# Therapeutic Class Overview
## Attention-Deficit/Hyperactivity Disorder (ADHD) Agents

## INTRODUCTION

- Attention-deficit/hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder among children, with an estimated prevalence of up to 10% of school-age children in the United States (U.S.). It is more common in boys than girls and frequently persists into adulthood (*Feldman et al 2014*). Epidemiologic studies of adult ADHD have estimated the current prevalence to be 4.4% in the U.S. (*Bukstein 2018*).
  - In children, this chronic disorder is characterized by symptoms of hyperactivity, impulsivity, and/or inattention. These symptoms affect cognitive, academic, behavioral, emotional, and social functioning (*Krull 2019a*). Common comorbid psychiatric disorders include oppositional defiant disorder, conduct disorder, depression, anxiety disorder, and learning disabilities (*Krull 2019b*). Approximately 20% of children with ADHD develop chronic tic disorders and approximately 50% of children with chronic tics or Tourette syndrome have comorbid ADHD (*Krull 2020b*).
  - ADHD in adults is characterized by symptoms of inattention, impulsivity, and restlessness. Impairment in executive function and emotional dysregulation frequently occur. Common comorbid psychiatric disorders include mood and anxiety disorders, substance use disorder, and intermittent explosive disorder (*Bukstein 2018*).
- For children < 17 years of age, the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) diagnosis of ADHD requires ≥ 6 symptoms of hyperactivity and impulsivity or ≥ 6 symptoms of inattention. For adolescents ≥ 17 years of age and adults, ≥ 5 symptoms of hyperactivity and impulsivity or ≥ 5 symptoms of inattention are required.
  - The symptoms of hyperactivity/impulsivity or inattention must occur often; be present in more than 1 setting; persist for at least 6 months; be present before the age of 12 years; impair function in academic, social, or occupational activities; and be excessive for the developmental level of the child.
  - Other physical, situational, or mental health conditions that could account for the symptoms must be excluded.
- Treatment of ADHD may involve behavioral/psychologic interventions, medication, and/or educational interventions, alone or in combination (*Krull 2019c*).
  - For preschool children (age 4 through 5 years), behavioral therapy is considered the first-line treatment; when medication is necessary, methylphenidate is generally recommended.
  - For children and adolescents with moderate to severe ADHD, medication and behavioral therapy are recommended. In general, stimulants are the first-line agents; however, non-stimulant medications may be more appropriate for certain children.
    - About 30% of patients do not respond to or may not tolerate the initial stimulant treatment. At least one-half of children who do not respond to one type of stimulant will respond to the other. If there is still no improvement, consideration should be given to switching to or adding a non-stimulant ADHD medication (*Pharmacist's Letter 2015, Krull 2020a*).
- Multiple agents are currently approved by the Food and Drug Administration (FDA) for the treatment of ADHD. They include central nervous system (CNS) stimulants (amphetamine- and methylphenidate-based formulations), as well as non-stimulants: a selective norepinephrine reuptake inhibitor (SNRI), atomoxetine, and 2 alpha$_2$-adrenergic agonists, clonidine extended-release (ER) and guanfacine ER.
  - Due to the potential for abuse, the stimulant agents are classified as Schedule II controlled substances.
  - Several stimulants are also approved for the treatment of narcolepsy and exogenous obesity; the use of stimulants for the treatment of obesity will not be covered in this review. Lisdexamfetamine dimesylate is the only FDA-approved drug for the treatment of binge eating disorder (BED).
- Medispan Classes: ADHD Agents – Amphetamines, Dexmethylphenidate, Methylphenidate, Selective Alpha Adrenergic Agonists, Selective Norepinephrine Reuptake Inhibitor

**Table 1. Medications Included Within Class Review**

| Drug | Generic Availability |
|---|---|
| **Stimulants** | |
| Evekeo (amphetamine sulfate) | ✔ |
| Evekeo ODT (amphetamine sulfate) | - |
| Adderall (mixed amphetamine salts) | ✔ |
| Focalin (dexmethylphenidate hydrochloride [HCl]) | ✔ |
| ProCentra (dextroamphetamine sulfate) | ✔ |
| Zenzedi (dextroamphetamine sulfate) | ✔ |
| Desoxyn (methamphetamine HCl) | ✔ |
| methylphenidate HCl chewable tablets | ✔ |
| Methylin Oral Solution (methylphenidate HCl) | ✔ |
| Ritalin (methylphenidate HCl) | ✔ |
| Dexedrine Spansule (dextroamphetamine sulfate sustained-release) | ✔ |
| Adzenys ER (amphetamine ER) | ✔ |
| Adzenys XR-ODT (amphetamine ER) | - |
| Dyanavel XR (amphetamine ER) | - |
| Adderall XR (mixed amphetamine salts ER) | ✔ |
| Mydayis (mixed amphetamine salts ER) | - |
| Focalin XR (dexmethylphenidate HCl ER) | ✔ |
| Vyvanse (lisdexamfetamine dimesylate) | - |
| Adhansia XR (methylphenidate HCl ER) | - |
| Aptensio XR (methylphenidate HCl ER) | ✔ |
| Concerta (methylphenidate HCl ER) | ✔ |
| Cotempla XR-ODT (methylphenidate ER) | - |
| Jornay PM (methylphenidate HCl ER) | - |
| methylphenidate HCl ER (CD) | ✔ |
| methylphenidate HCl ER | ✔ |
| QuilliChew ER (methylphenidate HCl ER) | - |
| Quillivant XR (methylphenidate HCl ER) | - |
| Ritalin LA (methylphenidate HCl ER) | ✔ |
| Daytrana (methylphenidate transdermal system) | - |
| **Non-stimulants** | |
| Strattera (atomoxetine HCl) | ✔ |
| Kapvay (clonidine HCl ER) | ✔ |
| Intuniv (guanfacine HCl ER) | ✔ |

