# Stimulants and Related Agents
# Therapeutic Class Review (TCR)

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## FDA-APPROVED INDICATIONS

| Drug | Manufacturer | ADHD | | | Narcolepsy (Age ≥ 6 years) | Other Indications |
|---|---|---|---|---|---|---|
| | | Age 3–5 years | Age ≥ 6 years | Adults | | |
| **Stimulants: Immediate-Release (IR)** | | | | | | |
| amphetamine sulfate tablet (Evekeo®)[1] | generic, Arbor | X | X | -- | X | Exogenous obesity age ≥ 12 years |
| amphetamine sulfate orally disintegrating tablet (ODT) (Evekeo ODT®)[2] | Arbor | --* | X | -- | -- | -- |
| armodafinil (Nuvigil®)[3] | generic, Cephalon | -- | -- | -- | -- | Excessive sleepiness associated with narcolepsy, OSA†, and SWD for age ≥ 17 years |
| dexmethylphenidate IR (Focalin®)[4] | generic, Novartis | -- | X | -- | -- | -- |
| dextroamphetamine IR tablets[5] | generic | X | X (≤ 16 years) | -- | X | -- |
| dextroamphetamine solution[6] | generic | X | X (≤ 16 years) | -- | X | -- |
| methamphetamine (Desoxyn®)[7] | generic, Recordati | -- | X | -- | -- | Exogenous obesity in adults and adolescents ≥ 12 years |
| methylphenidate IR (Methylin®, Ritalin®)[8,9] | generic, Shionogi, Novartis | -- | X | -- | X | -- |
| mixed amphetamine salts IR (Adderall®)[10] | generic, Teva | X | X | -- | X | -- |
| modafinil (Provigil®)[11] | generic, Cephalon/Teva | -- | -- | -- | -- | Excessive sleepiness associated with narcolepsy, OSA†, and SWD for age ≥ 17 years |

OSA – obstructive sleep apnea; SWD – shift work disorder

* In September 2022, the FDA approved the removal of the ADHD indication for patients 3 to 5 years of age from the product labeling for amphetamine sulfate ODT (Evekeo ODT). Approval for use in this age group remains in the labeling for amphetamine sulfate tablet (Evekeo).

† In OSA, modafinil and armodafinil are indicated as an adjunct to standard treatment(s) (e.g., continuous positive airway pressure [CPAP]) for the underlying obstruction.


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### *FDA-Approved Indications (continued)*

| Drug | Manufacturer | ADHD | | | Narcolepsy (age ≥ 6 years) | Other Indications |
|---|---|---|---|---|---|---|
| | | Age 3–5 years | Age ≥ 6 years | Adults | | |
| **Stimulants: Extended-Release (ER)** | | | | | | |
| amphetamine ER (Adzenys XR-ODT®)[12] | Neos/Aytu | -- | X | X | -- | -- |
| amphetamine ER (Dyanavel® XR)[13] | Tris | -- | X | X | -- | -- |
| dexmethylphenidate ER (Focalin XR®)[14] | generic, Novartis | -- | X | X | -- | -- |
| dextroamphetamine ER (Dexedrine®)[15] | generic, Amneal | -- | X (≤ 16 years) | -- | X | -- |
| lisdexamfetamine dimesylate (Vyvanse®)[16] | Shire | -- | X | X | -- | Moderate to severe binge eating disorder in adults |
| methylphenidate ER‡[17] | generic | -- | X | -- | -- | -- |
| methylphenidate ER (Adhansia XR®)[18] | Adlon | -- | X | X | -- | -- |
| methylphenidate ER (Aptensio XR®)[19] | generic, Rhodes | -- | X | X | -- | -- |
| methylphenidate ER (Cotempla XR-ODT®)[20] | Neos/Aytu | -- | X (≤17 years) | -- | -- | -- |
| methylphenidate ER (Jornay PM®)[21] | Ironshore | -- | X | X | -- | -- |
| methylphenidate ER§[22] | generic, Upstate | -- | X | X | X | -- |
| methylphenidate ER (Quillichew ER®)[23] | Tris | -- | X | X | -- | -- |
| methylphenidate ER (Quillivant XR®)[24] | Tris | -- | X | X | -- | -- |
| methylphenidate ER (Ritalin LA®)[25] | generic, Novartis | -- | X | -- | -- | -- |
| methylphenidate ER OROS (Concerta®)[26] | generic, Janssen | -- | X | X ≤ 65 years | -- | -- |
| methylphenidate ER OROS (Relexxii®)[27] | Vertical | -- | X | X (≤ 65 years) | -- | -- |
| methylphenidate transdermal (Daytrana®)[28] | Noven, Mylan | -- | X | -- | -- | -- |
| mixed amphetamine salts ER (Adderall XR®)[29] | generic, Shire | -- | X | X | -- | -- |
| mixed amphetamine salts ER (Mydayis®)[30] | Shire | -- | -- | X (≥ 13 years) | -- | -- |
| serdexmethylphenidate/ dexmethylphenidate (Azstarys®)[31] | Corium/Prasco | -- | X | X | -- | -- |

‡ Generics of Metadate CD

§Generics of Metadate ER, Ritalin SR, and Methylin ER


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***FDA-Approved Indications (continued)***

| Drug | Manufacturer | ADHD | | | Narcolepsy (age ≥ 6 years) | Other Indications |
|---|---|---|---|---|---|---|
| | | Age 3–5 years | Age ≥ 6 years | Adults | | |
| **Non-Stimulants** | | | | | | |
| atomoxetine (Strattera®)[32] | generic, Eli Lilly | -- | X | X | -- | -- |
| clonidine ER (Kapvay®)[33] | generic, Concordia | -- | X | -- | -- | Treatment of ADHD as adjunct to stimulants |
| guanfacine ER (Intuniv®)[34] | generic, Shire | -- | X | -- | -- | Treatment of ADHD as adjunct to stimulants |
| pitolisant (Wakix®)[35] | Harmony | -- | -- | -- | X¶ (adults only) | -- |
| solriamfetol (Sunosi®)[36] | Jazz/Axsome | -- | -- | -- | X‖ (adults only) | OSA (adults)** |
| viloxazine (Qelbree®)[37] | Supernus | -- | X | X | -- | -- |

OSA – obstructive sleep apnea; SWD – shift work disorder

¶ Pitolisant is indicated for the treatment of excessive daytime sleepiness or cataplexy in adults with narcolepsy.

‖ Solriamfetol is indicated for the treatment of excessive daytime sleepiness in adults with narcolepsy.

**Solriamfetol is not indicated to treat underlying airway obstruction in OSA. The underlying airway obstruction must be treated (e.g., with continuous positive airway pressure [CPAP]) for ≥ 1 month before initiating solriamfetol for EDS. Any treatment used for the underlying airway obstruction should be continued throughout treatment with solriamfetol.

Stimulant agents amphetamine, dexmethylphenidate, dextroamphetamine, lisdexamfetamine, methamphetamine, methylphenidate, mixed amphetamine salts, and serdexmethylphenidate/dexmethylphenidate are Scheduled II controlled substances, and armodafinil, modafinil, and solriamfetol are Scheduled IV controlled substances.

# OVERVIEW

## Attention Deficit Hyperactivity Disorder (ADHD)

Stimulants are the most common medication used for the treatment of ADHD, for which they are considered first-line pharmacologic therapy.[38,39] ADHD is one of the most prevalent childhood disorders and can continue into adulthood. According to data based on survey results from 2016 to 2019, ADHD has been diagnosed in approximately 9.8 % of children 3 to 17 years of age, and diagnosis is more often made in boys than girls (13% versus 6%, respectively).[40] Nearly two-thirds of children and adolescents with ADHD are taking medication to treat the condition, and approximately half receive behavioral therapy. ADHD is a chronic condition with core symptoms of inattention, hyperactivity, and difficulty controlling behavior.[41] It may also be accompanied by internalized disorders, such as depression and anxiety, as well as conduct and disruptive behavior disorders, autism spectrum disorder, and tics.[42] The 3 main types of ADHD are primary hyperactive, primary inattentive, and combined.[43]

Children with ADHD may experience academic underachievement, difficulties in personal relationships, and low self-esteem.[44,45] Early recognition of the signs and symptoms of ADHD, assessment, and treatment can help redirect the educational and social development of most children with ADHD.


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According to the 2019 ADHD guidelines developed by a subcommittee of the American Academy of Pediatrics (AAP), the primary care clinician should initiate an evaluation for ADHD for any child 4 through 18 years of age who presents with academic or behavioral problems and symptoms of inattention, hyperactivity, or impulsivity.[46] The AAP guidelines now include a recommendation to screen patients for comorbidities such as depression, anxiety, and substance use. The treatment of patients with ADHD should maximize function to improve relationships and performance at school, decrease disruptive behaviors, promote safety, increase independence, and improve self-esteem.

The AAP recommends parent- and/or teacher-administered behavior therapy as first-line treatment for children 4 to 5 years of age.[47] Methylphenidate (MPH) may be prescribed if the behavior interventions do not provide significant improvement and there continues to be moderate to severe disturbance in the child's function. For children 6 to 11 years of age, the evidence is particularly strong for FDA-approved stimulant use for ADHD, and sufficient, but less compelling for non-stimulants in the following order: atomoxetine (Strattera), guanfacine ER (Intuniv) and clonidine ER (Kapvay). Medication therapy in addition to behavioral therapy is recommended. For patients 12 to 18 years of age, the AAP recommends FDA-approved medications, with the adolescent's assent, and behavior therapy as treatment for ADHD, preferably both.

Numerous studies indicate that stimulants are effective in the treatment of ADHD in preschool children.[48,49] Some have expressed concern that the use of neuropsychiatric drugs in children in this age group could have long-term effects on neurotransmitters in the brain.[50] The 2007 American Academy of Child and Adolescent Psychiatry (AACAP) practice parameters for ADHD recommend individualized and comprehensive treatment plans for patients with ADHD.[51] Initial psychopharmacological treatment should be a trial with an FDA-approved agent for this age group. If satisfactory results are not achieved, the diagnosis of ADHD should be assessed and referral to a child and adolescent psychiatrist considered. The addition of behavior therapy may be beneficial. Off-label use of bupropion, tricyclic antidepressants, and α-agonists have been used in select pediatric patients. Periodic assessment should be performed to determine continued need for treatment or if symptoms have remitted and for effect of treatment on patient height and weight; treatment should continue while symptoms remain present and have patient impact. The AACAP practice parameters for ADHD are now categorized as historical and can no longer be assumed to reflect current knowledge, as they have not been updated in over 5 years.[52]

Symptoms of ADHD tend to improve with age; however, this may be due in part to improved coping skills. The continuation of synaptogenesis and myelinization into adolescence and young adulthood (especially in the frontal lobes) may also play a role in the improvement of symptoms.[53,54,55] ADHD symptoms can persist into adulthood.[56] The prevalence of ADHD in adults is estimated to range from 2% to 7%.

Studies have shown that 70% to 75% of patients respond to the first stimulant medication on which they are started.[57] Response increases to 90% to 95% when a second stimulant is tried. Treatment failures with stimulants are often due to improper doses rather than ineffectiveness of the medication. It may take 1 to 3 months to adequately establish the best dose and formulation for an individual patient. The AAP recommends that, if a trial with 1 drug compound group is ineffective or poorly tolerated, a trial of a medication from a different drug group should be used.[58]


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## Hypersomnolence

Excessive sleepiness, or hypersomnolence, is the primary and often debilitating symptom experienced by patients with narcolepsy, obstructive sleep apnea (OSA), and shift work sleep disorder (SWSD).[59] The defining characteristic of hypersomnolence is a consistent inability to stay awake and alert to safely and successfully accomplish tasks of daily living. Persons experiencing excessive sleepiness who seek medical attention typically complain of fatigue, tiredness, lapses of attention, lack of energy, low motivation, difficulty concentrating, disrupted sleep, snoring, or difficulties at work.

While continuous positive airway pressure (CPAP) therapy has been shown to improve daytime sleepiness in patients with OSA, the level of sleepiness does not always normalize.[60,61,62,63,64,65] To address this residual daytime sleepiness, pharmacologic treatments may be beneficial in users of CPAP. Modafinil (Provigil), armodafinil (Nuvigil), and solriamfetol (Sunosi) are FDA-approved for excessive daytime sleepiness associated with OSA. Modafinil and armodafinil are also indicated for sleep problems resulting from circadian rhythm disruption (e.g., SWSD).[66]

Modafinil, armodafinil, pitolisant (Wakix), and solriamfetol, along with central nervous system (CNS) stimulants, such as dextroamphetamine (immediate release tablets and oral solution, Dexedrine), methylphenidate (Methylin, Ritalin, Metadate ER, Ritalin LA, Ritalin SR), mixed amphetamine salts (Adderall), and amphetamine sulfate tablet (Evekeo), are used for narcolepsy. The potential for adverse cardiovascular events with CNS stimulant use may be of concern, especially in this overall high-risk patient population. Due to their lack of sympathomimetic activity, modafinil and armodafinil are relatively free of adverse cardiovascular effects.[67]

In 2021, the American Academy of Sleep Medicine published a systematic review and meta-analysis on the treatment of central disorders of hypersomnolence (108 studies with data suitable for inclusion) using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) process.[68] Regarding the treatment of narcolepsy with armodafinil, the overall quality of evidence was moderate and clinical thresholds were met for excessive daytime sleepiness and disease severity. Modafinil was also found to have moderate quality of evidence with clinical thresholds met for excessive daytime sleepiness, cataplexy, disease severity, and quality of life. Evidence for dextroamphetamine was found to be very low but clinical thresholds were met for the critical outcomes of excessive daytime sleepiness and cataplexy. Evidence for methylphenidate was found to be very low but clinical thresholds were met for the critical outcomes of excessive daytime sleepiness and disease severity. Pitolisant was found to have a high quality of evidence with clinical thresholds met for excessive daytime sleepiness, cataplexy, and disease severity. Evidence for solriamfetol was also found to be high with clinical thresholds met for excessive daytime sleepiness, disease severity, or quality of life. In general, fatigue and sleep quality were considered important outcomes, but were not considered critical for decision-making for these interventions. Several other interventions were also evaluated and graded. While patients with excessive daytime sleepiness due to other medical conditions were addressed, no specific findings were evaluated explicitly for excessive daytime sleepiness due to sleep apnea or shift work. As a result of their findings of all evaluated agents, the AASM developed several guideline statements for the treatment of hypersomnolence.[69] For adults with narcolepsy, the group strongly recommends treatment with the following agents: modafinil, pitolisant, sodium oxybate, and solriamfetol. For adults with narcolepsy, the group conditionally suggests treatment with the following agents: armodafinil, dextroamphetamine, and methylphenidate. For pediatric patients with narcolepsy, the group conditionally suggests treatment with modafinil and sodium oxybate. Notably, modafinil is


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not approved for this use in pediatric patients. Sodium oxybate is not included in this Therapeutic Class Review.

## Exogenous Obesity

Stimulants may have other CNS actions or metabolic effects, in addition to appetite suppression, that result in weight-loss.[70] In relatively short-term clinical trials, adult subjects instructed in dietary management and treated with stimulants lost more weight on average than those treated with placebo and diet. However, the magnitude of increased weight loss of drug-treated patients over placebo-treated patients is only a fraction of a pound per week. The study showed that the rate of weight loss is greatest in the first weeks of therapy for both drug and placebo subjects and tends to decrease in subsequent weeks. Studies have not permitted conclusions regarding the relative importance of drug and non-drug factors on weight loss. Furthermore, natural history of obesity is measured in years, whereas studies cited are limited to a few weeks; therefore, the impact of weight loss due to medication versus diet alone must be considered clinically limited. Methamphetamine (Desoxyn) and amphetamine sulfate tablet (Evekeo) are FDA-approved for short-term adjunctive therapy in adults on a weight reduction regimen (based on caloric restriction) in whom obesity is refractory to alternative therapy.

## Binge-Eating Disorder

Binge-eating disorder (BED) is the most common eating disorder in the United States (US) with 3.5% of women and 2% of men experiencing BED during their lifetime.[71] BED is characterized by uncontrolled eating occurring at least once every week for 3 months and ≥ 3 of the following behaviors: eating rapidly, eating until uncomfortably full, eating when not hungry, eating alone due to embarrassment, and/or feelings of guilt after eating. The 2006 Practice Guidelines for the Treatment of Patients with Eating Disorders from the American Psychiatric Association (APA) suggest that serotonin reuptake inhibitor (SSRI) treatment is associated with at least a short-term reduction in BED symptoms, but not with considerable weight loss.[72] The APA practices guidelines and guideline watch are more than 5 years old and can no longer be assumed to be current; they are included in this class review for historical purposes; updated guidelines are expected in the winter of 2023.[73] Additional studies support the off-label use of imipramine, sertraline, citalopram, escitalopram, and topiramate for BED. Lisdexamfetamine dimesylate (Vyvanse) is the first and only FDA-approved product for moderate to severe BED in adults. Lisdexamfetamine dimesylate is not indicated for weight loss and it is not known if it is safe and effective for obesity treatment.

# PHARMACOLOGY[74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100,101102,103,104,105,106,107,108,109,110,111]

Stimulants act by blocking the reuptake of norepinephrine and dopamine into the presynaptic neuron and increasing their release into the extraneuronal space. Amphetamines appear to release newly synthesized dopamine while MPH causes the release of stored dopamine.[112] Unlike MPH, the amphetamine-induced elevation of synaptic dopamine does not appear to be highly dependent upon impulse-released dopamine. Stimulants tend to have selectivity for cortical, rather than striatal, dopamine presynaptic terminals. As a result, lower doses have more of an effect on attention than on motor activity.


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Symptoms of inattention in ADHD may be due to dopamine and/or norepinephrine dysfunction in critical areas of the cerebral cortex controlling cognition. It appears that patients with inattention symptoms need a boost in their dopamine/norepinephrine levels and, when they are given agents such as stimulants that boost these systems, their symptoms of inattentiveness can improve.

Symptoms of hyperactivity and impulsivity associated with ADHD are more likely mediated by the nigrostriatal dopamine pathway, which controls motor activity. Due to a presumed greater sensitivity of the mesocortical dopamine terminals in patients with ADHD, lower doses of stimulants prefer the cerebral cortex. Thus, the effects of stimulants on inattentiveness usually appear before their effects on motor behaviors.

Amphetamine and MPH are available as racemic or single isomer products. The d-enantiomer of amphetamine, dextroamphetamine (immediate-release tablets and oral solution, Dexedrine), has much less of an effect on norepinephrine release than the l-enantiomer. Thus, the combination of the 2 isomers of amphetamine may provide additional benefit over dextroamphetamine in some patients. This combination is available as mixed amphetamine salts (Adderall, Adderall XR, Mydayis), which contains d- and l-amphetamine in a 3:1 ratio, amphetamine sulfate (Evekeo, Evekeo ODT), which contains d- and l- amphetamine in a 1:1 ratio, amphetamine extended-release (Dyanavel XR), which contains d- and l- amphetamine in a 3.2:1 ratio, or amphetamine extended-release (Adzenys XR-ODT), which contains d- and l- amphetamine in a 3:1 ratio.[113] Mixed amphetamine salts tend to have fewer adrenergic side effects than MPH. MPH is a racemic mixture of d- and l-enantiomers, the former of which is more pharmacologically active.[114,115] A product containing only the d-enantiomer, dexmethylphenidate (Focalin, Focalin XR), is also available. Lisdexamfetamine dimesylate (Vyvanse) is a prodrug in which d-amphetamine is covalently bonded to L-lysine and converted to these components by enzymatic hydrolysis, during first-pass intestinal and/or hepatic metabolism.[116] Serdexmethylphenidate, a component of Azstarys, is a prodrug of dexmethylphenidate. Azstarys capsules contain a fixed molar ratio of 30% dexmethylphenidate and 70% serdexmethylphenidate.

Compared to immediate-release dosage forms, advantages of extended-release preparations include less fluctuation in activity and elimination of the need for dose administration in school. Their prolonged action, however, may be less intense, and their use forfeits the advantages of flexibility and control of titrating than the more frequent dosing schedule of immediate-release dosage forms.[117] It is also important that extended-release dosage forms do not produce a flat stimulant plasma concentration, which could lead to acute tolerance.[118] There is increasing experience with combining immediate- and extended-release preparations to produce optimal symptom control throughout the day.

