): administer equivalent total daily doses<br><br>Extended-release suspension: initial, 20 mg once daily in the morning; maximum, 60 mg/day<br><br>Extended-release tablet (new starts): initial, 18 to 36 mg/day; maximum, 72 mg/day<br><br>Extended-release tablet (patients currently receiving methylphenidate): dosing is based on current dose regimen and clinical judgment | Treatment of ADHD:<br>Chewable tablet, solution, tablet: initial, 5 mg twice daily; maintenance, increase dose gradually<br><br>Extended-release tablet (new starts): initial, 18 mg once daily in the morning; maximum, 54 (children) and 72 mg/day (adolescents)<br><br>Extended-release tablet (patients currently receiving methylphenidate): dosing is based on current dose regimen and clinical judgment<br><br>Extended-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<br><br>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<br><br>Transdermal patch: initial, 10 mg; maintenance, titrate to effect | Chewable tablet:<br>2.5 mg<br>5 mg<br>10 mg<br><br>Extended-release capsule:<br>10 mg<br>20 mg<br>30 mg<br>40 mg<br>50 mg<br>60 mg<br><br>Extended-release capsule:<br>10 mg<br>20 mg<br>30 mg<br>40 mg<br><br>Extended-release suspension:<br>25 mg/ 5 mL<br><br>Extended-release tablet:<br>18 mg<br>27 mg<br>36 mg<br>54 mg<br><br>Extended-release tablet:<br>20 mg<br><br>Solution:<br>5 mg/5 mL<br>10 mg/5 mL<br><br>Sustained-release tablet:<br>20 mg |


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| Generic Name | Adult Dose | Pediatric Dose | Availability |
|---|---|---|---|
| | Extended-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<br><br>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<br><br>Transdermal patch: initial, 10 mg; maintenance, titrate to effect<br><br>Narcolepsy:<br>Chewable tablet, solution, tablet (adults): 20 to 30 mg/day administered in two or three divided doses<br><br>Extended-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<br><br>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 | Narcolepsy:<br>Chewable tablet, solution, tablet: initial, 5 mg twice daily; maintenance, increase dose gradually<br><br>Extended-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<br><br>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 | Tablet:<br>5 mg<br>10 mg<br>20 mg<br><br>Transdermal patch:<br>10 mg/9 hours (1.1.mg/hour)<br>15 mg/9 hours (1.6 mg/hour)<br>20 mg/9 hours (2.2 mg/hour)<br>30 mg/9 hours (3.3 mg/hour) |
| Modafinil | Improve wakefulness in patients with excessive sleepiness associated with obstructive sleep apnea and narcolepsy:<br>Tablet: 200 mg once daily in the morning | Safety and efficacy in children <17 years of age have not been established. | Tablet:<br>100 mg<br>200 mg |


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| Generic Name | Adult Dose | Pediatric Dose | Availability |
|---|---|---|---|
| | 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 | | |
| **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 six 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 six 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; maintenance, 80 mg/day; maximum, 100 mg/day | Treatment of ADHD: Capsule (≤70 kg): initial, 0.5 mg/kg/day; maintenance, 1.2 mg/kg/day; maximum, 1.4 mg/kg/day | Capsule: 10 mg 18 mg 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 children <16 years of age have not been established. | Solution: 500 mg/mL (180 mL) |

ADHD=attention deficit hyperactivity disorder


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## 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)**[24] | Preschool-aged children (four to five years of age)<br>• The primary care clinician should prescribe evidence-based parent- and/or teacher-administered behavior therapy as the first-line of treatment.<br>• 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.<br><br>Elementary school-aged children (six to 11 years of age)<br>• The primary care clinician should prescribe Food and Drug Administration (FDA)-approved medications for attention deficit-hyperactivity disorder (ADHD) and/or evidence-based parent and/or teacher-administered behavior therapy as treatment for ADHD, preferably both.<br>• 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).<br><br>Adolescents (12 to 18 years of age)<br>• 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.<br><br>General considerations<br>• Stimulant medications are highly effective for most children in reduction of core symptoms of ADHD.<br>• Atomoxetine, extended-release guanfacine and extended-release clonidine reduce core symptoms; however, they have a smaller evidence base than stimulants.<br>• Extended-release guanfacine and extended-release clonidine have evidence to support their use as adjunctive therapy with stimulant medications.<br>• Before beginning medication treatment for adolescents with newly diagnosed ADHD, clinicians should assess these patients for symptoms of substance abuse.<br>• Clinicians should monitor symptoms and prescription-refill requests for signs of misuse or diversion of ADHD medications and consider prescribing medications with no abuse potential, such as atomoxetine, extended-release guanfacine, or extended-release clonidine (which are not stimulants) or stimulant medications with less abuse potential, such as lisdexamfetamine, dermal methylphenidate, or osmotic-release oral system methylphenidate).<br>• 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** | Medication trials<br>• Prescribe FDA-approved treatments for ADHD in children, including psychostimulants and/or non-stimulants.<br>• 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. |