(*Drugs@FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020, Facts & Comparisons 2020*)

## INDICATIONS

**Table 2. Food and Drug Administration Approved Indications**

| Indication | Evekeo (amphetamine sulfate) | Evekeo ODT (amphetamine sulfate) | Adzenys ER, Adzenys XR-ODT, Dyanavel XR (amphetamine ER) | Adderall (mixed amphetamine salts) | Adderall XR, Mydayis (mixed amphetamine salts ER) | Strattera (atomoxetine HCl) | Kapvay (clonidine HCl ER) | Focalin (dexmethylphenidate IR); Focalin XR (dexmethylphenidate ER) | ProCentra, Zenzedi (dextroamphetamine sulfate IR); Dexedrine Spansule (dextroamphetamine sulfate SR) | Intuniv (guanfacine HCl ER) | Vyvanse (lisdexamfetamine dimesylate) | Desoxyn (methamphetamine HCl) | Methylin Oral Solution, Ritalin (methylphenidate HCl IR); methylphenidate HCl chewable tablets; Metadate ER (methylphenidate ER) | Adhansia XR, Aptensio XR, Concerta , Cotempla XR-ODT, Daytrana, methylphenidate ER (CD), Jornay PM, QuilliChew ER, Quillivant XR, Ritalin LA (methylphenidate ER) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ADHD* | | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ | | | ✓ | | | ✓ |
| ADHD, as an integral part of a total treatment program which typically includes other remedial measures (psychological, educational, and social) for a stabilizing effect in pediatric patients with a behavioral syndrome characterized by the following group of developmentally inappropriate symptoms: moderate to severe distractibility, short attention span, hyperactivity, emotional lability, and impulsivity. The diagnosis of this syndrome should not be made with finality when these symptoms are only of comparatively recent origin. Nonlocalizing (soft) neurological signs, learning disability, and abnormal electroencephalogram (EEG) may or may not be present, and a diagnosis of CNS dysfunction may or may not be warranted.* | ✓ | | | | | | | | ✓ | | | ✓ | ✓ | |
| Treatment of ADHD as monotherapy and as adjunctive therapy to stimulant medications | | | | | | | ✓ | | | ✓ | | | | |
| Narcolepsy** | ✓ | | | ✓ | | | | | ✓ | | | | ✓ | |
| Exogenous obesity, as a short term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction for patients refractory to alternative therapy (eg, repeated diets, group programs, and other drugs).† | ✓ | | | | | | | | | | | ✓ | | |
| Moderate to severe BED in adults | | | | | | | | | | | ✓ | | | |

(*Prescribing Information*: *Adderall 2020*, *Adderall XR 2019*, *Adhansia XR 2019*, *Adzenys ER 2017*, *Adzenys XR-ODT 2018*, *Aptensio XR 2019*, *Concerta 2017*, *Cotempla 2017*, *Daytrana 2019, Desoxyn 2019, Dexedrine Spansule 2019*, *Dyanavel XR 2019*, *Evekeo 2019*, *Evekeo ODT 2019*, *Focalin 2019*, *Focalin XR 2019*, *Intuniv 2019, Jornay PM 2019, Kapvay 2020, Mydayis 2019, Methylin Oral Solution 2017, methylphenidate chewable tablets 2019, methylphenidate ER 2019, methylphenidate ER (CD) 2018, ProCentra 2017*, *QuilliChew ER 2018*, *Quillivant XR 2018*, *Ritalin 2019*, *Ritalin LA 2019*, *Strattera 2020*, *Vyvanse 2018, Zenzedi 2019*)

* Adderall, Evekeo, ProCentra, and Zenzedi are approved for use in children 3 years of age and older. Adhansia XR, Daytrana, Desoxyn, Dexedrine Spansule, Dyanavel XR, Intuniv, and Kapvay are approved for use in children 6 years of age and older. Adderall XR, Adzenys ER, Adzenys XR-ODT, Aptensio XR, Focalin, Focalin XR, Jornay PM, methylphenidate ER (CD), Methylphenidate ER, Methylin Oral Solution, methylphenidate chewable tablets, QuilliChew ER, Quillivant XR, Ritalin, Ritalin LA, Strattera, and Vyvanse are approved for use in patients 6 years of age and older. Cotempla XR-ODT and Evekeo ODT are approved for use in pediatric patients 6 to 17 years of age. Concerta is approved for use in children 6 years of age and older, adolescents, and adults up to 65 years of age. Mydayis is approved for use in patients 13 years of age and older.
**These drugs are approved for use in patients 6 years of age and older.
†These drugs are not recommended for use in children under 12 years of age for treatment of exogenous obesity. The limited usefulness of these products should be weighed against possible risks inherent in use of the drugs.