Atomoxetine (Strattera) is a selective inhibitor of the presynaptic norepinephrine transporter. It increases norepinephrine and dopamine levels, especially in the prefrontal cortex.[119] It has minimal affinity for other monoamine transporters. Its mechanism of action suggests that atomoxetine is unlikely to have abuse potential or to cause motor tics.[120,121] Atomoxetine has a slower onset of action than stimulants; therapeutic effects may not be seen until a week after the start of treatment. It also has a longer duration of action compared to stimulants with the possibility of symptom relief during the evening and early-morning hours.[122]

Guanfacine ER (Intuniv) is a selective alpha-2A-adrenergic receptor agonist. Clonidine ER (Kapvay) is a centrally acting alpha-2-adrenergic receptor agonist. These drugs reduce sympathetic nerve impulses to the heart and blood vessels leading to a decrease in blood pressure. This mechanism of action in the treatment of ADHD is not known.


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Viloxazine (Qelbree) is a selective norepinephrine reuptake inhibitor (SNRI). Its mechanism of action in the treatment of ADHD is not clear, but it may work by inhibiting the reuptake of norepinephrine.

Modafinil (Provigil) appears to act by selective activation of the cortex without generalized stimulation of the CNS. It has wake-promoting actions like the sympathomimetic agents. It also causes psychoactive and euphoric effects, as well as alterations in mood, perception, thinking, and feelings typical of other CNS stimulants. *In vitro*, modafinil binds to the dopamine reuptake site and causes an increase in extracellular dopamine. *In vivo* models, however, have not detected enhanced dopaminergic activity. Modafinil may also work through other neurotransmitter systems. Armodafinil (Nuvigil) is the R-enantiomer of modafinil. Both armodafinil and modafinil have similar pharmacological properties.

The mechanism by which pitolisant (Wakix) improves excessive daytime sleepiness in patients with narcolepsy is not fully elucidated; however, pitolisant has high affinity for histamine-3 (H3) receptors which are primarily found in the CNS. Via its actions at the H3 receptor, pitolisant may promote wakefulness by facilitating the release (disinhibition) of histamine.

Solriamfetol (Sunosi) is a dopamine and norepinephrine reuptake inhibitor (DNRI). Its mechanism to improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy or OSA is unclear.

## PHARMACOKINETICS[123,124,125,126,127,128,129,130,131,132,133,134,135,136,137,138,139,140,141,142,143,144,145,146,147,148,149,150,151,152,153,154,155,156,157,158,159,160]

| Drug | Time(s) to Peak Concentration(s) (hours) | Onset of Action (minutes) | Half-Life (mean, in hours) | Duration of Action (hours) | Extended-Release Delivery System (where applicable) |
|---|---|---|---|---|---|
| **Stimulants: Immediate-Release** | | | | | |
| amphetamine sulfate (Evekeo, Evekeo ODT)[161] | 3-3.5 | 45 | 11.7 | -- | -- |
| armodafinil (Nuvigil) | 2 | -- | 15 | -- | -- |
| dexmethylphenidate (Focalin) | 1–1.5 | 30 | 2.2 | 4–6 | -- |
| dextroamphetamine IR tablets | 3 | 20–60 | 12 | 4–6 | -- |
| dextroamphetamine solution | -- | -- | 11.75 | -- | -- |
| methamphetamine (Desoxyn) | -- | -- | 4–5 | -- | -- |
| methylphenidate IR (Methylin, Ritalin)[162] | 1.5–3 | 15–20 | 2–4 | 2–4 | -- |
| mixed amphetamine salts IR (Adderall) | 3 | 30–60 | children: 9–11<br>adults: 10–13 | 4–8 | -- |
| modafinil (Provigil) | 2–4 | -- | 15 | -- | -- |
| **Stimulants: Extended-Release** | | | | | |
| amphetamine ER (Adzenys XR-ODT) | 5 (d-amphetamine [d])/5.25 (l-amphetamine [l]) | -- | children: 9–10 (d)/ 10–11 (l)<br>adults: 11 (d)/ 14 (l) | -- | 50% IR and 50% ER components |


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***Pharmacokinetics (continued)***

| Drug | Time(s) to Peak Concentration(s) (hours) | Onset of Action (minutes) | Half-Life (mean, in hours) | Duration of Action (hours) | Extended-Release Delivery System (where applicable) |
|---|---|---|---|---|---|
| **Stimulants: Extended-Release (*continued*)** | | | | | |
| amphetamine ER (Dyanavel XR) | children: 3.9 – 4.5<br>adults: 4 | -- | children: 10.43 (d)/12.14(l)<br>adults: 12.36 (d)/15.12(l) | -- | IR and ER components; ER component coated with pH-independent polymer |
| dexmethylphenidate (Focalin XR) | 1.5, then 6.5 | -- | children: 2–3<br>adults: 2–4.5 | children: 8–12<br>adults: 8 | 50% each IR and enteric-coated, delayed-release beads |
| dextroamphetamine ER (Dexedrine) | 8 | 60 | 12 | ≤ 24 | initial dose delivered immediately with remaining medication released over 6–8 hours |
| lisdexamfetamine dimesylate (Vyvanse)[163,164] | dexamfetamine = 3.5 (capsule) and 4.4 (chewable tablet)*<br>(prodrug = 1) | -- | 12<br>(prodrug <1) | ~10 | Active drug slowly released by rate-limited hydrolysis |
| methylphenidate ER (Adhansia XR) | 1-2.5, then 8.5-16 | 60 | 7 | adults: up to 16 hours<br>pediatrics: 13 | multilayered beads: 20% IR, 80% ER |
| methylphenidate ER (Aptensio XR) | 2, then 8 | 60 | 5 | 12 | multi-layer beads 40% IR, 60% ER |
| methylphenidate ER ODT (Cotempla XR-ODT) | 4.6-5.3 | 1 | 3.9-4.3 | 12 | 25% IR and 75% ER components |
| methylphenidate ER (Jornay PM) | 14 | -- | 5.9 | -- | Two coatings surrounding drug core: outer delayed-release coating, inner ER coating |
| methylphenidate ER (generics of Metadate CD) | 1.5, then 4.5 | 30–90 | 6.8 | 7–12 | 30% IR, 70% ER beads |
| methylphenidate ER (Metadate ER, Ritalin SR)[165,166] | 4.7 | 30–180 | 2–4 | 8 | Various |
| methylphenidate ER (Quillichew ER) | 5 | -- | 5.2 | -- | 30% IR, 70% ER |
| methylphenidate ER (Quillivant XR) | 5 | 45 | 4.2-6.2 | 12 | extended-release oral suspension |
| methylphenidate ER (Ritalin LA) | 1–3, then 4–8 | 30–110 | 2.5–3.5 | 7–12 | 50% dose IR beads, 50% dose enteric–coated, delayed release beads |

* Food prolongs the time to peak concentration (Tmax) of converted prodrug (d-amphetamine) by 1 hour


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***Pharmacokinetics (continued)***

| Drug | Time(s) to Peak Concentration(s) (hours) | Onset of Action (minutes) | Half-Life (mean, in hours) | Duration of Action (hours) | Extended-Release Delivery System (where applicable) |
|---|---|---|---|---|---|
| **Stimulants: Extended-Release (*continued*)** | | | | | |
| methylphenidate ER OROS (Concerta)[167] | 1–2, then 6–8 | 30–60 | 3.5 | 8–12 | 22% IR overcoat; 78% controlled release core; osmotic-release oral system |
| methylphenidate ER OROS (Relexxii) | 1.5, then 5–6 | -- | 3.5–3.6 | -- | IR overcoat; controlled-release core; osmotic-release oral system |
| methylphenidate transdermal (Daytrana) | 7.5–10.5 | 120 | 3–4 | ~3 following patch removal | concentrated drug cells in patch |
| mixed amphetamine salts ER (Adderall XR) | 7† | 30-60 | children: 9–11 adults: 10–13 | 8–10 | 50% each of immediate- and delayed-release beads |
| mixed amphetamine salts ER (Mydayis) | children: 7-10‡ adults: 8‡ | 2-16 | 10–13 | ≤16 | Triple-beaded providing immediate-, pulsatile delayed, and sustained-release activity |
| mixed amphetamine salts ER (Adderall XR) | 7† | 30-60 | children: 9–11 adults: 10–13 | 8–10 | 50% each of immediate- and delayed-release beads |
| serdexmethylphenidate/ dexmethylphenidate (Azstarys) | 2–4.5 | ~120 (peak) | 5.7/11.7 | ~12 | 70% to 30% ratio of prodrug to dexmethylphenidate |
| **Non-Stimulants** | | | | | |
| atomoxetine (Strattera) | 1–2 | 1 week | 5.2 | ~24 | -- |
| clonidine ER (Kapvay) | 6.5–6.8 | -- | 12–16 | -- | extended-release tablet |
| guanfacine ER (Intuniv) | 5–6 | -- | 18 (adults) | -- | matrix consisting of ionic polymers, enteric polymers, and organic acids |
| pitolisant (Wakix) | 2-5 | -- | 7.5–24 | -- | -- |
| solriamfetol (Sunosi) | 1.25–3 | -- | 7.1 | -- | -- |
| viloxazine (Qelbree) | 3–9 | -- | 7.02 | -- | -- |

† Food prolongs the Tmax of mixed amphetamine salts ER (Adderall XR) by 2.5 hours

‡ Food (high fat meal) prolongs the Tmax of mixed amphetamine salts ER (Mydayis) by 4.5 to 5 hours


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The half-life and blood concentration of amphetamine are directly related to urinary pH, increasing with alkaline pH and decreasing with acidic pH. For every unit increase in pH, the half-life of mixed amphetamine salts (Adderall XR, dextroamphetamine solution) increases by an average of 7 hours. As a result, urine acidifying and urine alkalinizing agents should be avoided with the use of amphetamine sulfate (Evekeo, Evekeo ODT), amphetamine extended-release (Dyanavel XR), amphetamine extended-release (Adzenys XR-ODT), and mixed amphetamine salts, if possible, to maintain consistent amounts of the active drug in the system.

Except for mixed amphetamine salts, stimulants are de-esterified in the liver to pharmacologically inactive metabolites. In contrast, mixed amphetamine salts are metabolized in the liver by hydroxylation, dealkylation, and deamination. Urinary excretion accounts for nearly all of the elimination of the stimulants and atomoxetine (Strattera), as well as their metabolites.

Mixed amphetamine salts (Mydayis) consists of 3 types of drug-releasing beads that deliver immediate, pulsatile delayed, and sustained release of mixed amphetamine salts.[168] Patients ≤ 12 years experienced higher plasma exposure of Mydayis than patients ≥ 13 years at the same dose and experienced higher rates of adverse reactions (e.g., insomnia, decreased appetite).

Methylphenidate extended-release OROS (Concerta) and dexmethylphenidate ER (Focalin XR) have similar pharmacodynamic profiles, with the main difference being that the latter contains only dexmethylphenidate. The release profiles of Ritalin LA, generic products equivalent to Metadate CD, and extended-release formulations of MPH are very similar to each other.

Atomoxetine has a slower onset of action than the stimulants; onset of effect may take 1 week and full effect may not be seen for up to 4 weeks.[169,170] The effects of atomoxetine appear to last longer than would be expected from its pharmacokinetic profile.[171] The reasons for these pharmacokinetic-pharmacodynamic differences are not clear but may be due to a variance between brain and plasma pharmacokinetics, or by continued effects on the norepinephrine transporter. Atomoxetine is metabolized in most patients primarily by the CYP2D6 enzymatic pathway. Medications that inhibit CYP2D6 (e.g., paroxetine, fluoxetine, quinidine) increase the bioavailability of atomoxetine. Atomoxetine does not appear to induce or inhibit the CYP2D6 enzyme system.[172] Approximately 5% to 10% of patients are “slow metabolizers” in which the mean half-life of atomoxetine is 21.6 hours, over 4 times longer than in “rapid metabolizers.”[173]

Exposure to guanfacine ER (Intuniv) was higher in children (6 to 12 years of age) compared to adolescents (13 to 17 years of age) and adults, probably attributable to the lower body weight of children compared to adolescents and adults. The pharmacokinetics of a single dose of guanfacine ER 4 mg was affected when administered with a high-fat breakfast. The mean exposure increased ($C_{max}$ 75% and area under the curve [AUC] 40%) compared to dosing in a fasted state.

When opened and sprinkled on cold applesauce, the bioavailability of methylphenidate ER (Adhansia XR, Aptensio XR, Jornay PM, generics of Metadate CD, and Ritalin LA), dexmethylphenidate ER (Focalin XR), and mixed amphetamine salts ER (Adderall XR, Mydayis) is considered clinically similar as that of the respective intact capsules.


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## CONTRAINDICATIONS/WARNINGS[174,175,176,177,178,179,180,181,182,183,184,185,186,187,188,189,190,191,192,193,194,195,196,197,198,199,200,201,202,203,204,205,206,207,208,209,210,211]

### Contraindications

All products in this review, with the exception of viloxazine (Qelbree), are contraindicated in patients with a history of hypersensitivity to active and inactive ingredients. Armodafinil (Nuvigil) and modafinil (Provigil) are contraindicated in patients with known hypersensitivity to either armodafinil or modafinil. Hypersensitivity reactions, including angioedema and anaphylaxis, have been reported with many medications used to treat ADHD, including amphetamine and methylphenidate products.

All products in this review, except clonidine ER (Kapvay), guanfacine ER (Intuniv), armodafinil (Nuvigil), modafinil (Provigil), and pitolisant (Wakix), are contraindicated during or within 14 days following administration of a monoamine oxidase inhibitor (MAOI); concurrent use can prolong and intensify the cardiac stimulation and vasopressor effects of stimulants. However, while armodafinil and modafinil have not been evaluated for interactions with drugs with MAOI activity, prescribers should be cautious with use of these agents in the presence of an MAOI.

Stimulants are inappropriate for use in patients with marked anxiety or agitation as these symptoms may be aggravated. If paradoxical aggravation occurs, a decrease in dose or cessation of therapy may be needed.

Amphetamines are contraindicated in patients with advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, or a history of drug abuse.

Methylphenidate (Concerta, Daytrana, Methylin, generics of Metadate CD, Metadate ER, Ritalin, Ritalin SR, Ritalin LA) and dexmethylphenidate (Focalin, Focalin XR) are contraindicated in patients with tics, or a diagnosis or family history of, Tourette's syndrome. While this may be a class effect, labeling for Adhansia XR, Aptensio XR, Azstarys, Cotempla XR-ODT, Quillichew ER, and Quillivant XR do not include this contraindication.

Atomoxetine (Strattera) is contraindicated in patients with severe cardiac or vascular disorders whose condition would be expected to deteriorate with clinically significant increases in blood pressure or heart rate. Increases in blood pressure and heart rate, orthostasis, and syncope have been reported.

Pitolisant (Wakix) is contraindicated in patients with severe hepatic impairment.

Viloxazine (Qelbree) is contraindicated in patients who are also receiving sensitive CYP1A2 substrates or CYP1A2 substrates with a narrow therapeutic range.

### Warnings

Stimulants have warnings, many with boxed warnings, regarding the high potential for abuse. Prolonged use of these agents can lead to drug dependence, tolerance, and social disability. Prescribers should assess the risk of abuse prior to prescribing, monitor patients for signs of abuse and dependence, and re-evaluate the need for stimulants.

#### *Behavioral/Mental Health*

Stimulants should be used with caution in patients with pre-existing psychosis, bipolar disorder, or aggression as these conditions may be exacerbated. Treatment-emergent psychotic or manic


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symptoms have been reported in 0.1% of patients receiving stimulants and 0.2% of patients receiving atomoxetine (Strattera).

Patients should be carefully supervised during withdrawal from MPH and dexmethylphenidate as it may result in depression and/or unmasking of symptoms.

Atomoxetine has a boxed warning regarding the increased risk of suicidal ideation in children and adolescents. In a combined analysis of 12 short-term placebo-controlled trials of over 2,200 patients, suicidal ideation occurred in approximately 0.4% of patients compared with no patients receiving placebo. All occurrences were reported during the first month of treatment in children ≤ 12 years. Monitoring, including face-to-face contact with patients or caregivers, should occur weekly during the first 4 weeks of treatment, then every other week for 4 weeks, then again at 12 weeks.

Patients on atomoxetine should be monitored for the appearance or worsening of aggressive behavior or hostility or new psychotic or manic symptoms, as atomoxetine may cause the emergence or worsening of these behaviors or episodes. Atomoxetine may need to be discontinued should these occur. Patients should be screened for risk factors of bipolar disorder prior to treatment initiation.

Modafinil (Provigil) and armodafinil (Nuvigil) have also been reported to induce mania, delusions, hallucinations, suicidal ideations, and aggression in patients with and without a prior history of psychiatric illness. Two cases of suicidal ideation were observed in armodafinil clinical trials.

Anxiety, insomnia, and irritability have been observed in clinical trials with solriamfetol (Sunosi). Solriamfetol has not been evaluated in patients with psychosis or bipolar disorder and should be used with caution in these patients. The risk for psychiatric adverse events may be higher in patients with severe to moderate renal impairment. All patients should be observed for psychiatric symptoms, and if these symptoms develop in relation to solriamfetol administration, a dose reduction or discontinuation is warranted.

Somnolence and sedation with guanfacine ER and clonidine ER were commonly reported adverse reactions in clinical studies, especially during initial use. Caution should be used when operating heavy equipment or driving and when using with other CNS depressants, including alcohol. Furthermore, alcohol should be avoided while taking MPH.

Viloxazine (Qelbree) carries a boxed warning regarding the potential for suicidal thoughts and behaviors; clinical studies demonstrated increased rates of these events in pediatric ADHD patients who received viloxazine compared to those who received placebo. A total of 9 pediatric viloxazine-treated patients (0.9%) reported suicidal ideation, behavior, or both in the studies compared to 2 patients (0.4%) who reported suicidal ideation on placebo; however, no completed suicides occurred. In an adult trial, 3 patients (1.6%) treated with viloxazine reported suicidal ideation compared with none of the placebo-treated patients. Viloxazine-treated patients had increased rates of insomnia and irritability, which could potentially be precursors to suicidal ideation or behavior. All viloxazine-treated patients should be carefully monitored for worsening and for new suicidal thoughts or behaviors as well as for potential precursors.

Viloxazine carries a warning for activation of manic or mixed episodes in those with bipolar disorder. Patients should be screened for the risk of bipolar disorder, which should include a detailed psychiatric history and a personal/family history of suicide, bipolar disorder, and depression.

Viloxazine carries a warning for somnolence and fatigue. Patients should be advised not to perform activities that require mental alertness until the effects of viloxazine are known.


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***Cardiovascular***

Sudden death, stroke, and myocardial infarction have been reported in adults using stimulants at recommended dosages. Sudden death has also been reported in association with stimulants and with atomoxetine at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. Stimulants and atomoxetine generally should not be used in patients with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the noradrenergic effects. In addition, stimulants and atomoxetine can cause increased blood pressure and heart rate. All patients being considered for pharmacologic treatment for ADHD should be evaluated for the presence of cardiac disease (e.g., personal history, family history, physical exam). Caution is indicated in treating patients with pre-existing hypertension, heart failure, recent myocardial infarction, or ventricular arrhythmia. Pulse and blood pressure should be monitored at baseline and during therapy, and heart rate and blood pressure may be increased by stimulants.

Viloxazine (Qelbree) also has a warning for the potential to increase heart rate and diastolic blood pressure. Evaluate heart rate and blood pressure before starting therapy, after dose increases, and regularly during therapy.

Dose-dependent decreases in blood pressure and heart rate have been seen in patients using clonidine ER or guanfacine ER. Heart rate and blood pressure should be measured prior to initiation of therapy, following dose increases, and periodically while on therapy. Use with caution in patients with a history of hypotension, heart block, bradycardia, cardiovascular disease, or syncope. The sympatholytic action of clonidine ER and guanfacine ER may worsen sinus node dysfunction and atrioventricular (AV) block, especially in patients taking other sympatholytic drugs. Advise patients to avoid becoming dehydrated or overheated. Guanfacine ER should be titrated slowly in patients with history of hypotension or underlying conditions that may be worsened by hypotension and bradycardia, as well as patients with cardiac conduction abnormalities. To avoid adverse effects on blood pressure (rebound hypertension and hypertension encephalopathy, which was reported for guanfacine ER only,) when discontinuing therapy, the clonidine ER or guanfacine ER dose should generally be tapered off.