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| **Adolescents (2012)**[31] | • Obtain cardiology consultation for patients with known structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems that could place patients at an increased risk to the sympathomimetic effects of central nervous system stimulants and/or atomoxetine.<br>• Review the personal and family cardiovascular history, and complete a physical examination of each patient prior to starting stimulant therapy and/or atomoxetine. Medication history or physical exam changes consistent with possible cardiac disease during treatment with stimulant medication and/or atomoxetine may require additional evaluation by a cardiologist.<br>• Optimal medication management alone is superior to other modalities for the core symptoms of ADHD.<br>• 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.<br>• Treatment with psychostimulants is often safe and effective in managing many children with ADHD with mild to moderate tics. Nevertheless, frequency and severity of tics should be carefully monitored in these patients. No routine blood work is necessary before or during psychostimulant therapy.<br>• Current evidence does not support a higher risk of sudden cardiac death with stimulant medication compared to the general population; however, certain conditions may place a patient at higher risk for such an outcome.<br>• 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.<br>• Extended-release guanfacine and extended-release clonidine are the first ADHD medications to achieve FDA approval as adjunctive therapy with stimulant medications.<br>• Extended-release guanfacine is the first ADHD medication to look for improvement of oppositional symptoms in addition to ADHD core symptoms.<br><br><u>Alternative medications</u><br>• When adequate stimulant, atomoxetine or alpha adrenergic trials are unsuccessful due to either poor response or adverse effects, or if associated comorbidity is present, alternative medication trials should be considered. Second-line medications for ADHD therapy include tricyclic antidepressants (imipramine, desipramine), alpha adrenergic agonist (clonidine) a non- tricyclic antidepressant (bupropion), or immediate-release guanfacine. |
| National Institute for Health and Clinical Excellence: **Attention Deficit Hyperactivity Disorder: Diagnosis and Management of Attention Deficit Hyperactivity Disorder in Children, Young People, and** | <u>Treatment for children and adolescents with ADHD</u><br>• Methylphenidate, atomoxetine and dexamphetamine are recommended as options for the management of ADHD in children and adolescents.<br>• The decision regarding which product to use should be based on the following:<br>  o The presence of comorbid conditions.<br>  o The different adverse effects of the drugs.<br>  o Specific issues regarding compliance identified for the individual child or adolescent.<br>  o The potential for drug diversion.<br>  o The preferences of the child/adolescent and/or his or her parent or |


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| **Adults (2008)**[32] | guardian.<br>• Healthcare professionals should consider the following treatment recommendations:<br>o Methylphenidate for patients with ADHD without significant comorbidities.<br>o Methylphenidate for patients with ADHD with comorbid conduct disorder.<br>o Methylphenidate or atomoxetine when tics, Tourette's syndrome, anxiety disorder, stimulant misuse or risk of stimulant diversion are present.<br>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.<br>• Modified-release preparations should be considered for the following reasons:<br>o Convenience.<br>o Improving adherence.<br>o Reducing stigma (because the child or young person does not need to take medication at school).<br>o Reducing problems schools have in storing and administering controlled drugs.<br>o Their pharmacokinetic profiles.<br>• Immediate-release preparations may be considered if more flexible dosing regimens are required, or during initial titration to determine correct dosing levels.<br><br><u>Treatment of adults with ADHD</u><br>• Drug treatment is the first-line treatment for adults with ADHD with either moderate or severe levels of impairment.<br>• Methylphenidate is recommended as the first-line drug.<br>• If methylphenidate is ineffective or unacceptable, atomoxetine or dexamphetamine can be tried.<br>• 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.<br>• Stimulants have been shown to be highly effective for the treatment of ADHD in many clinical trials.<br>• Available evidence suggests that both methylphenidate and amphetamines are equally efficacious in the treatment of ADHD.<br>• 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.<br>• The long-acting formulations are equally efficacious as immediate-release formulations.<br>• 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.<br>• 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 |