- Limitation of use:
  - Lisdexamfetamine: Lisdexamfetamine is not indicated or recommended for weight loss. Use of other sympathomimetic drugs for weight loss has been associated with serious cardiovascular (CV) adverse events (AEs). The safety and effectiveness of this drug for the treatment of obesity have not been established.
  - Mydayis: Pediatric patients 12 years and younger experienced higher plasma exposure than patients 13 years and older at the same dose and experienced higher rates of AEs, mainly insomnia and decreased appetite.

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

## CLINICAL EFFICACY SUMMARY

- Randomized trials, systematic reviews, and meta-analyses have found stimulants, atomoxetine, and alpha$_2$-adrenergic agonists to be more efficacious than placebo in reducing the core symptoms of ADHD in children and adolescents.
  - Adzenys ER, an amphetamine ER oral suspension, was approved under the 505(b)(2) regulatory pathway and was found to be bioequivalent to Adderall XR. No clinical efficacy studies were conducted.
  - Evekeo (amphetamine sulfate) was approved based on a randomized, double-blind (DB), multicenter (MC), placebo-controlled (PC) laboratory classroom study that was conducted in 107 children between the ages of 6 and 12 years (*Childress et al 2015*). The study found Evekeo to be associated with significant improvements in the average Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) combined score compared to placebo (least squares [LS] mean difference -7.9; 95% CI, -10.1 to -5.6; $p < 0.0001$).
    - Evekeo ODT, an orally disintegrating amphetamine tablet, was approved under the 505(b)(2) regulatory pathway. The safety and effectiveness of Evekeo ODT for the treatment of ADHD was established based on an adequate and well-controlled study of Evekeo (*Childress et al 2015*).
  - Cotempla XR-ODT, a new methylphenidate ER orally disintegrating tablet formulation, was approved based on a randomized, DB, MC, PC laboratory classroom study (*Childress et al 2017*) (N = 87) which found that the average SKAMP-combined score was significantly better for Cotempla XR-ODT than for placebo (LS mean 14.3 [95% CI, 12.2 to 16.4] vs 25.3 [9% CI, 23.0 to 27.6], respectively, $p < 0.0001$).
  - Adhansia XR, a recently approved methylphenidate ER capsule, was approved via the 505(b)(2) regulatory pathway, and its efficacy was supported by 4 clinical studies in patients with ADHD including 2 studies conducted in adults, 1 study in adolescents 12 to 17 years of age, and 1 study in pediatric patients 6 to 12 years of age (*Adhansia XR FDA Clinical Review 2019):*
    - One randomized, DB, MC, PC 4-week study conducted in 368 adult patients with ADHD evaluated the safety and efficacy of 4 doses of Adhansia XR (25 mg, 45 mg, 70 mg, and 100 mg) compared to placebo. The primary

endpoint, change in the ADHD-Rating Scale (ADHD-RS)-5 total score from baseline to Week 5, was significantly improved compared to placebo in the Adhansia XR 45 mg group (LS mean difference, -6.9; 95% CI, -11.5 to -2.2; p = 0.0013), 100 mg group (LS mean difference, -8.1; 95% CI, -12.9 to -3.2; p = 0.0002), and when combining all dosage groups compared to placebo (LS mean difference, -4.7; 95% CI, -7.7 to -1.6; p = 0.0026). No significant difference was seen in the 25 mg or 70 mg groups compared to placebo.

- A second randomized, DB, crossover, PC study was conducted in 45 adults in an adult workplace environment. The study aimed to assess efficacy parameters for Adhansia XR vs placebo over 16 hours post-dose. Patients were titrated to an optimal dose of Adhansia XR (either 25, 35, 45, 55, 70, 85, or 100 mg) during an open-label (OL) treatment period between 2 and 7 weeks, then entered into a 1-week PC, DB treatment phase prior to the adult workplace environment session, followed by a 7-day washout period between crossover periods, then another 1-week treatment phase followed by another adult workplace environment session. The primary endpoint was the average Permanent Product Measure of Performance (PERMP) score for various time points up to 16 hours post-dose. When combining data from all time points, patients treated with Adhansia XR had significant improvements in the PERMP score compared to placebo (LS mean difference, 13.05; 95% CI, 3.88 to 22.23; p = 0.0064).
- A 4-week randomized, DB, PC trial assessed efficacy of Adhansia XR in 354 adolescent patients 12 to 17 years of age. The study compared Adhansia XR 25, 45, 70, and 85 mg to placebo and found significant improvements in the ADHD-5-RS score from baseline to Week 5 in adolescents treated with Adhansia XR 45 mg (LS mean difference, -5.4; 95% CI, -9.2 to -1.6; p = 0.0052), 70 mg (LS mean difference, -5.2; 95% CI, -9.0 to -1.4; p = 0.0069), and when combining all dosage groups compared to placebo (LS mean difference, -4.3; 95% CI, -7.3 to -1.3; p = 0.0049). Adolescents treated with Adhansia XR 25 or 85 mg did not achieve significant improvements in the ADHD-5-RS score compared to placebo.
- A fourth study, which included a 6 week OL dose optimization period (majority of patients received between 45 and 55 mg of Adhansia XR) followed by a 1- week DB PC study, was conducted to assess the efficacy of Adhansia XR in 147 children 6 to 12 years of age in an analog classroom setting. The primary endpoint, average SKAMP-C score (taken at various time points up to 13 hours post-dose), was significantly improved in children treated with Adhansia XR compared to placebo (LS mean difference, -8.6; 95% CI, -10.6 to -6.6).