In 2011, the FDA published 2 safety communications. The first publication was based on studies that evaluated heart attacks, strokes, and sudden cardiac death in children, adolescents, and young adults (≤ 24 years) treated with certain ADHD medications.[212] The study did not find an association between the use of these agents and cardiovascular events. The second publication addressed heart attacks, sudden cardiac death, and strokes in adults aged 25 to 64 years.[213] The publication stated studies did not show an increased risk of serious adverse cardiovascular events in adults treated with ADHD medications. The medications included in both of these publications were amphetamines, methylphenidate, atomoxetine, and an agent no longer marketed in the US.

Stimulants used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Improvement in signs and symptoms usually occurs after reduction in dose or discontinuation of the drug. Monitor for digital changes during treatment with ADHD stimulants.

Atomoxetine should be used with caution in patients with hypertension, tachycardia, or cardiovascular or cerebrovascular disease.

Solriamfetol causes a dose-dependent increase in systolic blood pressure, diastolic blood pressure, and heart rate. The need for continued treatment with solriamfetol should be reassessed periodically, and


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any patient who develops increased blood pressure or heart rate that is not controlled by a dose reduction of solriamfetol or medical intervention should consider discontinuation of this medication. Due to the prolonged half-life of solriamfetol, patients with severe to moderate renal impairment (estimated glomerular filtration rate [eGFR], 15 to 59 mL/min/1.73 $m^2$) may be at a higher risk of increased blood pressure and/or heart rate.

Pitolisant (Wakix) prolongs the QT interval, with a corrected QT (QTc) increase of 4.2 msec at the highest recommended dose. It should be avoided in patients with known QT prolongation or those who are using other medications known to cause a similar effect. Pitolisant should be avoided in patients with a history of cardiac arrhythmias or those at risk for torsade de pointe or sudden death.

***Dermatological***

Use of MPH transdermal system (Daytrana) may lead to contact sensitization as evidenced by allergic contact dermatitis. MPH transdermal system should be discontinued if this occurs. Patients may develop systemic sensitization or other systemic reactions to MPH-containing products given via other routes. It is possible that some patients sensitized to MPH may not be able to take MPH in any form.

In June 2015, the FDA issued a warning that MPH transdermal system (Daytrana) use may result in permanent loss of skin color, or chemical leukoderma, in areas up to ≤ 8 inches in diameter.[214] A review of chemical leukoderma cases associated with the drug suggest that the skin condition's time to onset ranged from 2 months to 4 years after starting the MPH transdermal system. Patients and caregivers should watch for new areas of lightened skin, particularly in areas where the skin patch was rotated; however, skin color changes have been reported in other areas where the patch was never applied.

Rare cases of serious rash, such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS), have occurred in patients taking modafinil or armodafinil. The cases reported have occurred within 1 to 5 weeks after initiating drug treatment, and predictors to occurrence of rash are not known.

***Other***

Stimulants approved for use in pediatric patients may cause long-term suppression of growth, and patients not exhibiting growth and/or weight gain as expected may need their therapy interrupted. However, other studies have concluded final growth at maturity is not impacted by ADHD or medications used to treat ADHD (see Effects on Growth section).

Stimulants, except armodafinil and modafinil, may lower the seizure threshold.

Accommodation and vision blurring have been reported with stimulant treatment.

Rare cases of gastrointestinal obstruction have been reported with nondeformable controlled-release formulations similar to MPH OROS (Concerta, Relexxii). These formulations should not be administered to patients with preexisting severe gastrointestinal narrowing or known strictures.

Methylphenidate ER (Quillichew ER) contains phenylalanine, which may be harmful to patients with phenylketonuria (PKU).

Painful and prolonged penile erections and priapism have been reported with atomoxetine, mixed amphetamine salts, dextroamphetamine, methamphetamine, lisdexamfetamine, methylphenidate, serdexmethylphenidate/dexmethylphenidate, and dexmethylphenidate products. Priapism has not


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been reported with drug initiation but developed after some time on the drug, often subsequent to a dosage increase. Priapism has also appeared during a period of drug withdrawal (e.g., drug holidays, during discontinuation). Immediate medical attention should be sought if signs or symptoms of painful or prolonged penile erections are observed.

Limited reports of multi-organ hypersensitivity reactions have been reported after initiation of treatment between 4 to 33 days in patients taking modafinil. Some of the presenting signs and symptoms were fever, rash, pruritus, asthenia, myocarditis, hepatitis, liver function test abnormalities, and dermatological abnormalities. A similar risk of multi-organ hypersensitivity reactions with armodafinil has also been reported.

Atomoxetine has a warning regarding severe liver injury; rare, but marked elevations of hepatic enzymes and bilirubin have been reported. In 2 case reports, liver injury resolved after discontinuation of atomoxetine (with concomitant immunosuppressive therapy in 1 case).[215] The manufacturer recommends permanent discontinuation in patients with any sign of jaundice or hepatic lab abnormality; other treatment options should be considered.

Methylphenidate HCl ER (Adhansia XR) 45 mg contains yellow dye number 5 (tartrazine), which may cause allergic-type reactions in susceptible patients.

## DRUG INTERACTIONS[216,217,218,219,220,221,222,223,224,225,226,227,228,229,230,231,232,233,234,235,236,237,238,239,240,241,242,243,244,245,246,247,248,249,250,251,252,253]

Gastrointestinal (e.g., antacids) and urinary (e.g., acetazolamide, some thiazides) alkalinizing agents increase blood levels and activity of amphetamines and possibly methylphenidate. Gastrointestinal (e.g., ascorbic acid) and urinary (e.g., ammonium chloride) acidifying agents decrease absorption and activity of the amphetamines and possibly methylphenidate. Proton pump inhibitors reduce gastric acidity; patients who co-administer them with amphetamines should be monitored for changes in clinical effect due to the potential for decreases in the time to maximum concentration of amphetamine products. Amphetamines may delay the intestinal absorption of ethosuximide and the anticonvulsants, phenytoin and phenobarbital, which may produce a synergistic anticonvulsant action.

Extended-release amphetamine (Adzenys XR-ODT, Dyanavel XR) may enhance the effect of tricyclic antidepressants, including cardiac effects. Patients taking these agents concomitantly should have increased monitoring and dose adjustments as clinically indicated.

Lithium may antagonize the central stimulating effects of amphetamines and should be avoided.[254] Likewise, MPH should not be used concurrently with lithium since this may alter the effects of the agents on the underlying mood disorder. Haloperidol and chlorpromazine also inhibit the central stimulant effects of the amphetamines.

Serotonin syndrome may occur when amphetamines are used with other medications that impact the serotonergic neurotransmitter systems (e.g., MAOIs, SSRIs, SNRIs, triptans, tricyclic antidepressants [TCAs], fentanyl, lithium, tramadol, tryptophan, buspirone, St. John's wort) and CYP2D6 inhibitors. Monitor for signs and symptoms of serotonin syndrome including mental status changes, autonomic instability, neuromuscular symptoms, seizures, and gastrointestinal symptoms.[255]

Amphetamines inhibit adrenergic blocking agents and may decrease the effects of antihistamines and antihypertensives; however, amphetamines potentiate the effects of meperidine and norepinephrine. Similarly, antihypertensive agents may be less effective when used with any stimulant.


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Effects can be additive when stimulants are used concurrently with other psychostimulants or sympathomimetics.[256] Due to the potential for excessive CNS or cardiovascular stimulation, combination therapy should be avoided unless necessary, and, if unavoidable, then used with caution.[257] In general, the concurrent use of MPH-containing products with amphetamines is not recommended. Since there are no clinical data regarding the concurrent use of MPH and atomoxetine (Strattera), concurrent use should be avoided. Likewise, concomitant use of halogenated anesthetics with stimulants may increase the risk of acute blood pressure and heart rate changes during surgery.

MPH and dexmethylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (e.g., phenobarbital, phenytoin, primidone), and some antidepressants (tricyclic antidepressants [TCAs], selective serotonin reuptake inhibitors [SSRIs]). Downward dose adjustment of these drugs may be required when given concomitantly with MPH.

Concomitant use of MAOI and noradrenergic drugs, such as stimulants, may increase the risk of a hypertensive reaction, potentially leading to death, stroke, myocardial infarction, aortic dissection, ophthalmological complications, eclampsia, pulmonary edema, and/or renal failure.

Concomitant use of methylphenidate- and dexmethylphenidate-containing medications with select antipsychotics, particularly during dose changes of either agent, may impact the occurrence of extrapyramidal symptoms (EPS).

Armodafinil (Nuvigil) and modafinil (Provigil) have not been evaluated for interactions with drugs with MAOI activity. Until more is known regarding the pharmacology of modafinil, it may be prudent to caution against the use of these agents in the presence of a MAOI.

Armodafinil and modafinil moderately induce CYP3A activity. Drugs that are substrates of CYP3A4/5, such as cyclosporine, may require dosage adjustment. Armodafinil and modafinil moderately inhibit CYP2C19 activity. Drugs that are substrates of CYP2C19 (e.g., phenytoin, diazepam, propranolol, omeprazole, and clomipramine) may require dosage reduction. In patients who are deficient in the CYP2D6 enzyme, the levels of CYP2D6 substrates, such as TCAs and SSRIs, which have ancillary routes of elimination through CYP2C19 may be increased with concurrent use of modafinil; dose adjustments of the TCA or SSRI may be warranted.

While no significant effect on the pharmacokinetic profiles were found, the rate of absorption of modafinil was delayed up to 1 hour with concomitant use of dextroamphetamine or MPH.

The effectiveness of steroidal contraceptives may be reduced with concurrent use of either armodafinil or modafinil and for 1 month after discontinuation of therapy. Alternative or concomitant methods of contraception are recommended during therapy and for 1 month after discontinuation of armodafinil or modafinil.

Where data specific to armodafinil drug interactions are not available, any available information on modafinil should be applicable to armodafinil, according to the prescribing information.

Antihypertensive drugs and drugs affecting sinus node function or AV nodal conduction have the potential for additive effects when used with clonidine. Serious adverse events have been reported during concomitant use of MPH and clonidine; however, no causality has been established.

Caution should be used when guanfacine ER (Intuniv) is administered to patients taking strong CYP3A4/5 inhibitors (e.g., ketoconazole), which can cause a substantial increase in the rate and extent


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of guanfacine exposure (AUC) leading to an increased risk of adverse events such as hypotension, bradycardia, and sedation.

Concomitant use of guanfacine ER with a CYP3A4 inducer (e.g., rifampin) can cause a significant decrease in the rate and extent of guanfacine exposure (AUC). An increase in the dose of guanfacine ER within the recommended dose range may be considered.

Co-administration of guanfacine and valproic acid can result in increased concentrations of valproic acid. Adjustments in the dose of valproic acid may be required.

Strong CYP2D6 inhibitors can increase pitolisant (Wakix) exposure while strong CYP3A4 inducers can decrease pitolisant exposure. Both situations require adjustments to the pitolisant dose. Pitolisant is also a weak inducer of CYP3A4 and may affect sensitive CYP3A4 substrates. Monitor for decreased efficacy and if patients are taking hormonal contraceptives, an additional non-hormonal contraceptive should be used. Histamine-1 (H1) receptor antagonists may reduce the effectiveness of pitolisant and concomitant use should be avoided. Agents that prolong the QT interval should also be avoided with pitolisant due to the risk of additive QT prolongation/increased risk of arrhythmia.

Solriamfetol should be used with caution if used concomitantly with other drugs that can increase blood pressure and/or heart rate; concomitant use has not been evaluated.

Drugs that increase levels of dopamine or bind directly to dopamine receptors may result in pharmacodynamics interactions with solriamfetol. These interactions have not been evaluated; therefore, use caution when using solriamfetol with one of these agents.

Since viloxazine (Qelbree) is a strong CYP1A2 inhibitor, concurrent use with sensitive CYP1A2 substrates or CYP1A2 substrates with a narrow therapeutic range (e.g., alosetron, duloxetine, ramelteon,) is contraindicated. Similarly, concurrent use of viloxazine with moderate sensitive CYP1A2 substrates (e.g., clozapine, pirfenidone) is not recommended; however, if use cannot be avoided, a dose decrease may be needed.

Viloxazine, a weak CYP2D6 inhibitor, can increase the exposure of concurrently administered CYP2D6 substrates (e.g., atomoxetine, metoprolol, tolterodine, venlafaxine, risperidone). Viloxazine is also a weak CYP3A4 inhibitor and can increase the drug levels of concurrently administered CYP3A4 substrates. Patients receiving these combinations should be monitored for adverse reactions and the dose of the CYP3A4 substrate should be adjusted as clinically warranted.

## ADVERSE EFFECTS[258,259,260,261,262,263,264,265,266,267,268,269,270,271,272,273,274,275,276,277,278,279,280,281,282,283,284,285,286,287,288,289,290,291,292,293,294,295]

For the most part, adverse effects of stimulants are dose-dependent, mild to moderate in severity, and diminish with alteration of medication dose or timing.[296] They commonly subside spontaneously during the first 1 to 2 weeks of treatment.[297] Nonetheless, the majority of children treated with stimulants do experience some adverse effects, and these adverse effects are often the reason stimulant treatment is discontinued.[298,299]

Most side effects associated with stimulants, such as decreased appetite, headaches, stomach aches, insomnia, nervousness, and social withdrawal, can usually be managed by adjusting the dosage and/or timing of administration. For instance, administering stimulants with or after meals can reduce appetite suppression. Moving the last daily dose to an earlier time may reduce insomnia. If children are


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on too high of a dosage or are overly sensitive to the stimulants, the agents may cause them to be over focused, appear dull, or overly restricted. Lowering the dosage of medication or changing to a different medication can usually reduce the effects.

In a double-blind study, investigators found that, based on parent assessment, only 2 adverse effects were more prevalent after initiation of stimulants than prior to initiation. These were insomnia (dextroamphetamine) and poor appetite (dextroamphetamine and MPH).[300] Investigators also found that the severity of several adverse effects (insomnia, irritability, crying, anxiousness, sadness/unhappiness, and nightmares) was higher with dextroamphetamine than with MPH; there were no adverse effects of higher severity with MPH than with dextroamphetamine.

In general, a review of the evidence shows no statistically significant differences in the incidence of adverse effects between immediate-release and extended-release formulations. There is no evidence to support statistically significant differences with respect to adverse effects of dextroamphetamine and MPH-containing products.

Long-term use of stimulant therapy has not demonstrated any obvious ill effects through observational data; however, there are no formal long-term studies.

The most common (incidence > 10%) adverse effect reported with solriamfetol when used for narcolepsy was headache (16% solriamfetol versus 7% placebo). Other adverse effects (incidence 5% to 10%) occurring in patients with narcolepsy or OSA treated with solriamfetol versus placebo, respectively, include decreased appetite (6% to 9% versus 1%), nausea (7% to 8% versus 4% to 6%), anxiety (4% to 6% versus 1%), and insomnia (5% versus 4%).

The most common adverse effects (incidence ≥ 5% and twice the rate of placebo) reported with pitolisant (Wakix) in clinical trials were anxiety (5% versus 1% with placebo), insomnia (6% versus 2% with placebo), and nausea (6% versus 3% with placebo).

In pediatric clinical trials, the most common adverse effects (incidence ≥ 5% and at least twice the rate of placebo at any dose) reported with viloxazine (Qelbree) relative to placebo, respectively, were somnolence (16% versus 4%), decreased appetite (7% versus 0.4%), fatigue (6% versus 2%), nausea (5% versus 3%), vomiting (4% versus 2%), insomnia (4% versus 1%), and irritability (3% versus 1%). About 3% of pediatric viloxazine-treated patients in clinical studies discontinued therapy due to an adverse effect; the most common adverse effects leading to discontinuation were somnolence, nausea, headache, irritability, tachycardia, fatigue, and decreased appetite. In a trial of 189 adults treated with viloxazine, the most common adverse effects occurring in ≥ 2% of patients and more frequently than with placebo were insomnia (23% versus 7%), headache (17% versus 7%), nausea (12% versus 3%), fatigue (12% versus 3%), decreased appetite (10% versus 3%), and dry mouth (10% versus 2%). The discontinuation rate due to adverse effects among adult patients was 9%.


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## Adverse Effects in Children

| Drug | Headache | Abdominal pain | Anorexia | Insomnia |
|---|---|---|---|---|
| **Stimulants: Immediate-Release** | | | | |
| amphetamine sulfate (Evekeo) | reported | nr | reported | nr |
| amphetamine sulfate (Evekeo ODT) | 13 | 15 | 28 | 10 |
| armodafinil (Nuvigil)* | 17<br>(9) | 2<br>(1) | 1<br>(0) | 5<br>(1) |
| dexmethylphenidate (Focalin) | nr | 15<br>(6) | 6<br>(1) | nr |
| dextroamphetamine IR tablets | reported | reported† | reported | reported |
| dextroamphetamine solution | reported | nr | reported | reported |
| methamphetamine (Desoxyn) | reported | nr | reported | reported |
| methylphenidate IR (Methylin, Ritalin) | reported | reported | reported | reported |
| mixed salt amphetamines IR (Adderall) | reported | nr | reported | reported |
| modafinil (Provigil)* | 34<br>(23) | 1<br>(≥1) | 4<br>(1) | 5<br>(1) |
| **Stimulants: Extended-Release** | | | | |
| amphetamine ER (Adzenys XR-ODT) | nr | 11–14<br>(2–10) | 22–36<br>(2) | 12–17<br>(2–4) |
| amphetamine ER (Dyanavel XR) | nr | 3.8<br>(2.1) | reported | reported |
| dexmethylphenidate (Focalin XR) | 25<br>(11) | nr | 30<br>(9) | reported |
| dextroamphetamine ER (Dexedrine) | reported | nr | reported | reported |
| lisdexamfetamine (Vyvanse) | reported | 12<br>(6) | 2-5<br>(0) | 13–27<br>(3–4) |
| methylphenidate ER (Adhansia XR) | 10 | 4<br>(1) | 20<br>(0) | 6<br>(1) |
| methylphenidate ER (Aptensio XR) | 10.9<br>(8.5) | 8.2<br>(0) | 4.9<br>(0) | 9.8<br>(2.1) |
| methylphenidate ER (Cotempla XR-ODT) | nr | reported | reported | reported |
| methylphenidate ER (Jornay PM) | 10–19<br>(5) | 9 | 19–27<br>(4) | 33–41<br>(9) |
| methylphenidate ER (Metadate ER, Ritalin SR) | reported | reported | reported | reported |
| methylphenidate ER (generics of Metadate CD) | 12<br>(8) | 7<br>(4) | 9<br>(2) | 5<br>(2) |

Adverse effects are reported as a percentage. Adverse effects data are obtained from prescribing information and are not meant to be comparative or all inclusive. Incidences for the placebo group are indicated in parentheses. nr = not reported

* Adults only

† reported as GI disturbance


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***Adverse Effects in Children (continued)***

| Drug | Headache | Abdominal pain | Anorexia | Insomnia |
|---|---|---|---|---|
| **Stimulants: Extended-Release *(continued)*** | | | | |
| methylphenidate ER (Quillichew ER) | 2.4<br>(0) | reported | 2.4<br>(0) | reported |
| methylphenidate ER (Quillivant XR) | nr | ≥ 5 | 2<br>(0) | 2<br>(0) |
| methylphenidate ER (Ritalin LA) | >5<br>(nr) | >5<br>(nr) | >5<br>(nr) | >5<br>(nr) |
| methylphenidate ER OROS (Concerta, Relexxii) | <1 | 6.2<br>(3.8) | <1 | 2.8<br>(0.3) |
| methylphenidate transdermal (Daytrana) | 12.4–15.3<br>(11.8–12.5) | 4.8–7.1<br>(0–5.9) | 4.8–5.1<br>(1.2–1.4) | 6.2–13.3<br>(2.8–4.7) |
| mixed salt amphetamines (Adderall XR) | reported | 11–14<br>(2–10) | 22<br>(2) | 12–17<br>(2–4) |
| mixed salt amphetamines (Mydayis) | reported | reported | 22<br>(6) | 8<br>(3) |
| **Non-Stimulants** | | | | |
| atomoxetine (Strattera) | 19<br>(15) | 18<br>(10) | 3<br>(1) | ≥2<br>(nr) |
| clonidine ER (Kapvay) | 19–29<br>(18) | 13–20<br>(17) | nr | 4–6<br>(1) |
| guanfacine ER (Intuniv) | 21–24<br>(13–19) | 10–11<br>(3–9) | 5–7<br>(3–4) | 12<br>(6) |
| viloxazine (Qelbree) | 11<br>(7) | 5<br>(4) | 7<br>(0.4) | 4<br>(1) |

Adverse effects are reported as a percentage. Adverse effects data are obtained from prescribing information and are not meant to be comparative or all inclusive. Incidences for the placebo group are indicated in parentheses. nr = not reported

Other side effects common to the stimulants include irritability, flattened affect, social withdrawal, weepiness, mood lability, tremor, weight loss, and reduced growth velocity.