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| | remit, or side effects prevent further titration.<br>• 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.<br>• Some patients may respond similarly to different stimulant classes; whereas, other patients may preferentially respond to only one class of stimulants. There is no method to predict which stimulant will produce the best response in a given patient.<br>• 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.<br>• In studies published comparing atomoxetine to stimulants, greater efficacy was seen in those patients treated with stimulants.<br>• Atomoxetine may have less pronounced effects on appetite and sleep than stimulants, although they may produce relatively more nausea or sedation.<br>• 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.<br>• 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)**[33] | Treatment recommendations for children<br>• Proven first-line treatments in children include psychostimulants and atomoxetine.<br>• Second-line treatment options include imipramine and bupropion.<br>• Clonidine and guanfacine may be used as adjunctive treatments.<br>• Qualitative assessments suggest that all agents are more effective than placebo and have similar efficacy; however, there have been few head-to-head comparisons.<br>• The agents are not equivalent in terms of adverse effects.<br>• The response to different agents varies between individuals and with different doses.<br><br>Treatment recommendations for adults<br>• Drug treatment needs to be chosen and adapted to best fit the individual, including the patient's preferences and concerns.<br>• Use of methylphenidate in adults has been shown to demonstrate similar drug response effect to that seen in children.<br>• 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.<br><br>Abuse potential<br>• 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** | • Most of the agents used to treat excessive sleepiness have little effect on cataplexy or other rapid eye movement sleep associated symptoms. Most antidepressants and anticataplectics have little effect on alertness. |


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| **for the Treatment of Narcolepsy and Other Hypersomnias of Central Origin (2007)**[34] | 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.<br>• Modafinil is effective for treatment of daytime sleepiness due to narcolepsy.<br>• Sodium oxybate is effective for treatment of cataplexy, daytime sleepiness, and disrupted sleep due to narcolepsy. Sodium oxybate may be effective for treatment of hypnagogic hallucinations and sleep paralysis.<br>• Amphetamine, methamphetamine, dextroamphetamine, and methylphenidate are effective for treatment of daytime sleepiness due to narcolepsy.<br>• Selegiline may be an effective treatment for cataplexy and daytime sleepiness.<br>• Tricyclic antidepressants, selective serotonin reuptake inhibitors, and venlafaxine may be effective treatment for cataplexy.<br>• Scheduled naps can be beneficial to combat sleepiness, but seldom suffice as primary therapy for narcolepsy. |
| European Federation of Neurological Sciences: **Guidelines on Management of Narcolepsy in Adults (2011)**[35] | <u>Excessive daytime sleepiness and irresistible episodes of sleep</u><br>• Modafinil should be prescribed when excessive daytime sleepiness is present. Modafinil should be dosed as 100 to 400 mg/day, given once in the morning or twice daily.<br>• Sodium oxybate may be used when excessive daytime somnolence coexists with cataplexy and poor sleep. Depressed patients should not receive sodium oxybate.<br>• Sodium oxybate should be initiated with 4.5 g/night, increasing by increments of 1.5 g at four-week intervals and should not be used with other sedatives, respiratory depressants or muscle relaxants. Monitor patients for possible development of sleep-disordered breathing. Adverse effects may limit the dose, and require slower titration.<br>• The optimal response on excessive daytime sleepiness may take up to 12 weeks.<br>• Supplementation with modafinil is generally more successful than sodium oxybate alone.<br>• Methylphenidate may be considered if modafinil is insufficient and sodium oxybate is not recommended.<br>• The short-acting effect of methylphenidate is of interest when modafinil needs to be supplemented at a specific time of the day, or in situations where maximum alertness is required.<br><br><u>Cataplexy</u><br>• First-line pharmacological treatment of cataplexy is sodium oxybate at a starting dose of 4.5 g/night divided into two equal doses of 2.25 g/night. The dose may be increased to a maximum of 9 g/night, divided into two equal doses of 4.5 g/night, by increments of 1.5 g at two-week intervals.<br>• Adverse effects may limit the dose, and require slower titration and the optimal response on excessive daytime sleepiness may take up to 12 weeks.<br>• Antidepressants are recommended as second-line pharmacological treatment. Tricyclic antidepressants, particularly clomipramine (10 to 75 mg), are potent anticataplectic drugs; however, anticholinergic adverse effects are common.<br>• Selective serotonin reuptake inhibitors are slightly less active but have |