- Jornay PM, an ER methylphenidate capsule formulation, was approved based on the results of 2 clinical studies conducted in patients 6 to 12 years of age with ADHD:
  - The first study was a 6-week OL dose-optimization study, followed by a 1-week DB, PC withdrawal phase where patients were randomized to continue treatment with Jornay PM or switch to placebo (*Jornay PM Prescribing Information 2019*). The study, which was conducted in an analog classroom setting and included 117 children aged 6 to 12 years, found that Jornay PM was associated with a significant reduction in the SKAMP symptom score over a 12-hour period (LS mean difference -5.9; 95% CI, -9.1 to -2.7).
  - A randomized, DB, MC, PC, parallel group, forced-dose titration trial was conducted over 3 weeks in 161 children 6 to 12 years of age with ADHD (*Pliszka et al 2017*). The study found that 40 to 80 mg/day of Jornay PM achieved significant improvements vs placebo in ADHD symptoms (LS mean ADHD rating scale-IV 24.1 vs 31.2; p = 0.002) at 3 weeks. Significant improvements were also seen vs placebo in key secondary outcomes including at-home early morning and late afternoon/evening functional impairment at 3 weeks. The most commonly reported treatment-emergent AEs were insomnia and decreased appetite.
- Mydayis, a mixed amphetamine salts product, was approved for the treatment of ADHD based on the results of 5 MC, DB, PC, randomized controlled trials (RCTs): 3 in adults and 2 in pediatric patients 13 to 17 years of age. The studies found that Mydayis demonstrated a statistically significant treatment effect compared with placebo on various ADHD outcomes measures (eg, ADHD-RS score, PERMP score) (*Mydayis Prescribing Information 2019, Weisler et al 2017, Wigal et al 2018a, Wigal et al 2018b, Wigal et al 2019*) (see results below in Table 3 below).

**Table 3. Summary of Primary Efficacy Results for Mydayis**

| Study Number (Age range) | Primary Endpoint | Treatment Group | Mean Baseline Score (SD) | LS Mean Change from Baseline | Placebo-subtracted Difference (95% CI) |
|---|---|---|---|---|---|
| ***Adult Studies*** | | | | | |
| Study 1 (18 to 55 years) | ADHD-RS | Mydayis 12.5 mg/day[§]<br>Mydayis 37.5 mg/day[§]<br><br>Placebo | 39.8 (6.38)<br>39.9 (7.07)<br><br>40.5 (6.52) | -18.5<br>-23.8<br><br>-10.4 | -8.1 (-11.7 to -4.4)<br>-13.4 (-17.1 to -9.7) |

| | | | | | |
|---|---|---|---|---|---|
| Study 2 (18 to 55 years) | Average PERMP | Mydayis 50 mg/day§<br><br>Placebo | 239.2 (75.6)†<br><br>249.6 (76.7)† | 293.23*<br><br>274.85* | 18.38 (11.28 to 25.47) |
| Study 3 (18 to 55 years) | Average PERMP | Mydayis 25 mg/day§<br><br>Placebo | 217.5 (59.6)†<br><br>226.9 (61.7)† | 267.96*<br><br>248.67* | 19.29 (10.95 to 27.63) |
| ***Pediatric Studies*** | | | | | |
| Study 4 (13 to 17 years)‡ | ADHD-RS-IV | Mydayis 12.5 to 25 mg/day§<br><br>Placebo | 36.7 (6.15)<br><br>38.3 (6.67) | -20.3<br><br>-11.6 | -8.7 (-12.6 to -4.8) |
| Study 5 (13 to 17 years) | Average PERMP | Mydayis 25 mg/day§<br><br>Placebo | 214.5 (87.8)†<br><br>228.7 (101)† | 272.67*<br><br>231.41* | 41.26 (32.24 to 50.29) |

SD= standard deviation; LS = least squares; CI = confidence interval
†Pre-dose PERMP total score
*LS mean for PERMP is post-dose average score over all sessions of the treatment day, rather than change from baseline
‡Results are for a subgroup of study 4 and not the total population
§Doses statistically significant for placebo