Stimulants can cause unpredictable motor tics, which transiently occur in 15% to 30% of children. Tics may appear in some patients when they are on stimulant medication and disappear with discontinuation of the medication. Fifty percent of patients with Tourette's disorder also have ADHD which may present 2 or 3 years before the tics appear. It is believed that stimulants do not cause Tourette's disorder, but simply unmask the disorder. Motor and verbal tics have not been associated with armodafinil (Nuvigil), modafinil (Provigil), atomoxetine (Strattera), clonidine ER (Kapvay), or guanfacine ER (Intuniv).[301]

In clinical trials for mixed amphetamine salt ER (Mydayis), pediatric patients 6 to 12 years of age experienced higher rates of adverse reactions compared to patients 13 years and older, including insomnia (30% versus 8%) and decreased appetite (43% versus 22%).

The safety and efficacy of methylphenidate ER (Aptensio XR) in pediatric patients under 6 years of age have not been established. In a clinical trial, pediatric patients under 6 years of age experienced higher rates of adverse reactions, most notably weight loss, than patients 6 years of age and older. The


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benefits of methylphenidate ER (Aptensio XR) do not outweigh the risk of adverse reactions in patients between the ages of 4 and 6 years.

Paresthesia (including formication) has been associated with treatment on mixed amphetamine salts (Adderall, Adderall XR, Mydayis).

Amphetamines have been associated with intestinal ischemia.

The majority of patients in the pivotal phase 3 clinical trial of MPH transdermal (Daytrana) had minimal to definite erythema. Erythema generally caused little discomfort and did not usually result in discontinuation from treatment. However, use of MPH transdermal may lead to contact sensitization and should be discontinued if contact sensitization is suspected. Patients sensitized from use of MPH transdermal may develop systemic sensitization or other systemic reactions if methylphenidate-containing products are taken via other routes (e.g., orally). The most common adverse reactions with the extended-release suspension (Quillivant XR) reported in the phase 3 controlled study conducted in 45 ADHD patients (6 to 12 years) were affect lability, excoriation, initial insomnia, tic, decreased appetite, vomiting, motion sickness, eye pain, and rash. Other common adverse reactions with the extended-release methylphenidate (Quillichew ER) not reported above but reported in a controlled study conducted in 90 ADHD patients (6 to 12 years) were aggression, emotional poverty, nausea, and decreased weight.

Adverse effects described in product labeling for serdexmethylphenidate/dexmethylphenidate (Azstarys) are based on data from methylphenidate-containing products.

Post-marketing adverse effects cited for armodafinil (Nuvigil) include mania, delusions, hallucinations, and suicidal ideation. Many of the patients who developed psychiatric adverse reactions had previous history of psychiatric conditions.

Rhabdomyolysis has been identified as an adverse reaction during post-approval use of stimulants and atomoxetine (Strattera).

## Effects on Growth

The 2019 AAP Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of ADHD in Children and Adolescents acknowledges the results of the Multimodal Treatment of ADHD (MTA) study which indicated that stimulant use could result in decreased growth velocity more persistently than was found in previous studies.[302] A decrease in growth of 1 cm to 2 cm from the predicted adult height was found, particularly among children taking higher and more consistent doses of a stimulant. The study also found that the effects diminished after 3 years of treatment and that the decrease in growth was not later compensated.

The use of atomoxetine (Strattera) has also been associated with growth delays in the first 2 years of treatment; however, with a return to predicted growth measurements after 2 to 3 years of treatment.[303] In general, decreases in growth were found in patients with above average height and weight prior to treatment with atomoxetine.


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## SPECIAL POPULATIONS[304,305,306,307,308,309,310,311,312,313,314,315,316,317,318,319,320,321,322,323,324,325,326,327,328,329,330,331,332,333,334,335,336,337,338,339,340,341]

### Pediatrics

Many immediate-release stimulants, dextroamphetamine IR tablets, dextroamphetamine solution, amphetamine sulfate tablet (Evekeo), and mixed amphetamine salts (Adderall), are indicated for children as young as 3 years. Dextroamphetamine IR tablets and solution are approved through the age of 16 for ADHD. Amphetamine sulfate orally disintegrating tablet (Evekeo ODT), methamphetamine (Desoxyn), MPH (Adhansia XR, Aptensio XR, Concerta, Cotempla XR-ODT, Daytrana, Jornay PM, Methylin, generics of Metadate CD, Metadate ER, Quillichew ER, Quillivant XR, Relexxii, Ritalin, Ritalin SR, Ritalin LA), dexmethylphenidate (Focalin, Focalin XR), amphetamine extended-release (Adzenys XR-ODT, Dyanavel XR), serdexmethylphenidate/dexmethylphenidate (Azstarys), mixed amphetamine salts ER (Adderall XR), lisdexamfetamine (Vyvanse), and atomoxetine (Strattera) are indicated for children ≥ 6 years of age for the treatment of ADHD. Pediatric patients with ADHD treated with lisdexamfetamine < 6 years old experienced more adverse effects, including long-term weight loss, than patients ≥ 6 years old. Dextroamphetamine ER (Dexedrine) is indicated for children 6 to 16 years of age. Mixed amphetamine salts ER (Mydayis) is indicated for children ≥ 13 years for the treatment of ADHD. The prescribing information for the drugs in this class used for the treatment of ADHD include a warning about using the drugs in children younger than the indicated age, but there are some data on the use of these drugs in younger children.

The safety and efficacy of guanfacine ER (Intuniv) in pediatric patients < 6 years of age have not been established. For children and adolescents ≥ 6 years, efficacy beyond 9 weeks and safety beyond 2 years of treatment have not been established.

The safety and efficacy of clonidine ER (Kapvay) in ADHD patients < 6 years of age have not been established. Maintenance therapy beyond 5 weeks has not been evaluated; patients should be periodically re-evaluated to determine the long-term usefulness of clonidine ER.

Safety and efficacy of viloxazine (Qelbree) have been established in pediatric patients 6 to 17 years of age with ADHD. Safety and efficacy have not been established in pediatric patients < 6 years of age.

Safety and effectiveness in patients ≤ 17 years for modafinil (Provigil) and armodafinil (Nuvigil) have not been established. Serious rash has been reported in pediatric patients receiving these agents.

Agents approved for narcolepsy (amphetamine sulfate tablet [Evekeo], dextroamphetamine IR [tablets, oral solution], methylphenidate IR [Methylin, Ritalin], mixed amphetamine salts IR [Adderall], dextroamphetamine ER [Dexedrine], and methylphenidate ER [Metadate ER, Ritalin SR]) are approved in pediatric patients ages ≥ 6 years. Amphetamine sulfate tablet (Evekeo) also is approved for exogenous obesity in patients > 12 years.

Solriamfetol (Sunosi) is indicated in patients with narcolepsy or OSA. Its safety and efficacy have not been established in patients < 18 years of age.

For exogenous obesity, methamphetamine (Desoxyn) is indicated in patients ≥ 12 years. Safety and efficacy of lisdexamfetamine (Vyvanse) for the treatment of binge-eating disorder have not been established in patients < 18 years old.


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Pitolisant (Wakix) is only indicated in adults with narcolepsy. Its safety and efficacy have not been established in pediatric patients.

## Pregnancy

Guanfacine ER (Intuniv), previously categorized as Pregnancy Category B, has received updated labeling to comply with the Pregnancy and Lactation Labeling Rule (PLLR). Available data does not indicate that there is a drug-associated risk of major birth defects, miscarriage, or other adverse outcomes for mother and child.

Amphetamine extended-release (Dyanavel XR), mixed amphetamine salts extended-release (Mydayis), lisdexamfetamine (Vyvanse), serdexmethylphenidate/dexmethylphenidate (Azstarys), and extended-release methylphenidate (Adhansia XR, Aptensio XR, Cotempla XR-ODT, Jornay PM, Quillichew ER, Quillivant XR, Relexxii) have not been assigned a Pregnancy Category based on the FDA's revised pregnancy risk formatting; data on use of amphetamines and methylphenidate in this population are too limited to inform of drug-associated risks.

Armodafinil (Nuvigil), atomoxetine (Strattera), clonidine ER (Kapvay), dextroamphetamine (Dexedrine), dexmethylphenidate (Focalin, Focalin XR) and certain methylphenidate products (Ritalin SR, Ritalin LA, Daytrana) were previously assigned Pregnancy Category C. Labeling has been updated for all to comply with the PLLR. For armodafinil, the label now advises that there are no adequate studies of its use in pregnant women, but intrauterine growth restriction and spontaneous abortion have been reported with armodafinil and modafinil use. Armodafinil should only be used during pregnancy if the potential benefits justify the potential risk to the fetus. Prolonged experience with clonidine in pregnant women over several decades has not identified drug-associated adverse maternal or fetal outcomes. All other agents in this class are Pregnancy Category C. Available data on atomoxetine, solriamfetol (Sunosi), and pitolisant (Wakix) in pregnant women are insufficient to inform of a drug-associated risk to the fetus.

Based on animal study data, viloxazine (Qelbree) may cause harm when administered to a pregnant woman; however, data from case series with use in pregnant women are inadequate to advise of maternal or fetal risk. Viloxazine should be discontinued once pregnant unless the benefits outweigh the risk to the mother.

There is a pregnancy exposure registry to monitor outcomes in women exposed to ADHD medications during pregnancy.

## Hepatic Impairment

Dose reductions of atomoxetine (Strattera) are required for patients with moderate (Child-Pugh Class B) and severe (Child-Pugh Class C) hepatic impairment.

The bioavailability of the inactive metabolite, modafinil acid, is increased 9-fold in patients with severe renal impairment (creatinine clearance [CrCl] ≤ 20 mL/min); safety and efficacy of modafinil (Provigil) in this patient group have not been determined. For patients with severe hepatic impairment, the dosage of modafinil should be reduced by 50%.

The dose of armodafinil (Nuvigil) should be reduced in patients with severe hepatic impairment.

Pitolisant (Wakix) is extensively metabolized by the liver. Pitolisant is contraindicated in patients with severe hepatic impairment. Pitolisant dose should be reduced in patients with moderate hepatic impairment. Monitor patients with mild or moderate impairment who are taking pitolisant.


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Since the impact of hepatic impairment on the pharmacokinetics of viloxazine (Qelbree) is unknown, its use is not recommended in those with hepatic impairment.

## Renal Impairment

Clearance of amphetamine is reduced in patients with severe renal insufficiency (estimated glomerular filtration rate [eGFR], 15 to < 30 mL/min/1.73 $m^2$); therefore, the maximum dose of mixed amphetamine salts extended-release (Adderall XR, Mydayis) in adults should be reduced. Patients 13 to 17 years of age with severe renal impairment may receive the recommended starting dose if tolerated; however, the dose should not be increased. Mixed amphetamine salts extended-release (Adderall XR, Mydayis) is not recommended for use in patients with end-stage renal disease (eGFR < 15 mL/min/1.73 $m^2$).

Patients with severe renal impairment taking lisdexamfetamine (Vyvanse) should not exceed a maximum dose of 50 mg/day. The recommended maximum dose of lisdexamfetamine in patients with end stage renal disease (ESRD) is 30 mg/day.

Dose adjustments of solriamfetol are recommended for patients with moderate to severe renal impairment. Its use is not recommended with ESRD (eGFR < 15 mL/min/1.73 $m^2$).

The dose of pitolisant must be adjusted for patients with moderate (eGFR 30 to 59 mL/min/1.73 $m^2$) and severe (eGFR 15 to 29 mL/min/1.73 $m^2$) renal impairment. Its use is not recommended in patients with ESRD.

Dose adjustments are not required for viloxazine (Qelbree) patients with mild to moderate renal impairment (eGFR 30 to 89 mL/min/1.73$m^2$); however, drug levels of viloxazine increase in renal impairment, and a dose reduction is recommended for those with severe renal impairment (eGFR < 30 mL/min/1.73$m^2$).

## Geriatric Use

The majority of agents evaluated in this therapeutic class have not been studied in the elderly and/or are not indicated for use in this patient population. Consult the FDA-approved indications table for approved age ranges for individual products. The following agents have not been studied in geriatric patients: amphetamine (Evekeo ODT), amphetamine ER (Adzenys XR-ODT, Dyanavel XR), dexmethylphenidate (Focalin), dexmethylphenidate ER (Focalin XR), lisdexamfetamine dimesylate (Vyvanse), methylphenidate IR (Methylin, Ritalin), methylphenidate ER (Adhansia XR, Aptensio XR, Cotempla XR-ODT, Jornay PM, Quillichew ER, Quillivant XR, Ritalin LA), methylphenidate ER OROS (Concerta, Relexxii), methylphenidate transdermal (Daytrana), mixed amphetamine salts IR (Adderall), mixed amphetamine salts ER (Adderall XR, Mydayis, Azstarys), atomoxetine (Strattera), and guanfacine ER (Intuniv). Labeling for a few of the agents does not address use in the elderly: amphetamine (Evekeo), dextroamphetamine, dextroamphetamine ER (Dexedrine), and clonidine ER (Kapvay).

A reduced dose and careful monitoring should be considered in elderly patients receiving armodafinil (Nuvigil) or modafinil (Provigil) due to the potential for decreased elimination. There are limited data available for pitolisant (Wakix) suggesting no overall differences in safety or efficacy with elderly patients compared to younger patients; however, the potential exists for elderly patients to have greater sensitivity. Solriamfetol (Sunosi) did not exhibit substantial differences in safety or efficacy with elderly patients compared to younger patients. Data are inadequate to determine if elderly patients treated with methamphetamine (Desoxyn) or viloxazine (Qelbree) respond differently than younger


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patients.

### Other

A pitolisant dosage reduction is recommended in patients who are known poor CYP2D6 metabolizers.

## DOSAGES[342,343,344,345,346,347,348,349,350,351,352,353,354,355,356,357,358,359,360,361,362,363,364,365,366,367,368,369,370,371,372,373,374,375,376,377,378,379]

| Drug | Ages | Usual Initial Dosage | Maximum Dosage | Dosage Forms |
|---|---|---|---|---|
| **Stimulants: Immediate-Release** | | | | |
| amphetamine sulfate (Evekeo, Evekeo ODT) | 3–5 years (tablet only) | 2.5 mg once daily | 40 mg/day in 2 or 3 divided doses | Tablets: 5 mg, 10 mg<br>Orally disintegrating tablets (ODT): 5 mg, 10 mg, 15 mg, 20 mg |
| | 6–17 years | 5 mg once or twice daily | | |
| armodafinil (Nuvigil) | ≥ 17 years | 150 mg to 250 mg once daily in the morning | 250 mg/day | Tablets: 50 mg, 150 mg, 200 mg, 250 mg |
| dexmethylphenidate (Focalin) | 6–17 years | 2.5 mg twice daily | 10 mg twice daily | Tablets: 2.5 mg, 5 mg, 10 mg |
| dextroamphetamine IR tablets | 3–5 years | 2.5 mg once daily | 40 mg/day | Tablets: 5 mg, 10 mg<br>Tablets (Zenzedi®*): 2.5 mg *(brand only),* 5 mg, 7.5 mg *(brand only),* 10 mg, 15 mg, 20 mg, 30 mg |
| | 6–16 years | 5 mg once or twice daily | 40 mg/day in 2 or 3 divided doses | |
| dextroamphetamine solution | 3–5 years | 2.5 mg once daily | 40 mg/day; initial dose upon wakening, additional 1-2 doses every 4 to 6 hours | Oral solution: 5 mg/5 mL† |
| | 6–16 years | 5 mg once or twice daily | 40 mg/day; initial dose upon wakening, additional 1-2 doses every 4 to 6 hours | |
| methamphetamine (Desoxyn) | 6–17 years | 5 mg once or twice daily | 20 to 25 mg/day in 2 divided doses | Tablets: 5 mg |
| methylphenidate IR (Methylin, Ritalin) | 6–17 years | 5 mg twice daily | 60 mg/day in 2 or 3 divided doses | Tablets (*Ritalin and generics*): 5 mg, 10 mg, 20 mg<br>Chewable tablets *(generic only)*: 2.5 mg, 5 mg, 10 mg<br>Oral solution *(Methylin and generics)*: 5 mg/5 mL, 10 mg/5 mL |
| mixed amphetamine salts IR (Adderall) | 3–5 years<br>6–17 years | 2.5 mg once daily<br>5 mg 1 or 2 times daily | 40 mg/day | Tablets: 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg, 20 mg, 30 mg |
| modafinil (Provigil) | ≥ 18 years | 200 mg once daily in the morning | 400 mg/day | Tablets: 100 mg, 200 mg |

* Tablets approved via an Abbreviated New Drug Application (ANDA) from Arbor marketed under the trade name Zenzedi as well as the generic name from Wilshire in select strengths (5 mg, 10 mg, 15 mg, 20 mg, 30 mg).

† One of the oral solutions approved via an ANDA from Independence is marketed under the trade name Procentra®.


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***Dosages (continued)***

| Drug | Ages | Usual Initial Dosage | Maximum Dosage | Dosage Forms |
|---|---|---|---|---|
| **Stimulants: Extended-Release** | | | | |
| amphetamine ER (Adzenys XR-ODT) | 6–17 years | 6.3 mg once daily in the morning | 6 to 12 years: 18.8 mg/day<br>13 to 17 years: 12.5 mg/day | ODT: 3.1 mg, 6.3 mg, 9.4 mg, 12.5 mg, 15.7 mg, 18.8 mg |
| | ≥ 18 years | 12.5 mg once daily in the morning | 12.5 mg/day | |
| amphetamine ER (Dyanavel XR) | ≥ 6 years | 2.5 to 5 mg once daily in the morning | 20 mg/day | Suspension: 1,160 mg/ 464 mL (2.5 mg/mL)<br>Tablets: 5 mg, 10 mg, 15 mg, 20 mg |
| dexmethylphenidate ER (Focalin XR) | 6–17 years | 5 mg once daily | 30 mg/day | Capsules: 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg |
| | ≥ 18 years | 10 mg once daily | 40 mg/day | |
| dextroamphetamine ER (Dexedrine) | 6–16 years | 5 mg once daily | 40 mg once daily | Capsules: 5 mg, 10 mg, 15 mg |
| lisdexamfetamine (Vyvanse) | ≥ 6 years | 30 mg daily in the morning | 70 mg daily in the morning | Capsules: 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg<br>Chewable tablets: 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg |
| methylphenidate ER (Adhansia XR) | ≥ 6 years | 25 mg once daily | Adults: 100 mg daily<br>Pediatrics: 85 mg daily | Capsules: 25 mg, 35 mg, 45 mg, 55 mg, 70 mg, 85 mg |
| methylphenidate ER (Aptensio XR) | ≥ 6 years | 10 mg once daily | 60 mg once daily | Capsules: 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg |
| methylphenidate ER (Cotempla XR-ODT) | ≥ 6 years | 17.3 mg once daily in the morning | 51.8 mg once daily | Extended-release ODT: 8.6 mg, 17.3 mg, 25.9 mg |
| methylphenidate ER (Jornay PM) | ≥ 6 years | 20 mg once daily in the evening | 100 mg once daily in the evening | Capsules: 20 mg, 40 mg, 60 mg, 80 mg, 100 mg |
| methylphenidate ER (generics of Metadate CD) | 6–17 years | 20 mg once daily, in the morning before breakfast | 60 mg once daily, in the morning before breakfast | Capsules *(generic only)*: 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg |
| methylphenidate ER (generics of Metadate ER, Ritalin SR) | 6–17 years | 5 mg twice daily or equivalent (e.g., 10 mg once daily) | 60 mg/day in 1 or 2 divided doses | Tablets *(generic only)*: 10 mg, 20 mg |
| | ≥ 18 years | 20 to 30 mg daily | | |
| methylphenidate ER (Quillichew ER) | ≥ 6 years | 20 mg once daily in the morning | 60 mg/day | Chewable tablets: 20 mg, 30 mg, 40 mg (20 and 30 mg are scored; 40 mg is not scored) |
| methylphenidate ER (Quillivant XR) | ≥ 6 years | 20 mg once daily | 60 mg once daily | Suspension for reconstitution (25 mg/5 mL): 300 mg/60 mL, 600 mg/120 mL, 750 mg/150 mL, 900 mg/180 mL |