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| | fewer adverse effects.<br>• Venlafaxine is widely used but clinical evidence supporting its use is limited.<br>• Reboxetine and atomoxetine, also lack published clinical evidence.<br>• Given the efficacy of sodium oxybate and antidepressants, the place for other compounds is fairly limited.<br>• There is no accepted behavioral treatment of cataplexy.<br><br>Poor sleep<br>• Sodium oxybate appears to be the most appropriate to treat poor sleep.<br>• Benzodiazepine or non-benzodiazepine hypnotics may be effective in consolidating nocturnal sleep, but objective evidence is lacking over intermediate- or long-term follow-up.<br>• The improvement in poor sleep reported by some patients once established on modafinil is noteworthy.<br><br>Obstructive sleep apnea/hypopnea syndrome, periodic limb movements in sleep, neuropsychiatric symptoms<br>• Obstructive sleep apnea/hypopnea syndrome should be similarly in narcoleptic patients and general population, although continuous positive airway pressure does not improve excessive daytime sleepiness in most narcolepsy subjects.<br>• There is usually no need to treat periodic limb movements in narcoleptic patients. Antidepressants and psychotherapy should be used in depressed narcoleptic patients as in non-narcoleptic depressed patients. |
| American Academy of Sleep Medicine: **Clinical Guideline for the Evaluation, Management and Long-term Care of Obstructive Sleep Apnea in Adults (2009)**[25] | Weight reduction<br>• Successful dietary weight loss may improve the apnea-hypopnea index in obese obstructive sleep apnea patients.<br>• Dietary weight loss should be combined with a primary treatment for obstructive sleep apnea.<br>• Bariatric surgery may be adjunctive in the treatment of obstructive sleep apnea in obese patients.<br><br>Pharmacologic agents<br>• Modafinil is recommended for the treatment of residual excessive daytime sleepiness in obstructive sleep apnea patients who have sleepiness despite effective positive airway pressure treatment and who are lacking any other identifiable cause for their sleepiness.<br>• Selective serotonin reuptake inhibitors, protriptyline, methylxanthine derivatives (aminophylline and theophylline), and estrogen therapy are not recommended for treatment of obstructive sleep apnea.<br><br>Supplemental oxygen<br>• Oxygen supplementation is not recommended as a primary treatment for obstructive sleep apnea.<br><br>Medical therapies intended to improve nasal patency<br>• Short-acting nasal decongestants are not recommended for treatment of obstructive sleep apnea.<br>• Topical nasal corticosteroids may improve the apnea-hypopnea index in patients with obstructive sleep apnea and concurrent rhinitis, and thus may be a useful adjunct to primary therapies for obstructive sleep apnea. |


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| | Positional therapies<br>• Positional therapy is an effective secondary therapy or can be a supplement to primary therapies for obstructive sleep apnea in patients who have a low apnea-hypopnea index in the non-supine vs that in the supine position. |
| American Academy of Sleep Medicine: **Practice Parameters for the Clinical Evaluation and Treatment of Circadian Rhythm Sleep Disorders (2007)**[36] | Shift work disorder<br>• Planned napping before or during the night shift is indicated to improve alertness and performance among night shift workers.<br>• 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.<br>• Administration of melatonin prior to daytime sleep is indicated to promote daytime sleep among night shift workers.<br>• 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.<br>• Modafinil is indicated to enhance alertness during the night shift for shift work disorder.<br>• 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), atomoxetine (Strattera®), clonidine extended-release (Kapvay®) and guanfacine extended-release (Intuniv®).[3-23] The cerebral stimulants are classified as Schedule II controlled substances, and are associated with Boxed Warnings regarding risk of abuse.[3-21,23] Atomoxetine, clonidine extended-release and guanfacine extended-release are not classified as controlled substances.[12,13,22] 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] Both agents are available generically in immediate-release formulations; however, these formulations are not FDA-approved 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] Atomoxetine is associated with a Boxed Warning regarding an increased risk of suicidal ideation observed in short-term trials in children and adolescents with ADHD.[22,37]

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 (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.[27,28] Sodium oxybate (Xyrem®) is γ-hydroxybutyric acid, 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.[29]

There are currently several generic ADHD agents and stimulants. At least one short-, intermediate- and long-acting agents are available generically.[30] Several clinical trials have demonstrated the effectiveness of the ADHD agents and stimulants in their respective FDA-approved indications. Evidence consistently


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demonstrates that these agents significantly improve ADHD and sleepiness rating scales compared to placebo. 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.[38-156] 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.[2,24,31-33] With regard to the use of non stimulant 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.[24] With regard to the treatment of ADHD in adults, methylphenidate is recommended first-line, with atomoxetine and dexamphetamine recommended second line.[32,33] 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 following its approval.[25,34-36]


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