- A systematic (Cochrane) review of 185 RCTs (*Storebø et al 2015*) (N = 12,245) in children and adolescents with ADHD found that methylphenidate may improve teacher-rated ADHD symptoms, teacher-reported general behavior, and parent-reported quality of life (QOL) vs placebo. However, the evidence was of low quality.
- An RCT called the Preschool ADHD Treatment Study (PATS) (*Greenhill et al 2006*) evaluated the efficacy of methylphenidate immediate-release (IR) in 303 preschool children with ADHD and found that it demonstrated significant reductions on ADHD symptom scales; however, the effect sizes (0.4 to 0.8) were smaller than those generally reported for school-age children.
- A systematic (Cochrane) review of 23 PC, RCTs (*Punja et al 2016*) (N = 2675) found that amphetamines were effective at improving the core symptoms of ADHD, but they were also associated with a higher risk of AEs compared to placebo. There was no evidence that one kind of amphetamine was better than another and there was no difference between short-acting and long-acting formulations.
- A meta-analysis of 25 DB, PC, RCTs (*Schwartz et al 2014*) (N = 3928) in children and adolescents with ADHD found atomoxetine to be superior to placebo for overall ADHD symptoms, with a medium effect size (-0.64).
- A meta-analysis of 12 RCTs (*Hirota et al 2014*) (N = 2276) in pediatric patients with ADHD found that alpha$_2$-adrenergic agonists were significantly superior to placebo for overall ADHD symptoms both as monotherapy and, to a lesser extent, as augmentation therapy to stimulants.
  - Meta-analytic results failed to demonstrate a significant difference in efficacy between alpha$_2$-adrenergic agonists. In sub-analyses of individual formulations, the ER formulations separated robustly from placebo whereas the IR formulations did not separate from placebo.
- A systematic review of 16 RCTs and 1 meta-analysis (*Chan et al 2016*) (N = 2668) found evidence supporting the use of methylphenidate ER and amphetamine ER formulations, atomoxetine, and guanfacine ER for the treatment of ADHD in adolescents. For the primary outcome measure of mean change in ADHD-RS total symptom score, both stimulant and non-stimulant medications led to clinically significant reductions of 14.93 to 24.60 points.

- For the treatment of ADHD in children and adolescents, stimulants typically have a slightly larger treatment effect size (standardized mean difference [SMD]) than non-stimulants (approximately 1.0 vs approximately 0.7 for both atomoxetine and alpha$_2$-adrenergic agonists). However, there is insufficient evidence to definitively conclude that one stimulant is more efficacious than another (*Krull 2020a*, *AAP 2019).*
  - An Agency for Healthcare Research and Quality (AHRQ) review of 78 studies (*Jadad et al 1999*) evaluating the efficacy of various interventions for the treatment of ADHD in children and adults found few, if any, differences between methylphenidate and dextroamphetamine.
  - A meta-analysis of 23 DB, PC trials (*Faraone 2010a*) comparing the efficacy of methylphenidate and amphetamine formulations found that amphetamine products may be moderately more efficacious than methylphenidate products.
  - A DB, PC, RCT (*Newcorn et al 2008*) (N = 516) comparing the efficacy of atomoxetine vs methylphenidate ER (osmotic-release formulation) in patients 6 to 16 years of age with ADHD found that both drugs were superior to placebo in terms of response rate, and that methylphenidate ER was superior to atomoxetine.

- A meta-analysis of 29 DB, PC trials (*Faraone et al 2006*) evaluated the efficacy of various medications (methylphenidate and amphetamine compounds, atomoxetine, pemoline [no longer available in the U.S.], bupropion, and modafinil) for the treatment of ADHD. The effect sizes for non-stimulant medications were significantly less than those for IR stimulants or long-acting stimulants. The 2 classes of stimulant medications did not differ significantly from one another.
- A meta-analysis of 28 DB, PC, RCTs (*Stuhec et al 2015*) (N = 4699) compared the efficacy of various medications for the treatment of ADHD in children and adolescents. Efficacy in reducing ADHD symptoms compared to placebo was small for bupropion (SMD = -0.32; 95% confidence interval [CI], -0.69 to 0.05), modest for atomoxetine (SMD = -0.68; 95% CI, -0.76 to -0.59) and methylphenidate (SMD = -0.75; 95% CI, -0.98 to -0.52), and highest for lisdexamfetamine (SMD = -1.28; 95% CI, -1.84 to -0.71).
- A network meta-analysis and mixed treatment comparison of 36 RCTs (*Joseph et al 2017*) evaluating the comparative efficacy and safety of ADHD pharmacotherapies in children and adolescents found that lisdexamfetamine had greater efficacy than guanfacine ER, atomoxetine, and methylphenidate ER. Guanfacine ER had a high posterior probability of being more efficacious than atomoxetine, but their credible intervals overlapped.
- A network meta-analysis of 48 DB, RCTs (*Padilha et al 2018*) compared the safety and efficacy of various ADHD medications in children and adolescents. Of the 12 trials that were evaluated for efficacy, analysis was performed using the Clinical Global Impression Improvement (CGI-I) scale for 3 drugs, which showed that methylphenidate was more effective than atomoxetine (MD, 3.15; 95% CI, 0.75 to 13.71) and guanfacine (MD, 1.92; 95% CI, 0.64 to 5.94). Thirty-three trials were evaluated for safety. Ranking of AEs showed that lisdexamfetamine was more likely to cause sleep disorders, loss of appetite, and behavior problems compared to other treatments.