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***Dosages (continued)***

| Drug | Ages | Usual Initial Dosage | Maximum Dosage | Dosage Forms |
|---|---|---|---|---|
| **Stimulants: Extended-Release *(continued)*** | | | | |
| methylphenidate ER (Ritalin LA) | 6–17 years | 20 mg once daily | 60 mg once daily | Capsules: 10 mg, 20 mg, 30 mg, 40 mg, 60 mg (generic only) |
| methylphenidate ER OROS (Concerta) | 6–12 years | 18 mg once daily | 54 mg once daily | Tablets: 18 mg, 27 mg, 36 mg, 54 mg, 72 mg *(generic only)* |
| | 13–17 years | 18 mg once daily | 72 mg once daily (< 2 mg/kg/day) | |
| | 18–65 years | 18 or 36 mg once daily | 72 mg once daily | |
| methylphenidate ER OROS (Relexxii) | 6–12 years | 18 mg once daily | 54 mg once daily | Tablets: ‡ 45 mg, 63 mg, 72 mg *(generic only)*§ |
| | 13–17 years | 18 mg once daily | 72 mg once daily (< 2 mg/kg/day) | |
| | 18–65 years | 18 or 36 mg once daily | 72 mg once daily | |
| methylphenidate transdermal (Daytrana) | 6–17 years | 10 mg patch worn 9 hours daily | 30 mg patch worn 9 hours daily | Patches: 10 mg, 15 mg, 20 mg, 30 mg per 9 hours |
| mixed amphetamine salts ER (Adderall XR) | 6–17 years | 10 mg once daily | 30 mg once daily | Capsules: 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg |
| | ≥ 18 years (adults) | 20 mg once daily | 20 mg once daily | |
| mixed amphetamine salts ER (Mydayis) | 13-17 years | 12.5 mg once daily in the morning upon awakening | 25 mg once daily | Capsules: 12.5 mg, 25 mg, 37.5 mg, 50 mg |
| | ≥ 18 years | | 50 mg once daily | |
| serdexmethylphenidate/ dexmethylphenidate (Azstarys) | 6–12 years | 39.2/7.8 mg once daily in the morning | 52.3/10.4 mg once daily in the morning | Capsules: 26.1/5.2 mg, 39.2/7.8 mg, 52.3/10.4 mg |
| | ≥ 13 years | | | |
| **Non-Stimulants** | | | | |
| atomoxetine (Strattera) | ≥ 6 years and < 70 kg | 0.5 mg/kg/day in 1 or 2 divided doses | 1.4 mg/kg/day in 1 or 2 divided doses | Capsules: 10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg, 100 mg |
| | ≥ 6 years and >70 kg and adults | 40 mg/day in 1 or 2 divided doses | 100 mg/day given in 1 or 2 divided doses | |
| clonidine ER (Kapvay) | 6–17 years | 0.1 mg at bedtime | 0.2 mg twice daily | Tablets: 0.1 mg |
| guanfacine ER (Intuniv) | 6–17 years | 1 mg once daily in the morning or evening | 4 mg once daily in the morning or evening | Tablets: 1 mg, 2 mg, 3 mg, 4 mg |
| pitolisant (Wakix) | ≥ 18 years | 8.9 mg once daily | 35.6 mg once daily | Tablets: 4.45 mg, 17.8 mg |
| solriamfetol (Sunosi) | ≥ 18 years | Narcolepsy: 75 mg once daily upon waking<br>OSA: 37.5 mg once daily upon waking | Narcolepsy: 150 mg<br>OSA: 150 mg | Tablets, functionally-scored: 75 mg, 150 mg |
| viloxazine (Qelbree) | 6-11 years | 100 mg once daily | 400 mg once daily | Capsules: 100 mg, 150 mg, 200 mg |
| | 12-17 years | 200 mg once daily | 400 mg once daily | |
| | ≥ 18 years | 200 mg once daily | 600 mg once daily | |

‡ Other FDA-approved strengths of Relexxii that are not commercially available include 18 mg, 27 mg, 36 mg, and 54 mg.

§ Only a generic formulation, approved under an abbreviated new drug application (ANDA), of the 72 mg tablet is available.[380]

The above table represents doses used for the treatment of ADHD, except in the cases of Nuvigil (armodafinil) and Provigil (modafinil), which are only approved to treat shift work disorder, narcolepsy, and sleep apnea. Wakix (pitolisant) is only approved for the treatment of narcolepsy.


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Amphetamine extended-release (Dyanavel XR) dosage may be increased by 2.5 mg to 10 mg per day every 4 to 7 days. Tablets may be chewed or swallowed whole and the 5 mg tablet is functionally scored. Dyanavel XR tablets and suspension are interchangeable with one another, however, these products are not substitutable with other amphetamine agents on an equal milligram basis.

Mixed amphetamine salts ER (Mydayis) should be taken consistently with or without food and upon wakening since its effects can last for 16 hours. Doses of mixed amphetamine salts ER (Mydayis) may be titrated in increments of 12.5 mg on a weekly basis in pediatric patients. In patients with severe renal impairment, the daily dose of mixed amphetamine salts ER (Mydayis) should not exceed 25 mg in adults and 12.5 mg in pediatrics. Do not substitute mixed amphetamine salts ER (Mydayis) for other amphetamine products.

Prior to starting treatment with mixed amphetamine salts ER (Adderall XR) patients should be evaluated for the presence of cardiac disease. Patients should also be assessed for risk of abuse and monitored for signs of abuse throughout treatment. The recommended dose of mixed amphetamine salts ER (Adderall XR) in adults with severe renal impairment (eGFR, 15 to < 30 mL/min/1.73 $m^2$) is 15 mg once daily in the morning and is 5 mg once daily in pediatric patients (ages 6 to 17 years) with severe renal impairment (maximum dose in ages 6 to 12 years is 20 mg once daily). Use is not recommended in patients with ESRD (eGFR < 15 mL/min/1.73$m^2$).

For patients with moderate (Child-Pugh Class B) hepatic impairment, the initial and target doses of atomoxetine (Strattera) should be reduced by 50%. For patients with severe (Child-Pugh Class C) hepatic impairment, the initial and target doses should be reduced by 75%. For patients taking strong CYP2D6 inhibitors (e.g., paroxetine, fluoxetine, quinidine) or in patients who are known to be CYP2D6 poor metabolizers, atomoxetine should be started at 0.5 mg/kg/day and only increased to the usual target dose of 1.2 mg/kg/day if symptoms fail to improve after 4 weeks and the initial dose is well tolerated.

For patients with severe hepatic impairment, the dosage of modafinil (Provigil) should be reduced by 50%.

Methylphenidate (MPH) extended-release orally disintegrating tablets (Cotempla XR-ODT) should be taken consistently with or without food. Dexmethylphenidate (Focalin, Focalin XR) and MPH extended-release can be administered without regard to meals. MPH immediate-release (Methylin, Ritalin) should be administered 30 to 45 minutes before meals. The timing of the mid-day dose of MPH immediate-release and dexmethylphenidate immediate-release should be individualized based on patient response. The last daily dose of MPH extended-release should be given several hours before bedtime, and MPH extended-release tablets (Concerta, Relexxii) should be taken once daily in the morning. Do not substitute other methylphenidate products on a milligram-per-milligram basis due to different methylphenidate base compositions and pharmacokinetic profiles. The initial administration of methylphenidate ER capsules (Jornay PM) should occur at 8:00 pm, adjusting the administration between 6:30 pm and 9:30 pm to optimize the tolerability and efficacy the following day. The dose of Jornay PM should be titrated in weekly increments of 20 mg.

Lisdexamfetamine capsules can be substituted with lisdexamfetamine chewable tablets on a milligram-per-milligram basis. Lisdexamfetamine (Vyvanse) should not exceed a maximum dose of 50 mg/day in patients with severe renal impairment. The recommended maximum dose of lisdexamfetamine in patients with end stage renal disease is 30 mg/day.


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Serdexmethylphenidate/dexmethylphenidate (Azstarys) dosing may be increased in 1-week intervals. Likewise, in patients 6 to 12 years old, the dose may be decreased to 26.1 mg/5.2 mg. The capsules should be taken whole with or without food, or the contents may be opened and sprinkled on 2 tablespoons of applesauce or into 50 mL of water and consumed within 10 minutes. When transitioning to or from this product and as described above for dexmethylphenidate-containing products, it should not be substituted on a milligram-per-milligram basis.

The recommended target dose range for guanfacine ER (Intuniv), depending on tolerability and the clinical response of the patient, is 0.05 to 0.12 mg/kg/day. Doses > 4 mg/day have not been evaluated in children between 6 and 12 years of age and doses > 7 mg/day have not been evaluated in patients between 13 and 17 years of age. If switching from guanfacine IR to guanfacine ER (Intuniv), discontinue guanfacine IR and titrate with guanfacine ER according to the recommended dosing schedule. Prescribers should re-evaluate patients often and adjust weight-based dosage, as needed. Patients may experience increases in blood pressure and heart rate after discontinuing guanfacine ER (Intuniv) treatment. Daily dose should be reduced in decrements no greater than 1 mg every 3 to 7 days to prevent rebound hypertension and patients should be closely monitored.

Clonidine ER (Kapvay) doses should be increased at a frequency of 0.1 mg per week. Do not substitute clonidine ER for immediate-release clonidine on a milligram-for-milligram basis. When discontinuing therapy, clonidine ER decrements should not exceed 0.1 mg every 3 to 7 days. Clonidine ER (Kapvay) tablets should not be chewed, crushed, or split.

For patients with swallowing difficulties, several ADHD therapy options exist. Many solid oral dosage forms (e.g., mixed amphetamine salts extended-release [Mydayis], methylphenidate extended-release [Adhansia XR, Aptensio XR]) may be opened up and their contents sprinkled over food; contents should not be chewed or divided. Lisdexamfetamine (Vyvanse) capsules may be opened and the entire contents dispersed in water, yogurt, or orange juice and consumed immediately. A spoon may be used to break apart any compacted powder in the water. The contents should be stirred until completely dispersed. The active ingredient dissolves completely once dispersed; however, a film containing the inactive ingredients may remain in the glass once the water is consumed.

Other products specifically designed for patients who may have difficulty swallowing include orally disintegrating tablets (amphetamine ER [Adzenys XR-ODT, dissolve in mouth's saliva prior to swallowing]; methylphenidate ER [Cotempla XR-ODT, no liquid is needed to be consumed]), chewable tablets (lisdexamfetamine [Vyvanse], methylphenidate ER [Quillichew ER]) which should be chewed thoroughly prior to swallowing, oral suspensions (methylphenidate ER [Quillivant XR, reconstitute and shake for ≥ 10 seconds]; amphetamine ER [Dyanavel XR, no reconstitution required]), and transdermal patches (methylphenidate [Daytrana, applied 2 hours prior to onset of activity and worn for 9 hours or individualized based on patient response]).

Atomoxetine capsules are not to be opened as they are an ocular irritant.

Viloxazine (Qelbree) should be taken orally with or without food. The capsules should be swallowed whole. Alternatively, capsules can be opened and the contents sprinkled onto a teaspoonful of applesauce or pudding and consumed within 2 hours for applesauce or 15 minutes for pudding, without chewing.

Depending on response and tolerability, viloxazine may be titrated in increments of 100 mg weekly to the maximum recommended dosage of 400 mg once daily for patients 6 to 11 years old. For pediatric


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patients 12 to 17 years old, the recommended initial dosage of 200 mg orally once daily may be increased after 1 week to the maximum recommended dosage of 400 mg once daily.

## Hypersomnolence

The armodafinil (Nuvigil) dosage for adults (≥ 17 years) with narcolepsy or obstructive sleep apnea/hypopnea syndrome is 150 mg or 250 mg is given once daily in the morning. For patients with shift work sleep disorder, 150 mg should be administered 1 hour prior to the start of the work shift.

The dosage of modafinil (Provigil) for adults (≥ 16 years) with narcolepsy or obstructive sleep apnea/hypopnea syndrome is 200 mg given once daily in the morning. For patients with shift work sleep disorder, the dose should be administered 1 hour prior to work.

The dosage of amphetamine sulfate tablet (Evekeo) and mixed amphetamine salts (Adderall) for the treatment of narcolepsy is 5 mg to 60 mg daily in divided doses. The suggested initial dose for patients 6 to 12 years of age is 5 mg daily; dose may be titrated in increments of 5 mg per day at weekly intervals until optimal response is obtained. In patients ≥ 12 years, start with 10 mg daily which may be titrated by 10 mg per day at weekly intervals until optimal response is obtained. Switching from amphetamine sulfate tablets (Evekeo) to amphetamine sulfate orally disintegrating tablets (Evekeo ODT) can be done on a milligram-per-milligram basis.

The dextroamphetamine IR (tablets, oral solution) dose for children 6 to 12 years is 5 mg once daily; for patients ≥ 12 years old, begin with 10 mg daily. The usual dose is 5 mg to 60 mg daily divided into doses every 4 to 6 hours. Once the dosage has been stabilized, patients can be converted to an equivalent dosage of dextroamphetamine extended-release (Dexedrine) given once daily.

The initial dose of dextroamphetamine ER (Dexedrine) in pediatric patients aged 6 to 12 years is 5 mg daily; in patients ≥ 12 years the initial dose is 10 mg daily. The usual dosage range is 5 mg to 60 mg daily in divided doses.

The methylphenidate (Ritalin, Methylin, Metadate ER, Ritalin SR) dosages for the treatment of narcolepsy are the same as those for ADHD.

Dosages of solriamfetol may be doubled after ≥ 3 days of starting therapy, as needed based on efficacy and tolerability. For patients with moderate renal impairment (eGFR, 30 to 59 mL/min/1.73 $m^2$), the dose should be initiated at 37.5 mg once daily and can be increased to a maximum of 75 mg once daily after a minimum of 7 days. For patients with severe renal impairment (eGFR, 15 to 29 mL/min/1.73 $m^2$), the dose should be initiated at 37.5 mg once daily, which is the maximum dose in this population.

The initial dose of pitolisant (Wakix) is 8.9 mg (two 4.45 mg tablets) once daily in the morning for 1 week (week 1), then increase dosage to 17.8 mg once daily for another week (week 2), and the dose can be further increased to 35.6 mg (2 x 17.8 mg tablets) once daily thereafter (week 3 and beyond). The dose may be adjusted based on tolerability. In patients with moderate hepatic impairment pitolisant should be initiated at 8.9 mg once daily and increased after 14 days to a maximum dosage of 17.8 mg once daily. For patients with moderate or severe renal impairment, pitolisant is to be initiated at 8.9 mg once daily and increased after 7 days to a maximum dosage of 17.8 mg once daily. For patients taking a strong CYP2D6 inhibitor, the initial dose of pitolisant is 8.9 mg once daily for 7 days, then increase to a maximum of 17.8 mg once daily. If the patient is on a stable pitolisant dose, reduce the dose by half upon initiating a strong CYP2D6 inhibitor. For patients stable on pitolisant 8.9 mg or 17.8 mg once daily, double the original daily dose of pitolisant (i.e., 17.8 mg or 35.6 mg, respectively)


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over 7 days upon initiation of a strong CYP3A4 inducer. Decrease the pitolisant dose by half if the strong CYP3A4 inducer is discontinued. In patients who are poor CYP2D6 metabolizers, the initial dose of pitolisant is 8.9 mg once daily and titrate to a maximum of 17.8 mg once daily after 7 days.

### Exogenous Obesity

For adjunctive treatment of exogenous obesity, in patients ≥ 12 years, methamphetamine (Desoxyn) 5 mg is administered 30 minutes before each meal. Treatment should last only a few weeks.

For exogenous obesity, the recommended dose of amphetamine sulfate tablet (Evekeo) is up to 30 mg daily divided in doses of 5 mg to 10 mg given 30 to 60 minutes before meals. Use in children < 12 years is not recommended.

### Binge Eating Disorder

The recommended dose of lisdexamfetamine dimesylate (Vyvanse) is 50 mg to 70 mg per day, following a starting dose of 30 mg every morning with a 20 mg weekly titration schedule.

## CLINICAL TRIALS

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the use of all drugs in this class. Randomized, controlled, comparative trials are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

Studies of ADHD of less than 4 weeks' duration were excluded as it is generally accepted that it takes at least this long to adequately titrate to the optimal dosage of a given agent. Studies conducted more than 25 years ago were excluded, primarily due to a lack of well-controlled clinical trials from that time period. Many of these older studies verified the effectiveness of the stimulants available at that time in treating the symptoms of ADHD.

The safety and efficacy of amphetamine ER (Adzenys XR-ODT) have been established based on adequate and well-controlled studies of mixed salts of a single-entity amphetamine product extended-release capsules in the treatment of ADHD.

Approval for amphetamine sulfate orally disintegrating tablets (Evekeo ODT) was via the 505(b)(2) pathway, which allows at least some of the information required for NDA approval, such as safety and efficacy information on the active ingredient, to come from studies not conducted by or for the applicant.[381] Similarly, FDA-approval of methylphenidate hydrochloride extended-release tablets (Relexxii) was also via the 505(b)(2) pathway and was based on another formulation of methylphenidate hydrochloride extended-release tablets.[382,383]


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## Attention Deficit Hyperactivity Disorder (ADHD)

***Rating Scales***

**Specific**

- Conners' Parent Rating Scale (CPRS) – The scale provides the parents' or caregivers' perspective on a child's behavior. The scale is 92% sensitive and 94% specific.
- Swanson, Nolan, and Pelham scale (SNAP) – The scale has been shown to have greater than 94% sensitivity and specificity in distinguishing hyperactive, inattentive, and impulsive children with ADHD from those without ADHD based on DSM-III-R criteria.
- Swanson, Kotlin, Agler, M-Flynn, and Pelham scale (SKAMP) – A validated rating scale that assesses ADHD manifestations in a classroom setting; specifically assesses context-bound behaviors critical to school settings.
- ADHD Rating Scale-IV (ADHD-RS-IV) – The validated scale, which can be completed by a parent, teacher, or clinician, is based on an 18-item scale, with subscales for hyperactivity/impulsivity and inattentiveness. It is scored on a 4-point frequency scale. ADHD-RS-IV is less effective than the SNAP in differentiating children with ADHD from those without ADHD. It has been shown to have good internal consistency and test-retest reliability. The parent form is 84% sensitive and 49% specific; the teacher form is 72% sensitive and 86% specific.
- ADHD Rating Scale-5 (ADHD-RS-5) – A validated measure of drug efficacy in ADHD treatment which includes 18 DSM-5 symptoms divided into subscales for Inattention and Hyperactivity/Impulsivity. It an updated version of the ADHD-RS-IV scale, with relatively minor changes.
- Permanent Product Measure of Performance (PERMP) – A skill adjusted math test; sum of the number of math problems attempted plus the number of math problems answered correctly in a 10-minute session.
- Weiss Functional Impairment Rating Scale – Parent (WFIRS-P) – A scale, completed by parents, which evaluates ADHD-related functional impairment using 50 items rated on a 4-point Likert scale grouped into 6 clinically relevant domains.

**Global**

Broad-band scales are not useful as tools to detect clinical-level problems in children presenting; they have low sensitivities and specificities of 70% to 80%.

- CGI-I – Clinical Global Impression improvement subscale
- CGI-S – Clinical Global Impression severity subscale
- C-GAS – Children's Global Assessment Scale

***atomoxetine (Strattera) versus MPH immediate-release***

Two identical 12-week double-blind trials were conducted in 291 children (ages 7 to 13 years) with ADHD.[384] Stimulant-naïve patients were randomized to atomoxetine (up to 2 mg/kg/day or 90 mg), methylphenidate (MPH) (up to 1.5 mg/kg/day, or 60 mg), or placebo. Patients with prior stimulant exposure were randomized only to atomoxetine or placebo. Atomoxetine significantly reduced ADHD RS total scores, the primary endpoint, compared with placebo in each study ($p<0.001$). Changes in the CGI-S and CPRS also showed atomoxetine to be significantly superior to placebo in reducing ADHD symptoms. There was no significant difference between atomoxetine and MPH. A subsequent


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subanalysis of 51 female subjects showed that atomoxetine was similarly superior to placebo in this patient subset.[385]

***atomoxetine (Strattera) versus MPH OROS (Concerta)***

A randomized, double-blind, placebo-controlled study compared the response, as measured by the ADHD Rating Scale of atomoxetine, MPH OROS, and placebo.[386] A total of 516 children ages 6 to 16 years with ADHD were randomized to receive 0.8 to 1.8 mg/kg per day of atomoxetine (n=222), 18 mg to54 mg/day of MPH OROS (n=220), or placebo (n=74) for 6 weeks. Patients who had previously had an inadequate response to stimulant treatment were excluded from the study. After 6 weeks, using double-blind conditions, the patients receiving MPH OROS were switched to atomoxetine. Response was determined by a 40% reduction from baseline as measured by the ADHD Rating Scale. Response results indicated that atomoxetine and MPH OROS were better than placebo, with atomoxetine resulting in a 45% response, MPH OROS resulting in a 56% response, and placebo resulting in a 24% response. The response rate for MPH OROS was significantly higher than atomoxetine (p=0.016). Seventy patients who received MPH OROS did not respond, but 30 of these patients (43%) responded after being switched to atomoxetine. Also, note that 69 patients did not respond to atomoxetine treatment, but 29 (42%) of these patients previously responded to MPH OROS treatment. Completion and discontinuations rates due to adverse events were low and similar for all treatment groups. Results indicated that response to MPH OROS was greater than atomoxetine, but patients not responding to MPH OROS initially may respond to atomoxetine treatment instead. Both agents had a superior response rate over placebo.