- Alpha$_2$-adrenergic agonists have been associated with improvements in ADHD symptoms and comorbid tics.
  - A meta-analysis of 9 DB, PC, RCTs (*Bloch et al 2009*) (N = 477) was conducted to determine the relative efficacy of different medications in treating ADHD and tic symptoms in children with both Tourette syndrome and ADHD.
  - Methylphenidate seemed to offer the greatest improvement of ADHD symptoms and did not seem to worsen tic symptoms.
  - Alpha$_2$-adrenergic agonists offered the best combined improvement in both tic and ADHD symptoms.
  - Atomoxetine significantly improved both tic and ADHD severity compared to placebo.
  - One small study found that tic severity was significantly increased with higher doses of dextroamphetamine treatment.
  - A Cochrane review of 8 RCTs (*Osland et al 2018*) including 510 children with both ADHD and a chronic tic disorder found low-quality evidence for improvement of ADHD symptoms with methylphenidate, atomoxetine, and clonidine, and very low-quality evidence for desipramine, dextroamphetamine, guanfacine, and deprenyl. Tic symptoms improved with guanfacine, desipramine, methylphenidate, clonidine, and a combination of methylphenidate and clonidine. The authors noted that in 1 study with a short duration (3 weeks), high doses of dextroamphetamine worsened tics.
- There are limited efficacy data regarding the treatment of ADHD in the adult population. Comparison of effect sizes in clinical trials suggests that stimulant medications are more efficacious in adult ADHD than non-stimulants.
  - In a meta-analysis of 12 clinical trials (*Cunill et al 2009*) (N = 3375) comparing atomoxetine with placebo in adult ADHD, atomoxetine led to a modestly greater reduction in ADHD symptom severity, but was associated with higher all-cause discontinuation.
  - A meta-analysis (*Faraone 2010b*) of 19 randomized trials of 13 medications for adult ADHD found a greater average effect size for reduction in ADHD symptoms in patients receiving short- and long-acting stimulant medications (vs placebo; 0.86 and 0.73, respectively) compared with patients receiving non-stimulant medication (vs placebo; 0.39). No difference in effect size was found between short- and long-acting stimulants.
  - A meta-analysis of 20 randomized trials (*Stuhec et al 2018*) compared the efficacy, acceptability, and tolerability of lisdexamfetamine, mixed amphetamine salts, methylphenidate, and modafinil in the treatment of ADHD in adults. The highest effect size in reducing ADHD symptoms was found with lisdexamfetamine (SMD -0.89; 95% CI, -1.09 to -0.70), while moderate reductions in symptoms were seen with mixed amphetamine salts (SMD -0.64; 95% CI, -0.83 to -0.45) and methylphenidate (SMD -0.50; 95% CI, -0.58 to -0.41). No efficacy was reported with modafinil.
  - A Cochrane review of 19 studies (*Castells et al 2018*, N = 2521) comparing dextroamphetamine, lisdexamfetamine, and mixed amphetamine salts for the treatment of ADHD in adults found that overall, amphetamines reduced the patient- and clinician-rated severity of ADHD symptoms compared to placebo; however, they did not improve retention in treatment. Amphetamines were associated with an increased proportion of patients who withdrew because of AEs. When comparing different types of amphetamines, lisdexamfetamine and mixed amphetamine salts

reduced the severity of ADHD symptoms as rated by clinicians, but dextroamphetamine did not. No differences in any outcome were found when comparing immediate- and sustained-release formulations.
  - Another meta-analysis (*Cortese et al 2018*) of 133 RCTs comparing the use of amphetamines, atomoxetine, bupropion, clonidine, guanfacine, methylphenidate, and modafinil for the treatment of ADHD found that all drugs were superior to placebo for ADHD core symptoms as rated by clinicians in children and adolescents, and all drugs except for modafinil were more efficacious than placebo in adults.
    - When comparing the various drugs based on teachers' ratings in children and adolescents, only methylphenidate and modafinil were found to be more efficacious than placebo.
    - In head-to-head comparisons, differences in efficacy based on clinicians' ratings were found, favoring amphetamines over modafinil (SMD -0.39; 95% CI -0.67 to -0.12), atomoxetine (SMD -0.46; 95% CI, -0.65 to -0.27), and methylphenidate (SMD-0.24; 95% CI, -0.44 to -0.05) in children and adolescents. Efficacy results based on clinicians' ratings were similar for adults, and favored amphetamines over modafinil (SMD -0.94; 95% CI -1.43 to -0.46), atomoxetine (SMD -0.34; 95% CI, -0.58 to -0.10), and methylphenidate (SMD-0.29; 95% CI, -0.54 to -0.05).
- Lisdexamfetamine dimesylate has demonstrated efficacy in the treatment of BED. Direct comparison trials between lisdexamfetamine and other drugs used off-label to treat BED are lacking.
  - In 2 Phase 3, 12-week, randomized, DB, PC trials (*McElroy et al 2016*) (N = 773) in patients with moderate to severe BED, lisdexamfetamine-treated patients had a statistically significantly greater reduction from baseline in mean number of binge days per week at week 12 vs placebo (treatment difference in study 1: -1.35 [-1.70 to -1.01]; study 2: -1.66 [-2.04 to -1.28]; both $p < 0.001$).
    - A 12-month, OL extension study (*Gasior et al 2017*) (N = 599) in adults with BED found that the long-term safety and tolerability of lisdexamfetamine were generally consistent with the safety profile observed in 3 previous short-term trials in BED as well as its established profile for ADHD. Common treatment-emergent AEs included dry mouth, headache, insomnia, and upper respiratory tract infection. Weight loss and increases in blood pressure and pulse rate were also observed.
  - In a phase 3, DB, randomized, PC, withdrawal study (*Hudson et al 2017*) (N = 418) in adults with moderate to severe BED, responders to lisdexamfetamine during a 12-week OL phase were randomized to placebo or continued lisdexamfetamine during a 26-week, DB phase. The percentage of patients meeting relapse criteria was 3.7% with lisdexamfetamine vs 32.1% with placebo; time to relapse statistically favored lisdexamfetamine ($p < 0.001$). The hazard ratio (HR) was 0.09 (95% CI, 0.04 to 0.23).
  - A systematic review and meta-analysis of 9 waitlist-controlled psychological trials and 25 PC trials evaluating pharmacologic (n = 19) or combination (n = 6) treatment for BED (*Brownley et al 2016*) found that therapist-led CBT, lisdexamfetamine, and second-generation antidepressants (SGAs) increased binge-eating abstinence (relative risk [RR], 4.95 [95% CI, 3.06 to 8.00], 2.61 [CI, 2.04 to 3.33], and 1.67 [CI, 1.24 to 2.26], respectively), while lisdexamfetamine and SGAs decreased binge-eating frequency (mean difference in days/week, -1.35 [CI, -1.77 to -0.93] and -0.67 [CI, -1.26 to -0.09], respectively). Topiramate and other forms of CBT also increased abstinence and reduced binge-eating frequency.
  - A 2018 systematic review and meta-analysis of 45 RCTs (*Ghaderi et al 2018*) compared various psychological, pharmacological, and combined treatments for BED, and found moderate support for the efficacy of cognitive behavioral therapy (CBT) and CBT-guided self-help (moderate quality of evidence), and low quality evidence to support interpersonal psychotherapy, selective serotonin reuptake inhibitors, and lisdexamfetamine for the cessation of or reduction in the frequency of binge eating. Only lisdexamfetamine showed a modest effect on weight loss (SMD for body mass index -5.23; 95% CI, -6.52 to -3.94).

## CLINICAL GUIDELINES

### ADHD

- Several clinical guidelines have provided recommendations on the treatment of ADHD in children and adolescents.
  - According to the American Academy of Pediatrics (AAP) guidelines (2019), the evidence is particularly strong for stimulant medications, and sufficient but less strong for atomoxetine, guanfacine ER, and clonidine ER (in that order). Guanfacine ER and clonidine ER have evidence to support their use as adjunctive therapy with stimulant medications. Methylphenidate is recommended for preschool-aged children who have had an inadequate response to behavioral interventions.

- The American Academy of Child and Adolescent Psychiatry (AACAP) guidelines (*Pliszka et al 2007*) state that both methylphenidate and amphetamines are equally efficacious in the treatment of ADHD. The long-acting formulations are equally efficacious as the IR formulations and may be used as initial therapy. Short-acting stimulants are often used as initial treatment in small children (< 16 kg in weight), for whom there are no long-acting preparations in a sufficiently low dose. Some patients may respond similarly to different stimulant classes, whereas other patients may respond preferentially to only 1 of the classes of stimulants. Although stimulants have demonstrated greater efficacy compared to atomoxetine in published studies, atomoxetine may be used first-line in patients with an active substance abuse problem, comorbid anxiety or tics, and in those who experience severe AEs with stimulants.
- The Medical Letter (2020) recommends that treatment of ADHD in school-age children or adults should begin with an oral stimulant, either a methylphenidate- or amphetamine-based formulation. Mixing short- and long-acting stimulants can be helpful to achieve an immediate effect for early-morning school classes or for reducing rebound irritability or overactivity, especially in the evening. An ER alpha$_2$-adrenergic agonist may be helpful as adjunctive therapy with a stimulant in patients who cannot tolerate usual doses of the stimulant, particularly those with tics. Atomoxetine is an alternative for patients who cannot tolerate stimulants or for whom treatment with a controlled substance is undesirable.
- The AACAP practice parameter for the treatment of children and adolescents with tic disorders (2013) states that alpha$_2$-adrenergic agonists have demonstrated an effect size of 0.5 for the amelioration of tics and may be preferred by some prescribers over antipsychotics due to their relatively favorable AE profile.

**Narcolepsy**

- The American Academy of Sleep Medicine (AASM) practice parameters (*Morgenthaler et al 2007*) recommend various drugs for the treatment of daytime sleepiness due to narcolepsy including modafinil (high degree of clinical certainty); amphetamine, methamphetamine, dextroamphetamine, and methylphenidate (moderate degree of clinical certainty); sodium oxybate (high degree of clinical certainty); and selegiline (uncertain clinical certainty).