***atomoxetine (Strattera) versus MPH immediate-release***

A randomized, double-blind, crossover trial compared the efficacy of atomoxetine and MPH for treating ADHD, as well as their effects on the sleep of children with ADHD.[387] Eighty-five children with ADHD, either in a private practice setting or a hospital setting, were given twice daily atomoxetine (mean dose 42.29 mg/day) and 3 times daily MPH (mean dose 58.27 mg/day), each for approximately 7 weeks. Relative to baseline, actigraphy data indicated that MPH increased sleep latency significantly more than did atomoxetine (39.2 versus 12.1 minutes; p<0.001); these results were consistent with polysomnography data. Compared with MPH, child diaries indicated that taking atomoxetine had less sleep disturbance adverse effects. For example, it was easier to wake up in the morning, took less time to fall asleep, and the patients recorded better sleep with atomoxetine treatment. Parents reported similar findings, such as the children were less irritable, had fewer difficulties with waking in the morning, and were less resistant at night to prepare for bed when administered atomoxetine as opposed to MPH. Using the main measures of efficacy, the medications had similar efficacy for treatment of ADHD. Greater incidence of decreased appetite and insomnia with MPH were the only significant differences in treatment-emergent adverse events. Both medications decreased nighttime awakenings, but the decrease was greater for MPH.

***clonidine extended-release (Kapvay) versus placebo***

The efficacy of clonidine ER in the treatment of ADHD was established in 2 manufacturer approval trials in pediatric patients with ADHD ages 6 to 17 years.[388] Signs and symptoms of ADHD were evaluated using the ADHD RS-IV total score including hyperactive/impulsivity and inattentive subscales. Study 1 was a randomized, double-blind, placebo-controlled, study of 236 patients who were randomly assigned to clonidine ER 0.2 mg or 0.4 mg daily or placebo daily. At both doses, improvements in ADHD


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symptoms were statistically significantly superior in clonidine ER patients compared with placebo patients at the end of 5 weeks as measured by the ADHD RS-IV total score. Study 2 was a randomized, double-blind, placebo-controlled, study in 198 pediatric patients. Patients had previously been treated with methylphenidate or amphetamine for 4 weeks with inadequate response. Patients were randomly assigned to clonidine ER as adjunct to the stimulant or the previous stimulant alone. The clonidine ER dose was initiated at 0.1 mg daily and titrated upward, as clinically appropriate. ADHD symptoms were statistically significantly improved in clonidine ER plus stimulant group compared with the stimulant-alone group at the end of 5 weeks as measured by the ADHD RS-IV total score.

***guanfacine extended-release (Intuniv) versus placebo***

The efficacy of guanfacine ER in the treatment of ADHD was evaluated in 2 placebo-controlled trials in children and adolescents ages 6 to 17 years.[389] Study 1 evaluated guanfacine ER 2, 3, or 4 mg dosed once daily in an 8-week, double-blind, placebo-controlled, parallel-group (n=345) trial. Study 2 evaluated guanfacine ER 1, 2, 3, or 4 mg dosed once daily in a 9-week, double-blind, placebo-controlled, parallel-group (n=324) trial. Doses were titrated in increments of up to 1 mg/week. The mean reductions in ADHD RS scores at endpoint were statistically significantly greater for guanfacine ER compared to placebo for both studies. Due to the relatively small proportion of adolescent patients (13–17 years of age) enrolled into these studies (approximately 25%), these data may not be sufficient to demonstrate efficacy in the adolescent subgroup. When evaluated regarding dose per body weight, clinically relevant improvements were observed beginning at doses in the range 0.05 to 0.08 mg/kg/day. In these studies, dosages were not optimized by body weight, and over half (55%) of the adolescent patients received doses of 0.01 to 0.04 mg/kg. The most commonly reported treatment-emergent adverse events were headache, somnolence, fatigue, upper abdominal pain, and sedation. Small to modest changes in blood pressure, pulse rate, and electrocardiogram parameters were observed but were not clinically meaningful.

***mixed amphetamine salts extended-release (Adderall XR) versus MPH OROS (Concerta)***

A randomized, double-blind, placebo-controlled study compared mixed amphetamine salts ER, MPH OROS, and placebo on ADHD neuropsychological functioning.[390] Adolescents (n=35, 19 males) with a diagnosis of ADHD completed 3 separate assessments (5:00 p.m., 8:00 p.m., 11:00 p.m.) on 3 different days and medications (mixed amphetamine salts ER, MPH OROS, placebo). Delayed Matching-to-Sample and Go/No-go (GNG) neuropsychological tests, which measure visual memory, attention span, and response inhibition, were used to evaluate outcomes. Neuropsychological functioning, as measured by commission errors, reaction time, and recall accuracy, showed significant improvement when patients were taking MPH OROS as opposed to placebo. Results suggest that MPH OROS impacts both symptomatic behavior and cognitive functioning, which have implications for both academic performance and daily functioning.

***mixed amphetamine salts extended-release (Mydayis) versus placebo***

The efficacy of mixed amphetamine salts ER (MAS) in adults was evaluated in 3 randomized, double-blind, placebo-controlled studies.[391] Study 1 assigned 275 patients, who met DMS-V criteria for ADHD, to daily doses of MAS of 12.5mg for the entire study, 12.5 mg with a forced titration to 37.5 mg, or placebo. At week 4, both doses of MAS demonstrated a statistically significant change from baseline in ADHD-RS total score compared with placebo (-8.1 [-11.7, -4.4] for 12.5 mg/day; -13.4 [-17.1, -9.7] for 37.5 mg/day). Studies 2 and 3 were cross-over studies in patients who met DSM-IV TR criteria for


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ADHD, which determined efficacy based on the Permanent Product Measure of Performance (PERMP) scale with uses mathematical problems. Efficacy assessments were conducted at 2, 4, 8, 12, 14, and 16 hours post-dose (Study 2 50 mg/day; Study 3 25 mg/day). MAS treatment achieved statistically significant difference compared to placebo at either 2 hours (Study 2) or 4 hours (Study 3) post-dose to 16 hours post-dose in both studies. In a pre-specified supplementary analysis for Study 2, the maximum approved dose of MYDAYIS (50 mg) demonstrated a statistically significant treatment effect compared with placebo beginning at 2 to 16 hours post-dose.

The efficacy of mixed amphetamine salts ER (MAS) in pediatric patients, ages 13 to 17 years meeting the DSM-IV TR criteria for ADHD, was evaluated in 2 randomized, double-blind, placebo-controlled trials.[392] Study 1 patients (n = 157) were titrated from a dose of 12.5 mg/day until an optimal dose was reached, up to a maximum dose of 25 mg, which was then maintained during a dose-maintenance period. At week 4, MAS demonstrated a statistically significant change in ADHD RS-IV total score from baseline compared to placebo (-8.7 [-12.6, -4.8]). In Study 2, patients were given 25 mg per day or placebo. Efficacy assessments, based on PERMP, were conducted at 2, 4, 8, 12, 14, and 16 hours post-dose. MAS achieved statistical significance at 2 to 16 hours post-dose compared to placebo (difference 41.26 [32.24, 50.29]).

***amphetamine sulfate tablet (Evekeo) versus placebo***

A multicenter, dose-optimized, randomized, double-blind, placebo-controlled crossover laboratory classroom study was conducted to evaluate the safety and efficacy of amphetamine sulfate tablet (Evekeo) in children with ADHD.[393] After an 8-week open-label dose optimization period, 97 children between the ages of 6 and 12 were randomized to 2 weeks of treatment (amphetamine sulfate followed by placebo or placebo followed by amphetamine sulfate). Efficacy measures included the SKAMP rating scale and Permanent Product Measure of Performance (PERMP) which was administered before dose and at 0.75, 2, 4, 6, 8, and 10 hours after dose on 2 laboratory classroom days. Compared to placebo, a single daily dose of amphetamine sulfate significantly improved SKAMP-Combined scores at each time point during classroom days ($p<0.0001$). Amphetamine sulfate also significantly improved PERMP number of problems attempted and correct ($p<0.0001$).

***dexmethylphenidate (Focalin), MPH immediate-release, and placebo***

In a randomized, double-blind study, 132 subjects received dexmethylphenidate, MPH, or placebo twice daily for 4 weeks, with titration of the dose based on weekly clinic visits.[394] The primary efficacy variable was change from baseline of Teacher SNAP to last study visit. Secondary efficacy measures included the change on Parent SNAP, CGI-I, and Math Test performance. Treatment with either dexmethylphenidate ($p=0.0004$) or MPH immediate-release ($p=0.0042$) significantly improved Teacher SNAP ratings compared with placebo. The dexmethylphenidate group showed significant improvements compared with placebo on the afternoon Parent SNAP ($p=0.0003$) and on the Math Test scores obtained at 6:00 p.m. ($p=0.0236$). Improvement based on CGI-I occurred in 67% of patients on dexmethylphenidate and 49% of patients on MPH immediate-release. Both active treatments were well tolerated.

***MPH immediate-release, MPH OROS (Concerta), and placebo***

A double-blind, placebo-controlled, randomized, 5-period crossover study in 49 healthy subjects with a history of light (occasional) recreational stimulant use was performed to evaluate the abuse-related subjective effects of MPH OROS with comparable doses of MPH immediate-release.[395] Patients were


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included in the study if they demonstrated a positive response to a 20 mg dose of dextroamphetamine and a negative placebo response. Patients were then randomized to receive single doses of placebo, 54 and 108 mg MPH OROS, and 50 and 90 mg MPH immediate-release. For each treatment, patients were observed for 24 hours to assess pharmacokinetics, pharmacodynamics, and safety. Both doses of MPH immediate-release produced statistically significant higher positive stimulant effects with respect to placebo for all measures ($p<0.001$). MPH OROS 108 mg also produced statistically significant differences from placebo ($p<0.01$), but the more commonly prescribed dose, MPH OROS 54 mg, did not produce significant differences from placebo. Overall, for comparable dose levels, MPH OROS produced lower positive and stimulant subjective effects than MPH immediate-release, and the lowest MPH immediate-release doses produced more of an effect than the highest of MPH OROS doses, showing that formulation may help reduce abuse potential.

In a multicenter, double-blind trial, 282 children (ages 6 to 12 years) with ADHD were randomized to receive MPH immediate-release 5 mg, 10 mg, or 15 mg three times daily, MPH OROS 18 mg, 36 mg, or 54 mg once daily, or placebo for 28 days.[396] Response, defined as >30% reduction from baseline IOWA Conners Oppositional/Defiance (O/D) score, occurred in 52%, 59%, and 26% of patients in the MPH immediate-release, MPH OROS, and placebo groups, respectively, as rated by parents ($p<0.0001$ for comparison of both active treatments to placebo). Teacher-rated response rates were 63%, 68%, and 43%, respectively ($p<0.0107$ for comparison of active treatments to placebo). The response rate for the 2 higher doses of MPH OROS (77%) was significantly higher than for MPH immediate-release based on parent ratings ($p<0.05$). Forty-eight percent of the placebo group discontinued study drug early compared with 14% and 16% in the MPH and OROS MPH groups, respectively.

***MPH extended-release orally disintegrating tablet (Cotempla XR-ODT) versus placebo***

The efficacy of MPH extended-release ODT was evaluated in 87 patients with ADHD (6 to 12 years of age) in a laboratory classroom study.[397,398] Following washout period, patients entered a 4-week open-label dose-optimization period with an initial dose of 17.3 mg of MPH extended-release ODT once daily in the morning. The dose could be titrated from 17.3 mg to 25.9 mg, 34.6 mg, or 51.8 mg on a weekly basis until an optimal dose or the maximum daily dose of 51.8 mg was reached. Patients were then randomized to a 1-week, double-blind, parallel group treatment period with the individually optimized dose or to placebo. At the end of the week, the primary efficacy endpoint of the average of the SKAMP-Combined (Attention and Deportment), a validated 13-item teacher-rated scale that assesses manifestations of ADHD in a classroom setting, was measured. SKAMP scores over the test day at 1, 3, 5, 7, 10, 12, and 13 hours post-dosing was statistically significantly lower with MPH ER ODT compared to placebo (14.3 versus 25.3, respectively).

***MPH extended-release (Jornay PM) and placebo***

Two clinical studies in pediatric patients ages 6 to 12 years with ADHD (inattentive, hyperactive-impulsive, or combined inattentive/hyperactive-impulsive subtypes by DSM-5) established the efficacy of MPH ER capsules (Jornay PM).[399] Study 1 (NCT02493777) was a 6-week study in which 117 patients entered an open-label, dose-optimization phase (range, 20 to 100 mg) followed by a 1 week double-blind, placebo-controlled withdrawal phase, at which time participants were randomized to continue treatment or switch to placebo. At the end of the blinded period, the difference in least squares mean model-adjusted average of all post-dose SKAMP combined scores, the primary endpoint, was -5.9 (95% CI, -9.1 to -2.7), favoring treatment. Study 2 (NCT02520388) was a 3-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study in which 161 patients were randomized to an


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evening dose of 40 mg, 60 mg, or 80 mg MPH ER capsules or placebo. After 3 weeks, the difference in ADHD RS, the primary endpoint, was -7 (95% CI, -11.4 to -1.7), also favoring treatment.

***MPH extended-release (Quillichew ER) versus placebo***

A 1-week, randomized, double-blind, placebo-controlled, parallel-group laboratory school study evaluated the efficacy of MPH extended-release chewable tablet in 90 subjects (ages 6 to 12 years; ITT population n=85) diagnosed with ADHD (based on DSM-IV criteria).[400] Patients entered a 6-week open-label dose optimization period, followed by a 1-week period in which they were randomized to either placebo or the optimized dose (10 to 60 mg) of MPH extended-release chewable tablet. The primary outcome was the average of treatment effects (as measured by the SKAMP-combined score across all time points during the classroom day (0.75, 2, 4, 8, 10, 12, and 13 hours) as rated by teachers and raters. The placebo-subtracted difference in the average of treatment effect across all time points as measured by the SKAMP-combined score was -7 (95% CI, -10.9 to -3.1), demonstrating superiority of MPH extended-release chewable tablet over placebo.

***MPH extended-release (Quillivant XR) versus placebo***

A total of 45 subjects (ages 6 to 12 years) were enrolled in this dose-optimized, randomized, double-blind, placebo-controlled, crossover laboratory school study. The purpose of this study was to determine the efficacy of extended-release (ER) suspension of MPH compared with placebo in the treatment of ADHD in children.[401] Following a 4 to 6 week open-label dose optimization phase, subjects received 2 weeks of double-blind treatment, 1 week of MPH ER suspension, and 1 week of placebo. Efficacy measures included SKAMP Rating Scale-Combined and Permanent Product Measure of Performance (PERMP) mathematics tests measured at pre-dose and at 0.75, 2, 4, 8, 10, and 12 hours post-dose on each laboratory classroom day. MPH ER suspension resulted in significant ($p<0.0001$) improvements in the SKAMP-Combined score at 4 hours post-dose (mean=7.12) as compared with placebo (mean=19.58) in the completers (n=39). Significant separation from placebo occurred at each time point tested with onset of action at 45 minutes post-dose and duration of efficacy extending to 12 hours post-dose. Adverse events and changes in vital signs following MPH ER suspension were generally mild and consistent with the known safety profile of MPH. MPH ER suspension effectively reduced symptoms of ADHD in children beginning at 45 minutes and continuing for 12 hours post-dose.

***MPH OROS (Concerta) MPH transdermal (Daytrana), and placebo***

In a double-blind study, 270 children (ages 6 to 12 years) with ADHD were randomized to 1 of 3 treatment arms: MPH OROS + placebo patch, MPH transdermal + placebo capsule, or placebo capsule + placebo patch.[402] The study consisted of a 5-week dose-optimization phase followed by a 2-week maintenance phase. At the conclusion of the study, the mean daily doses were 43.4 mg and 22.9 mg for the oral and transdermal dosage forms, respectively. The primary endpoint was the change in ADHD RS from baseline. A reduction in ADHD RS of at least 30% was observed in 66%, 78%, and 29% of patients receiving MPH OROS, MPH transdermal and placebo, respectively (p=NS for comparison of active treatments; $p<0.05$ for comparison of each active treatment to placebo). Reductions from baseline in both the hyperactivity/impulsivity and the inattentiveness subscales were similar in both active treatment groups and were significantly greater than in the placebo group. The manufacturers of MPH transdermal funded the study.


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***lisdexamfetamine dimesylate (Vyvanse) versus placebo***

A phase 3, multicenter, randomized, double-blind, forced-dose, parallel-group study was conducted at 40 centers across the United States (US).[403] The purpose of the study was to assess the efficacy and tolerability of lisdexamfetamine in school-aged children with ADHD treated in the community, and to characterize the duration of action of lisdexamfetamine compared with placebo. The study included 290 randomized patients; 230 patients completed the study. Sixty patients did not complete the study, mostly due to either lack of efficacy or adverse effects. Significant improvements in ADHD RS-IV scores were seen with all doses (30, 50, or 70 mg) of lisdexamfetamine compared with placebo, and in CPRS scores with all lisdexamfetamine doses versus placebo throughout the day. Efficacy was observed by the first week of treatment, and improvements were observed throughout the day up to about 6:00 p.m. The most frequently reported adverse effects among patients receiving lisdexamfetamine were typical of amphetamine products. Most adverse effects were mild to moderate and occurred in the first week.

A multi-center, randomized, double-blind, placebo-controlled, crossover design, modified analog classroom study of lisdexamfetamine to simulate a workplace environment in 142 adults who met Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV-TR) criteria for ADHD.[404] There was a 4-week open-label, dose optimization phase with lisdexamfetamine (30, 50, or 70 mg/day in the morning). Subjects were then randomized to 1 of 2 treatment regimens: an optimized dose of lisdexamfetamine followed by placebo, each for 1 week, or placebo followed by lisdexamfetamine, each for 1 week. Efficacy assessments occurred at the end of each week, using the Permanent Product Measure of Performance (PERMP), a skill-adjusted math test that measures attention in ADHD. Lisdexamfetamine treatment, compared to placebo, resulted in a statistically significant improvement in attention across all post-dose time points, as measured by average PERMP total scores over the course of one assessment day, as well as at each time point measured. The PERMP assessments were administered at pre-dose (-0.5 hours) and at 2, 4, 8, 10, 12, and 14 hours post-dose.

***methylphenidate extended-release (Adhansia XR) versus placebo***

The efficacy of methylphenidate extended-release for the treatment of ADHD in adults was evaluated in 2 randomized, double-blind, placebo-controlled studies (Study 1 NCT02139124, 4 weeks, n=375; Study 2 NCT02225639, crossover study, workplace environment, n=90).[405,406] In Study 1, patients were randomized to receive methylphenidate ER 25 mg, 45 mg, 70 mg, 100 mg, or placebo. Doses were titrated over a 2-week period, then maintained at the assigned dose for an additional 2 weeks. Statistically significant improvement was observed for methylphenidate ER 45 mg and 100 mg compared to placebo in the primary efficacy endpoint of change in the adult ADHD-Rating Scale (ADHD-5-RS) from baseline (visit 2, week 1) to visit 6, week 5 (differences from placebo, -7.1 [95% CI -10.8 to -3.4] and -7.9 [95% CI, -11.6 to -4.1]); the 25 mg and 70 mg study doses did not meet statistical difference. In Study 2, adults were titrated to an optimal methylphenidate ER dose of 25 mg, 35 mg, 45 mg, 55 mg, 70 mg, 85 mg, or 100 mg in an open-label manner between 2 and 7 weeks. They were then randomized to 1 of 2 regimens, study drug for 1 week followed by placebo for 1 week, or placebo for 1 week followed by study drug for 1 week. Methylphenidate ER demonstrated statistically significant improvement over placebo in the primary efficacy determined by the change in the Permanent Product Measure of Performance Total (PERMP-T) score that measured number of math problems attempted and number answered correctly (difference, 26.8 [95% CI, 15.2 to 38.4]).

In Study 3 (NCT02139111), patients 12 to 17 years of age with ADHD (n=354) were randomized to methylphenidate ER 25 mg, 45 mg, 70 mg, 85 mg, or placebo.[407,408] Doses were titrated over 2 weeks


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to a dose that was maintained for an additional 2 weeks. Methylphenidate ER 45 mg and 70 mg demonstrated a statistically significant improvement measured by the change from baseline in ADHD-5-RS total score compared to placebo (differences, -5.4 [95% CI, -9.2 to -1.6] and -5.2 [95% CI, -9 to -1.4]); the 25 mg and 85 mg doses did not meet statistically significant difference.

In Study 4 (NCT03172481), patients 6 to 12 years of age with ADHD (n=147) were randomized to methylphenidate ER 25 mg, 35 mg, 45 mg, 55 mg, 70 mg, 85 mg, or placebo during a 6-week, open-label, dose-optimization period, followed by a 1-week, randomized, placebo-controlled, double-blind treatment phase.[409] Using SKAMP rating scale as the primary endpoint measure, methylphenidate ER demonstrated a statistically significant improvement over placebo (difference, -8.6 [95% CI, -10.6 to -6.6]).

Another study, a randomized, double-blind, placebo-controlled, parallel-group, adult laboratory classroom study (Study 5; NCT03618030), evaluated the efficacy of methylphenidate ER in adults 18 to 60 years of age who met the DSM5 criteria for ADHD.[410] During an open-label phase up to 7 weeks, patients were titrated to an optimal dose (mean, 67.5 mg). Patients were then randomized to placebo or to continue the optimal dose for 1 week in a double-blind manner. At the end of 1 week, patients were evaluated at pre-dose and at 0.5, 1, 2, 4, 6, 7.5, 9, 11, 13, 14, 15, and 16 hours post-dose using the PERMP-T score. MPH-treated subjects demonstrated a statistically significant improvement over placebo based on the primary efficacy endpoint. The secondary efficacy endpoints were onset and duration of clinical effect, as assessed by the treatment difference in PERMP-T scores at post-dose time points. Methylphenidate ER demonstrated a statistically significant improvement over placebo at all time points post-dose, with an average placebo-subtracted difference of 16.3 (95% CI, 7.6 to 24.9) in PERMP-T score.

***methylphenidate extended-release (Aptensio XR) versus placebo***

The efficacy of methylphenidate extended-release was evaluated in 2 studies; first in a randomized double-blind, placebo-controlled, flexible-dose, crossover trial in children ages 6 to 12 (n=26), secondly, in a randomized, double-blind multicenter, placebo-controlled, fixed-dose trial in patients ages 6 to 18 years (n=230).[411] In Trial 1, patients received flexible dose methylphenidate extended-release (15 mg, 20 mg, 30 mg, or 40 mg once daily) in a 2 to 4 week optimization phase and were then randomized to continue their dose from the open-label phase or receive placebo. After 1 week, patients were evaluated over a period of 12 hours and then were given the opposite treatment for 1 week, followed by a second evaluation. Patients were assessed at various time points ranging from 1 to 12 hours post-dose using the SKAMP score. SKAMP total scores were significantly lower for methylphenidate extended-release than for placebo at test day average and all time points post-dose. In Trial 2, patients were randomized to receive methylphenidate extended-release 10 mg, 15 mg, 20 mg, 40 mg, or placebo for 1 week, followed by an 11-week open label phase. The primary efficacy endpoint was the mean decrease from baseline to the end of Week 1 in the ADHD-RS-IV Total Score. Methylphenidate extended-release 20 mg/day and 40 mg/day doses were superior to placebo for the primary endpoint (p=0.0145 and p=0.0011, respectively).

***serdexmethylphenidate/dexmethylphenidate (Azstarys)***

A phase 3, double-blind, parallel group, randomized, placebo-controlled trial evaluated the safety and efficacy of serdexmethylphenidate/dexmethylphenidate (n=150).[412,413,414] Included patients were aged 6 to 12 years with a diagnosis of ADHD (based on DSM-5 criteria and confirmed by the Mini International Neuropsychiatric Interview for Children and Adolescents [MINI-KID]). The trial consisted


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of a 3-week, open-label, dose-optimization phase that was then followed by a 1-week, randomized, double-blind treatment phase. Following an initial washout period, all patients received a dose of 39.2/7.8 mg once daily in the morning, which could be adjusted weekly over 3 weeks to either 26.1/5.2 mg, 39.2 mg/7.8 mg, or 52.3 mg/10.4 mg (maximum dose) to determine the individual's optimal dose. Patients were then randomized to either continue the optimal dose (mean of 45.6/9 mg) or switch to placebo for 1 week. After 1 week (last dose received that morning following breakfast), laboratory classroom raters evaluated attention and behavior over 13 hours using the SKAMP rating scale. The primary endpoint was the change from baseline in SKAMP scores averaged across the assessment day (0.5, 1, 2, 4, 8, 10, 12, and 13 hours post-dose). At baseline, the treatment group had a SKAMP-combined score of 17.9 (standard deviation [SD], 9.2) and the placebo group had a score of 17.9 (SD, 10.4). The least squares mean change from baseline in SKAMP score was -4.87 (standard error [SE], 0.62) and 0.54 (SE, 0.7) in the treatment and placebo groups, respectively (placebo-subtracted difference, -5.4; 95% CI, -7.1 to -3.7). The change in SKAMP scores peaked at approximately 2 hours post-dose and then slowly returned to scores more similar to placebo over approximately 12 hours post-dose. Data from this study, other dexmethylphenidate-containing products, and pharmacokinetics evaluations were used to obtain approval in older pediatric patients and adults.

***viloxazine (Qelbree) versus placebo***

A phase 3, randomized, double-blind, placebo-controlled, 3-arm, parallel-group, multicenter, US, 6-week trial (NCT03247530), evaluated viloxazine once daily at doses of 100 mg and 200 mg in ADHD patients who were 6 to 11 years old (n=477).[415,416] Enrolled patients had a primary ADHD diagnosis, DSM-5 diagnosis of ADHD and a CGI-S score of ≥ 4 (moderate or greater overall illness severity). Patients were randomized 1:1:1 to receive placebo, 100 mg of viloxazine daily, or 200 mg of viloxazine daily for 6 weeks. Secondary endpoints included the investigator-rated CGI-Improvement (CGI-I) score at the end of study and the following parent self-rated assessments: Conners 3–Parent Short Form (Conners 3−PS) and Weiss Functional Impairment Rating Scale–Parent Form (WFIRS−P). The majority of patients in all 3 study arms were not receiving any ADHD medication at screening (placebo: 89.9%; 100 mg group: 89.6%; 200 mg: 84.5%), whereas 6.9%, 6.5%, and 10.6%, respectively, were taking stimulants, and 3.1%, 3.9%, and 5%, respectively, were taking nonstimulants. At week 6, the primary endpoint of change from baseline in the ADHD-RS-5 total score was significantly improved in the viloxazine 100 mg (p=0.0004) and 200 mg (p<0.0001) groups compared to placebo. Regarding secondary endpoints, the least squares (LS) mean change from baseline for the ADHD-Rating Scale-5 (ADHD-RS-5) total score was -10.9 for placebo, -16.6 for the 100 mg group, and -17.7 for the 200 mg group corresponding with a 50% response rate of 19.8%, 34.2% (p=0.0063 versus placebo), and 41.2% (p<0.0001) for each of the 3 study arms, respectively. Both treatment groups exhibited a significant improvement in the ADHD-RS-5 total score in the first week of treatment which was continued throughout the remainder of the study. The CGI-I score at the end of study was also significantly improved in the 100 mg group (p=0.002) and 200 mg group (p<0.0001) compared to placebo. The change from baseline in the Conners 3−PS Composite T-score at week 6 was significantly improved in the 100 mg group (p=0.0003) and 200 mg group (p=0.0002) compared to placebo, as was the change from baseline in the Weiss Functional Impairment Rating Scale-Parent form (WFIRS–P) total average score at week 6 compared to placebo (100 mg group: p=0.0019; 200 mg group: p=0.0002). The authors found the statistically significant improvements to be clinically meaningful across a variety of behavioral and social domains, and viloxazine to be generally well tolerated.


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A second study (NCT03247543) was a phase 3, randomized, double-blind, placebo-controlled, 3-arm, parallel-group, multicenter, US, 8-week trial evaluating viloxazine once daily at the doses of 200 mg and 400 mg in pediatric patients with ADHD who were 6 to 11 years old with a body weight of ≥ 20 kg.[417,418] Enrolled patients had a primary ADHD diagnosis, DSM-5 diagnosis of ADHD, and a CGI-S score of ≥ 4 (moderate or greater overall illness severity). Patients were excluded if they had a body mass index (BMI) > 95th percentile for age and gender. Patients (n=313) were randomized 1:1:1 to placebo, 200 mg of viloxazine daily, or 400 mg of viloxazine daily for 8 weeks (including ≤ 3-week titration). At week 8, the change from baseline in ADHD-RS-5 total score, the primary endpoint, was significantly improved in the 200 mg (p=0.0038) and 400 mg (p=0.0063) groups compared to placebo. The LS mean change from baseline for the ADHD-RS-5 total score was -11.7 for placebo, -17.6 for the 200 mg group, and -17.5 for the 400 mg group and corresponded with a 50% response rate of 25.8%, 36%, and 41.2% (p<0.05 versus placebo) for each of the 3 study arms, respectively. A significant difference from placebo was present for both the 200 mg and 400 mg study groups by week 5 (included ≤ 3-week titration) and continued throughout the remainder of the study. The secondary endpoint of CGI-I score also demonstrated significant improvements compared to placebo at the end of the study (200 mg group: p=0.0028; 400 mg group: p=0.0099). Although the change from baseline in Conners 3-PS composite T-score showed significant improvement with the 200 mg group (p=0.0064) compared to placebo at the end of the study, the 400 mg group did not demonstrate a significant difference (p=0.0917). For the change from baseline in WFIRS-P total average score, the score was not significantly decreased in either treatment group compared to placebo at the end of the study, but the change from baseline for the mean score for the WFIRS-P school domain measure demonstrated significant improvements for both treatment arms compared to placebo (200 mg group: p=0.0436; 400 mg group: p=0.0459). Viloxazine was found to be generally well tolerated with low discontinuation rates, and the majority of AEs were mild or moderate in severity. The authors concluded their findings suggest viloxazine could result in clinically meaningful improvement in ADHD symptoms in a significant proportion of pediatric patients soon after therapy is started.

A third study (NCT03247517) was a randomized, double-blind, placebo-controlled, 3-arm, parallel-group, multicenter, 6-week trial evaluating viloxazine once daily at the doses of 200 mg and 400 mg in pediatric patients with ADHD who were 12 to 17 years of age with a body weight of ≥ 35 kg (n=310).[419,420] Enrolled patients had a primary ADHD diagnosis, DSM-5 diagnosis of ADHD and a CGI-S score of ≥ 4 (moderate or greater overall illness severity). Patients with a BMI > 95th percentile for age and gender were excluded. Patients were randomized 1:1:1 to receive placebo, 200 mg of viloxazine daily, or 400 mg of viloxazine daily for 6 weeks (including a 1-week titration, initiated at 200 mg once daily). At week 6, the primary endpoint of change from baseline in ADHD-RS-5 total score was significantly improved in the 200 mg (placebo-subtracted difference, -4.5; 95% CI, -8.4 to -0.6) and 400 mg (-5.1; 95% CI, -8.9 to -1.3) groups compared to placebo. Additionally, a significantly greater improvement in CGI-I score was also seen for patients in the 200 mg group and 400 mg group compared with placebo patients at the end of the study.

A fourth study (NCT03247556), a multicenter, randomized, double-blind, placebo-controlled, 3-arm, parallel-group study as ADHD monotherapy for the treatment of adolescents 12 to 17 years old (n=297).[421,422] In this study, patients were randomized to placebo or viloxazine 400 mg or 600 mg daily. The primary outcome was the change from baseline in the ADHD-RS-5 at the end of week 7, which was -18.3 ± 1.36, -16.7 ± 1.39, and -13.2 ± 1.38 in the 400 mg, 600 mg, and placebo groups, respectively. Notably, only a statistically significant difference was seen in the 400 mg daily group compared to placebo (p=0.0082).


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A randomized, double-blind, placebo-controlled trial evaluated the safety and efficacy of viloxazine in 374 patients 18 to 65 years of age with ADHD.[423] Patients were randomized 1:1 to receive viloxazine at a flexible daily dose between 200 mg and 600 mg or placebo. The primary endpoint was the change from baseline at end of week 6 in the Adult ADHD Investigator Symptom Rating Scale (AISRS) total score. Viloxazine-treated patients demonstrated a significantly greater improvement (reduction) in the AISRS total score (−15.5 ± 0.91) compared to the placebo group (−11.7 ± 0.9), p=0.004; and the improvement was seen as early as week 2. CGI-S score was also significantly more improved with viloxazine. In the viloxazine group, 50.8% of patients experienced a treatment-emergent adverse effect compared with 32.8% in the placebo group.

## Hypersomnolence

### *Rating Scales*

Scales commonly used in the evaluation of hypersomnolence and its treatment include:

- Epworth Sleepiness Scale (ESS) – This is a self-administered questionnaire that has been shown to provide a measurement of the subject's general level of daytime sleepiness.[424] This scale has a high level of internal consistency.[425]
- Maintenance of Wakefulness Test (MWT) – In the test, the subject sits in bed, resting against pillows in a quiet, dimly lit room, attempting to stay awake for 20 (or 40) minutes while under scrutiny and with electrodes and wires attached.[426]
- Multiple Sleep Latency Test (MSLT) – The test measures how quickly the subject falls asleep, when asked to do so, when lying down in a quiet, darkened bedroom while under scrutiny and with electrodes and wires attached.[427] The test is considered by many to be the gold standard for measuring daytime sleepiness, although analysis has recently shown it to be the least accurate of the 3 tests.[428,429]

### *modafinil (Provigil) versus placebo – narcolepsy*

A total of 285 subjects between the ages of 18 and 68 years with a diagnosis of narcolepsy were enrolled in a randomized trial to receive modafinil 200 mg, modafinil 400 mg, or placebo once daily for 9 weeks.[430] The mean ESS score was significantly lower for each modafinil treatment group compared to placebo at weeks 3, 6, and 9. Subjective sleepiness ratings at each evaluation were reduced from baseline in all 3 groups. At baseline, 3% of the modafinil 400 mg group, 4% of the modafinil 200 mg group, and 3% of the placebo group were able to remain awake for at least 3 Maintenance of Wakefulness Tests (MWTs). At week 9, the percentage of subjects able to stay awake for at least 3 tests significantly increased to 20% for the modafinil 400 mg group and 14% for the modafinil 200 mg group; no change occurred in the placebo group. Headache was reported to occur statistically significantly more often in the modafinil groups versus the placebo group. This study had an open-label treatment arm with demonstrated efficacy and safety for up to 40 weeks.

### *modafinil (Provigil) versus placebo – OSA-related daytime sleepiness*

In a double-blind, parallel group, randomized study, investigators studied the efficacy and safety of modafinil verses placebo in 157 patients with OSA-related daytime sleepiness despite CPAP for a total of 4 weeks.[431] Patients were randomized to receive modafinil (n=77) at an initial dose of 200 mg per day during week 1, then increasing over 3 weeks up to 400 mg per day, or placebo (n=80) once daily. Modafinil significantly improved daytime sleepiness, with significantly greater mean changes from


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baseline in ESS scores at weeks 1 and 4 (p<0.001), but not significantly different from placebo in MSLT at week 4 (p<0.05). The percentage of patients with normalized daytime sleepiness (ESS <10) was significantly higher with modafinil (51%) than with placebo (27%; p<0.01). There was no difference between groups in the percentage of patients with normalized MSLT (25% to 29%).

***armodafinil (Nuvigil) versus placebo – OSAHS***

The effectiveness of armodafinil in improving wakefulness in patients with excessive sleepiness associated with OSAHS was established in two 12-week studies of outpatients who met the International Classification of Sleep Disorders (ICSD) criteria for OSAHS (which are also consistent with the American Psychiatric Association DSM-IV criteria).[432] In addition, all patients had excessive sleepiness per the ESS, despite treatment with continuous positive airway pressure (CPAP). In the first study, a total of 395 patients with OSAHS were randomized to receive armodafinil 150 mg/day, armodafinil 250 mg/day, or matching placebo every day for 12 weeks. In the second study, 263 patients with OSAHS were randomized to either armodafinil 150 mg/day or placebo. In both studies, patients treated with armodafinil showed improved wakefulness and overall clinical condition.

A 12-week, randomized, double-blind study evaluated armodafinil 150 mg/day compared to placebo as an adjunct treatment for residual excessive sleepiness in 259 patients with OSAHS who were otherwise well controlled with nasal CPAP (nCPAP).[433] The authors assessed the ability of armodafinil to improve wakefulness and cognition and reduce fatigue in this population. Efficacy assessments were done at baseline and weeks 4, 8, and 12. At the final visit, mean Maintenance of Wakefulness Test (MWT) sleep latency increased from baseline with armodafinil and decreased in the placebo group (p=0.0003). Armodafinil improved Clinical Global Impression of Change compared to placebo (p=0.0069). Armodafinil significantly improved episodic secondary memory (p=0.0102) and patient-estimated wakefulness (p<0.01) and reduced fatigue (p<0.05) compared with placebo. Armodafinil did not adversely affect nCPAP use. The most common adverse event associated with armodafinil was headache.

***armodafinil (Nuvigil) versus placebo – narcolepsy***

Patients with excessive sleepiness, as documented by a mean sleep latency test (MSLT) with a sleep latency of 6 minutes or less and the absence of any other clinically significant active medical or psychiatric disorder, were enrolled in a 12-week study of outpatients who met the ICSD criteria for narcolepsy.[434] A total of 196 patients were randomized to receive armodafinil 150 or 250 mg/day or matching placebo. Patients treated with armodafinil showed improved wakefulness and overall clinical condition.

***armodafinil (Nuvigil) versus placebo – SWSD***

The effectiveness of armodafinil in patients with excessive sleepiness associated with SWSD was demonstrated in a 12-week double-blind, placebo-controlled, parallel-group clinical trial. A total of 254 patients with chronic SWSD of moderate or greater severity were randomized to receive armodafinil 150 mg/day or placebo.[435,436] Patients treated with armodafinil showed a statistically significant prolongation in the time to sleep onset, as measured by the nighttime MSLT at final visit (armodafinil MSLT at baseline=2.3, week 12=5.3; placebo at baseline=2.4, week 12=2.8; p<0.001), and improvement in overall clinical condition ratings were seen for armodafinil (79%) compared to placebo-treated patients (59%; p=0.001).


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***pitolisant (Wakix) versus modafinil versus placebo***

The HARMONY-1 trial was a multicenter, randomized, double-blind, placebo- and active-controlled study that evaluated pitolisant in adults with International Classification of Sleep Disorders (ICSD-2) criteria for narcolepsy and an Epworth Sleepiness Scale (ESS) score ≥ 14 (8 items, ranging 0 to 3; maximum score of 24, with higher scores indicating more sleepiness).[437,438] It comprised an 8-week treatment period consisting of a 3-week dose titration period and a 5-week stable dose phase. Patients had no psychostimulants for ≥ 14 days prior to baseline assessments but were allowed to remain on stable doses of other drugs used for symptoms of narcolepsy (e.g., anti-cataplectic agents [sodium oxybate, non-tricyclic antidepressants]). A total of 95 patients were randomized 1:1:1 to pitolisant (8.9 mg, 17.8 mg, or 35.6 mg once daily; equivalent to pitolisant hydrochloride 10 mg, 20 mg, or 40 mg daily, respectively), modafinil (100 mg, 200 mg, or 400 mg per day), or placebo. The dosage used was based to investigator judgement and no dose adjustments were allowed during the 5-week stable dose phase. At baseline, 81% of patients had cataplexy, 45% had prior use of psychostimulants, and 35% continued stable doses of allowed agents for narcolepsy symptoms (anti-cataplectics), although 61% reported continued cataplexy during the trial. Efficacy of pitolisant was evaluated via superiority to placebo and noninferiority to modafinil based on mean final ESS score at the end of week 8 in the intent-to-treat (ITT) population (n=94). After the 3-week titration period, 61% achieved a stable dose of 17.8 mg/day of pitolisant. Pitolisant demonstrated superiority over placebo (ESS difference, -3 [95% CI, -5.6 to -0.4]; p=0.024), but not noninferiority to modafinil (ESS difference 0.12 [95% CI, -2.5 to 2.7]; p=0.25). Superiority over placebo and similar results to modafinil were demonstrated in the maintenance of wakefulness test (MWT) and the sustained attention to response task (SART) "NO GO" scores, but neither superiority over placebo nor noninferiority to modafinil was demonstrated in SART "GO" scores or total SART score.

A second study (NCT01638403) was double-blind, placebo- and active-controlled in design and evaluated the efficacy of pitolisant in adults with International Classification of Sleep Disorders (ICSD-2) criteria for narcolepsy and an ESS score ≥ 14.[439,440,441] The study contained an 8-week treatment period consisting of a 3-week dose titration period and a 5-week stable dose phase. Patients had no psychostimulants for ≥ 14 days prior to baseline assessments but were allowed to remain on stable doses of other drugs used for symptoms of narcolepsy (e.g., anti-cataplectic agents [sodium oxybate, non-tricyclic antidepressants]). The study randomized 166 patients 2:2:1 to pitolisant, modafinil, or placebo. Pitolisant doses could be increased at weekly intervals to 8.9 mg or 17.8 mg, based on efficacy response and tolerability. No dose adjustments were allowed during the 5-week stable-dose phase. After the 3-week titration period, 76% achieved a stable pitolisant dose of 17.8 mg per day. At the end of the 8 weeks, pitolisant demonstrated statistical superiority over placebo based on the mean ESS compared to placebo (difference, -2.2 [95% CI, -4.17 to -0.22]; p=0.03). Non-inferiority to modafinil was not demonstrated.

***pitolisant (Wakix) long-term use***

The HARMONY III trial, an open-label, single-arm safety study, evaluated long-term use of pitolisant in 102 adults with narcolepsy and ESS score ≥ 12.[442] Patients were treated for up to 1 year with pitolisant 35.6 mg once daily. Use of concomitant stimulants and anti-cataplectic treatment was allowed. Common treatment-emergent adverse events were headache (11.8%), insomnia (8.8%), weight gain (7.8%), anxiety (6.9%), depressive symptoms (4.9%), and nausea (4.9%). Treatment was discontinued in 19.6% of patients on pitolisant due to insufficient benefit. The ESS score decreased by 4.6 ± 0.6. Two-thirds of patients completing the study were considered responders (ESS ≤ 10 or ESS decrease ≥ 3), and


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one-third had normalized ESS (≤10). In the study there was reduction in complete and partial cataplexy, hallucinations, sleep paralysis, and sleep attacks by 76%, 65%, 54%, 63%, and 27%, respectively.

***solriamfetol (Sunosi) versus placebo***

A 12-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study assessed the efficacy of solriamfetol in adults (ages 18 to 70 years) with a DSM-5 diagnosis of narcolepsy (n=239).[443] Patients were randomized to solriamfetol 75 mg, 150 mg, or 300 mg or placebo orally once daily. The co-primary efficacy endpoints were the change from baseline in the MWT and ESS at week 12. At baseline, 51% of patients had cataplexy. Patients receiving 150 mg showed statistically significant improvements compared to placebo on both the MWT and the ESS at week 12. The least square mean (SE) change in MWT from baseline was 9.8 (SE, 1.3) minutes for solriamfetol 150 mg versus 2.1 (SE, 1.3) minutes for placebo. Change in solriamfetol 150 mg on the ESS was -5.4 (SE, 0.7) versus -1.6 (SE, 0.7) for placebo; all p<0.0001). Regarding secondary endpoints, at week 12, higher percentages of patients treated with solriamfetol 150 mg (78.2%) reported PGI-C improvement versus placebo (39.7%; p<0.0001). The 75 mg treatment group did not show statistically significant changes versus placebo. No differences were found between groups based on presence of cataplexy. While statistically significant differences were also seen in the 300 mg group, the risk versus benefit does not favor doses over 150 mg.

The efficacy of solriamfetol in adults with an ICSD-3 diagnosis of OSA was demonstrated in a 12-week, multicenter, randomized, double-blind, placebo-controlled study (TONES-3).[444] Included patients, ages 18 to 75 years, had current or prior use of a primary OSA therapy, including positive airway pressure (PAP), a mandibular advancement device, or surgical intervention (n=476). Participants without current primary OSA therapy use or a history of a surgical intervention to treat the underlying obstruction were required to have tried a primary OSA therapy for ≥ 1 month with ≥ 1 documented adjustment to the therapy (e.g., change in PAP pressure, change in mask, change in modality). Additional inclusion criteria were a baseline ESS score ≥ 10; baseline sleep latency < 30 minutes for the average of the first 4 of a 5-trial, 40-minute MWT; and a usual nightly sleep time ≥ 6 hours. Among the exclusion criteria were a usual bedtime later than 1 AM, an occupation requiring nighttime shift work or variable shift work, and use of any over-the-counter (OTC) or prescription medications that could affect the evaluation of excessive sleepiness. Patients were randomized 1:1:2:2:2 to receive solriamfetol 37.5 mg, 75 mg, 150 mg, or 300 mg or placebo once daily. Statistically significant differences were seen in both co-primary endpoints with all doses in MWT and ESS. Treatment effect differences were shown with the 37.5 mg, 75 mg, and 150 mg doses in MWT (treatment effect difference: 4.5 minutes [95% confidence interval {CI}, 1.2 to 7.9], 8.9 minutes [95% CI, 5.6 to 12.1], and 10.7 minutes [95% CI, 8.1 to 13.4], respectively) and ESS (treatment effect difference: -1.9 points [95% CI, -3.4 to -0.3], -1.7 points [95% CI, -3.2 to -0.2], and -4.5 points [95% CI, -5.7 to -3.2], respectively) at week 12. A significant difference in PGI-C was found with all doses except 37.5 mg.

A 6-week, multicenter, double-blind, placebo-controlled, randomized-withdrawal study in adult OSA patients evaluated the maintenance of efficacy of solriamfetol (TONES-4).[445] Included patients were initiated on solriamfetol 75 mg once daily and titrated to the maximum tolerable dose, up to 300 mg daily, during a 2-week, open-label titration phase. Patients were continued on this dose for another 2 weeks (stable-dose phase). At the end of the stable-dose phase, 124 patients who reported “much” or “very much” improvement on the PGI-C and who showed improvements on the MWT and ESS entered a double-blind withdrawal phase and were randomized 1:1 to either continue solriamfetol at the dose


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received in the stable-dose phase or switch to placebo. Co-primary endpoints were changes from week 4 to week 6 in MWT mean sleep latency and the ESS score. The key secondary endpoint was the percentage of participants who reported worsening of their condition on the PGI-C from week 4 to week 6. There were statistically significant changes in MWT and ESS in patients who switched to placebo (MWT difference, 11.2 [95% CI, 7.8 to 14.6] and ESS difference -4.6 [95% CI, -6.4 to -2.8]), indicating a worsening of sleepiness for those on placebo versus those who remained on solriamfetol. No statistically significant change was noted in those continuing treatment.

A 52-week trial included 638 patients with either narcolepsy or OSA who had completed a prior solriamfetol trial.[446] Patients received solriamfetol 75 mg to 300 mg once daily in an initial 2-week open-label titration phase. This was followed by an open-label treatment period of either 38 or 50 weeks, depending on prior study enrollment. After 6 months of stable-dose treatment, 282 patients (79 with narcolepsy; 203 with OSA) entered a 2-week randomized-withdrawal period in which they were randomized 1:1 to either continue solriamfetol or to switch to placebo. The primary efficacy endpoint was change from the beginning to the end of the randomized-withdrawal period in ESS. There was a statistically significant change in ESS for patients receiving placebo (-3.7 [95% CI, -4.8 to -2.7], indicating worsening of sleepiness. No statistically significant change was noted in those continuing treatment.

### Binge Eating Disorder

#### *lisdexamfetamine dimesylate (Vyvanse) versus placebo*

The effectiveness of lisdexamfetamine dimesylate in patients with moderate to severe binge eating disorder (BED) was demonstrated in two 12-week double-blind, placebo-controlled, parallel-group clinical trials.[447,448] A total of 724 patients aged 18 to 55 years who met DSV-IV criteria for BED were randomized to receive lisdexamfetamine dimesylate or placebo. The severity of BED was determined based on the patient having at least 3 binge days per week for 2 weeks prior to their baseline visit and based on the patient having a Clinical Global Impression Severity (CGI-S) score of ≥4 at the baseline visit. The primary efficacy outcome for each study was the change from baseline at week 12 in the number of binge days per week. Each study consisted of a 4-week dose-optimization phase, followed by an 8-week dose-maintenance phase. In the dose-optimization phase, patients assigned to lisdexamfetamine dimesylate began treatment at 30 mg/day and titrated to either 50 mg/day or 70 mg/day, as tolerated. In both trials, patients treated with lisdexamfetamine dimesylate showed a statistically significant reduction from baseline in mean number of binge days per week compared to placebo (Trial 1: -3.87 versus -2.51, respectively; Trial 2: -3.92 versus -2.26, respectively; $p<0.001$ for both). The efficacy of lisdexamfetamine dimesylate for BED has also been demonstrated using a treatment withdrawal study design.[449,450]

## META-ANALYSES

Several meta-analyses and reviews support the short-term efficacy of stimulant medications in reducing the core symptoms of ADHD—inattention, hyperactivity, and impulsivity.[451,452,453,454,455] Research to date has not shown clear advantages of 1 stimulant medication over another or between dosage forms of a given agent. In the policy statement, AAP states that stimulants are equally effective for ADHD. Many children who fail to respond to 1 medication will have a positive response to an alternative stimulant.[456] Notably, a meta-analysis of 32 studied comparing irritability associated with stimulant use versus placebo found that methylphenidate derivatives were associated with a


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decreased risk (risk ratio, 0.89 [95% CI, 0.82 to 0.96]; p=0.004) of irritability while amphetamine derivatives were associated with a higher risk (risk ratio, 2.9 [95% CI, 1.26 to 6.71]; p=0.01).[457] Comparative studies are needed to confirm this finding.

A meta-analysis of 29 randomized, double-blind, placebo-controlled studies involving over 4,465 children (mean age 10 years) with ADHD showed that MPH and MAS are significantly more effective than non-stimulant medications used to treat ADHD (atomoxetine, bupropion, desipramine, and modafinil).[458] Among stimulants, the meta-analysis found no difference in efficacy among MAS and MPH or among immediate-release or extended-release agents. The manufacturer of mixed amphetamine salts ER (Adderall XR) and MPH transdermal patch (Daytrana) funded this meta-analysis.

A Cochrane analysis of amphetamines, including 19 studies evaluating dexamphetamine, lisdexamfetamine, and MAS, found amphetamines reduced severity of clinician-rated and patient-rated symptoms compared to placebo (standardized mean difference [SMD], -0.9 [95% CI, -1.04 to -0.75] and SMD, -0.51 [95% CI, -0.75 to -0.28], respectively); however, no difference was found in treatment retention versus placebo (risk ratio, 1.06 [95% CI, 0.99 to 1.13]).[459] When broken down by amphetamine type, lisdexamfetamine (SMD, -1.06 [95% CI, -1.26 to -0.85]) and MAS (SMD, -0.8 [95% CI, -0.93 to -0.66]) reduced the severity of ADHD symptoms as rated by clinicians, but no statistical difference was found for dexamphetamine (SMD, -0.24 [95% CI, -0.8 to 0.32]). All were efficacious when rated by patients. Like other evaluations, most evaluated studies were short-term in follow-up, and the authors determined the results were not of rigorous quality due to limitations of the studies and their results.

## SUMMARY

The 2019 American Academy of Pediatrics guidelines for ADHD treatment in children recommend the use of stimulant medication and/or behavioral therapy. The guidelines state that, in many cases, stimulants improve the child's ability to follow rules and decrease emotional overactivity, leading to improved relationships.

Due to potential difficulties created by multiple daily dosing (e.g., compliance, social stigma, availability, drug diversion, willingness of schools to store and administer medication) once-daily dosage forms may, in some situations, be preferred.

Several medications have been shown to be effective in treating ADHD. Except for atomoxetine (Strattera), clonidine ER (Kapvay), guanfacine ER (Intuniv), and viloxazine (Qelbree), all of the drugs approved for treatment of ADHD by the FDA are stimulants and are classified as controlled substances. The individual agents used for the treatment of ADHD are associated with different contraindications and precautions for use; this may influence the selection of appropriate therapy in patients with comorbidities (e.g., coexistent tic disorders or Tourette's syndrome).

For school-age children, once-daily dosage forms may enhance compliance and decrease the risk of diversion. Methylphenidate extended-release capsules (Adhansia XR, Aptensio XR, Jornay PM, generics of Metadate CD, and Ritalin LA) and serdexmethylphenidate/dexmethylphenidate (Azstarys) can be opened and contents sprinkled on food. The extended-release methylphenidate products, Cotempla XR-ODT (extended-release orally disintegrating tablet), Quillivant XR (extended-release suspension), and Quillichew ER (extended-release chewable tablet), are options for those patients who cannot swallow tablets or capsules and have failed treatment with other long-acting products that can be opened over applesauce. Amphetamine sulfate (Evekeo, Evekeo ODT), mixed amphetamine salts


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(Adderall, Adderall XR, Mydayis), orally disintegrating extended-release amphetamine (Adzenys XR-ODT), and amphetamine extended-release suspension (Dyanavel XR) provide alternatives for patients who cannot tolerate MPH. Clinical trials of dextroamphetamine (immediate-release tablets and oral solution, Dexedrine) are generally of poor quality and are somewhat dated. Additionally, dextroamphetamine has a greater potential for diversion and misuse than the other drugs used for ADHD. As a result, the dextroamphetamine formulations would not be the best initial choice over methylphenidate to be used as first-line therapy for the majority of children and adolescents with ADHD. Notably, the methylphenidate ER capsules marketed as Jornay PM are dosed in the evening prior to its expected effect, as the pharmacokinetics of the formulation result in drug exposure beginning the following morning.

Lisdexamfetamine dimesylate (Vyvanse), a prodrug of dextroamphetamine, was designed to have an extended duration of effect to allow for once-daily dosing and to have less potential for abuse, diversion, or overdose toxicity. However, there is no evidence that it offers an advantage over any other formulation of amphetamine for treatment of children with ADHD.

Modafinil (Provigil), armodafinil (Nuvigil), and solriamfetol (Sunosi) may provide a slightly different profile of adverse effects than the stimulant medications traditionally used for the treatment of excessive daytime sleepiness (EDS) associated with narcolepsy or obstructive sleep apnea (OSA). Due to their lack of sympathomimetic activity, modafinil and armodafinil are relatively free of adverse cardiovascular effects. All 3 medications also have lower abuse potential and are considered Schedule IV controlled substances. Pitolisant (Wakix) is another non-stimulant option for the treatment of EDS and cataplexy associated with narcolepsy and lacks a controlled substance designation. Dose adjustments are required for special populations and drug interactions.

Methamphetamine (Desoxyn) and amphetamine sulfate tablet (Evekeo) are FDA-approved in adults for short-term adjunctive therapy in a weight reduction regimen based on caloric restriction for patients in whom obesity is refractory to alternative therapy; however, studies showed weight loss due to medication versus diet alone must be considered clinically limited.

Lisdexamfetamine dimesylate (Vyvanse) is the first and only FDA-approved treatment for moderate to severe binge eating disorder in adults.

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# Dextroamphetamine (Xelstrym™) Drug Bulletin

**April 2022**

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| **Drug Name** | dextroamphetamine (Xelstrym) |
| **Manufacturer** | Noven |
| **FDA Approval Information** | 505(b)(2) NDA approval 3/22/2022; Standard Review |
| **Market Availability** | Anticipated second half of 2022 |
| **Drug Class & Indication** | ▪ Central nervous system (CNS) stimulant; scheduled CII controlled-substance<br>▪ Indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in adults and pediatric patients ≥ 6 years of age[1] |
| **Dosage Strength/Form** | 4.5 mg/9 hours, 9 mg/9 hours, 13.5 mg/9 hours, 18 mg/9 hours transdermal system |
| **Dosage Regimen** | ▪ Pediatrics (6 to 17 years old): starting dose is 4.5 mg/9 hours. Titrate dosage by 4.5 mg in weekly increments up to a maximum dose of 18 mg/9 hours.<br>▪ Adults: starting dose is 9 mg/9 hours; maximum recommended dose is 18 mg/9 hours.<br>▪ The maximum dosage for renal impairment is 13.5 mg/9 hours with severe renal impairment (glomerular filtration rate [GFR] 15 to < 30 mL/min/1.73 $m^2$) and 9 mg/9 hours with end stage renal disease (GFR < 15 mL/min/1.73 $m^2$)<br>▪ Transdermal system should be applied to the hip, upper arm, chest, upper back, or flank 2 hours before an effect is needed and removed within 9 hours<br>▪ 1 transdermal system should be used per 24 hours. |
| **Clinical Comments** | ▪ Xelstrym offers the first and only amphetamine patch for the treatment of ADHD. Methylphenidate patch (Daytrana®) is also approved for ADHD in ages ≥ 6 years old.[2]<br>▪ Other forms of dextroamphetamine that share the same indication are dextroamphetamine extended-release 5 mg, 10 mg, and 15 mg capsules (generic, Dexedrine Spansule®), dextroamphetamine oral solution 5 mg/5 mL (generic, Procentra®), and dextroamphetamine 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, and 30 mg oral tablet (generic, Zenzedi®).[3]<br>▪ Xelstrym has a Boxed Warning for high potential of abuse and dependence. Prescribers should assess risk of abuse prior to starting and during therapy.[4]<br>▪ In addition to precautions associated with existing formulations of dextroamphetamine products, other safety considerations include application site reactions (e.g., pain, pruritus, burning sensation), allergic contact dermatitis, and avoidance of external heat.<br>▪ Xelstrym should not be substituted for other amphetamine products on a milligram-per-milligram basis due to different amphetamine base composition and pharmacokinetic profiles. For patients switching to Xelstrym, prior |

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| | treatment should be discontinued and Xelstrym can be initiated using the titration schedule.<br>▪ FDA-approved medications and behavioral interventions are recommended for ADHD.[5] |

## SUGGESTED UTILIZATION MANAGEMENT

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| **Anticipated Therapeutic Class Review (TCR) Placement** | Stimulants and Related Agents |
| **Clinical Edit** | **Initial Approval Criteria**<br>▪ Patient is ≥ 6 years of age; **AND**<br>▪ Patient has a diagnosis of attention deficit hyperactivity disorder (ADHD) according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5); **AND**<br>▪ Patient cannot tolerate, has medical reason, or has tried and failed at least 1 oral extended-release dextroamphetamine; **AND**<br>▪ Patient does NOT have a history of hypersensitivity (e.g., contact dermatitis) to any component of the product or amphetamine products; **AND**<br>▪ Patient is not currently using a monoamine oxidase inhibitor (MAOI) or has not used one within 14 days; **AND**<br>▪ Prescriber will assess heart rate and blood pressure before starting therapy, after dose increases, and regularly during treatment; **AND**<br>▪ Prescriber provides attestation that the patient will be monitored for changes in height and weight; **AND**<br>▪ Patient individual risks and benefits have been considered prior to initiating or continuing a Schedule II dextroamphetamine product with high potential for abuse and dependence; **AND**<br>▪ Counseling on proper patch application and rotation of sites has been provided; **AND**<br>▪ Prescriber attestation that behavior interventions will be used in conjunction with pharmacotherapy.<br><br>**Renewal Criteria**<br>▪ Patient must continue to meet the above criteria; **AND**<br>▪ Patient has experienced disease response as indicated by improvement in attention and/or decreased hyperactivity from baseline; **AND**<br>▪ Patient has NOT experienced any treatment-restricting adverse effects (e.g., allergic contact dermatitis, hypersensitivity reactions, serious cardiovascular reactions, blood pressure and heart rate increases, psychiatric adverse reactions, peripheral vasculopathy, long term suppression of growth, serotonin syndrome). |
| **Quantity Limit** | 30 patches/30 days |
| **Duration of Approval** | Initial: 6 months<br>Renewal: 6 months |
| **Drug to Disease Hard Edit** | None |


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