**BED**

- According to the American Psychiatric Association (APA) practice guidelines on eating disorders (*Yager et al 2006*, *Yager et al 2012* [guideline watch update]), treatment of BED may include the following:
  - Nutritional rehabilitation and counseling
  - Psychosocial treatment
    - CBT, behavior therapy, dialectical behavior therapy (DBT), and interpersonal therapy (IPT) have all been associated with binge frequency reduction rates of 67% or more and significant abstinence rates during active treatment.
    - Self-help programs using self-guided, professionally designed manuals have been effective in reducing the symptoms of BED in the short-run for some patients and may have long-term benefit.
  - Medications
    - Antidepressant treatment is associated with short-term reductions in binge-eating but generally does not result in substantial weight loss. Selective serotonin reuptake inhibitors (SSRIs) have the fewest difficulties with AEs and the most evidence for efficacy when used at the high end of the recommended dose range.
    - Topiramate can reduce bingeing and decrease weight, but its use may be limited by AEs.
  - Combination psychotherapy and pharmacotherapy
    - For most patients, adding antidepressant therapy to a behavioral weight control and/or CBT regimen does not have a significant effect on binge suppression.
    - Although limited evidence is available, combined treatment is frequently used in clinical practice.
- The American Association of Clinical Endocrinologists and the American College of Endocrinology (AACE/ACE) guidelines for medical care of patients with obesity (*Garvey et al 2016*) recommend the following for patients with overweight or obesity who have BED:
  - Patients should be treated with a structured behavioral/lifestyle program, combined with CBT or other psychological interventions
  - Treatment with orlistat or approved medications containing topiramate or bupropion may be considered in conjunction with structured lifestyle therapy, CBT, and/or psychological interventions
- The Task Force on Eating Disorders of the World Federation of Societies of Biological Psychiatry (*Aigner et al 2011*) concluded that for the treatment of BED, grade A evidence supports the use of imipramine (moderate risk-benefit ratio), sertraline (good risk-benefit ratio), citalopram/escitalopram (good risk-benefit ratio), orlistat (low to moderate risk-benefit ratio), and topiramate (moderate risk-benefit ratio). Atomoxetine has grade B evidence supporting its use.

## SAFETY SUMMARY

- Due to the potential for abuse, the stimulants are classified as Schedule II controlled substances. Atomoxetine, clonidine ER, and guanfacine ER are not classified as controlled substances.
- Various stimulants are contraindicated for use in patients with advanced arteriosclerosis, symptomatic CV disease, moderate to severe hypertension, hyperthyroidism, hypersensitivity to sympathomimetic amines, glaucoma, agitated states, history of drug abuse, tics, and in those using monoamine oxidase inhibitors (MAOIs). The stimulants carry a boxed warning for potential drug abuse and dependence. They also have warnings for increased risks of serious CV reactions, psychiatric AEs, suppression of growth, peripheral vasculopathy, and priapism. Amphetamines have a warning for risk of serotonin syndrome when used in combination with other drugs affecting the serotonergic neurotransmitter systems.
  - Common AEs of stimulants include anorexia, decreased weight, tachycardia, anxiety, irritability, and insomnia.
  - Refer to the prescribing information for details on warnings, precautions, and AEs for individual products. For example:
    - QuilliChew ER can be harmful to patients with phenylketonuria (PKU) since it contains phenylalanine.
    - Because the Concerta tablet is nondeformable and does not appreciably change in shape in the gastrointestinal tract, it should not ordinarily be administered to patients with preexisting severe gastrointestinal narrowing.
    - The use of Daytrana may result in chemical leukoderma and contact sensitization; in addition, exposure of the application site to external heat sources should be avoided due to increased absorption of the drug.
    - Adhansia XR capsules contain FD&C yellow No. 5 dye (tartrazine), which may cause allergic-type reactions in susceptible patients.
- Atomoxetine is contraindicated for use in patients with narrow angle glaucoma, pheochromocytoma, severe CV disorders, hypersensitivity to any component of the product, and in those taking MAOIs. It carries a boxed warning for a rare increased risk of suicidal ideation in children and adolescents. It also has warnings for serious CV events, effects on blood pressure and heart rate, effects on growth, psychiatric AEs, rare cases of severe liver injury, and priapism.
  - Common AEs associated with atomoxetine include somnolence, nausea, and vomiting.
- The alpha$_2$-adrenergic agonists are contraindicated in patients known to be hypersensitive to any constituent of the product. They carry warnings for increased risk of hypotension, bradycardia, and syncope; sedation and somnolence; rebound hypertension; and cardiac conduction abnormalities.
  - Common AEs associated with clonidine ER include somnolence, fatigue, and irritability while common AEs with guanfacine ER include somnolence, fatigue, and hypotension.

## DOSING AND ADMINISTRATION

**Table 4. Dosing and Administration**

| Drug | Duration of action* | Available Formulations | Route | Usual Recommended Frequency | Comments |
|---|---|---|---|---|---|
| **Stimulants** | | | | | |
| Evekeo (amphetamine) | 10 h | Tablets | Oral | *ADHD, narcolepsy*: Daily up to divided doses daily<br><br>*Exogenous obesity*: Divided doses daily | *ADHD and narcolepsy*<br>The first dose should be given upon awakening; additional doses at intervals of 4 to 6 hours. |
| Evekeo ODT (amphetamine) | 10 h | Orally disintegrating tablets | Oral | Once or twice daily in the morning | As soon as the blister pack is opened, the tablet should be placed on the patient's tongue and allowed to disintegrate without |

| Drug | Duration of action* | Available Formulations | Route | Usual Recommended Frequency | Comments |
|---|---|---|---|---|---|
| | | | | | chewing or crushing. The tablet will disintegrate in saliva so that it can be swallowed. |
| Adzenys ER (amphetamine ER) | 10 to 12 h | Suspension | Oral | Daily in the morning | |
| Adzenys XR-ODT (amphetamine ER) | 10 to 12 h | Orally disintegrating tablets | Oral | Daily in the morning | As soon as the blister pack is opened, the tablet should be placed on the patient's tongue and allowed to disintegrate without chewing or crushing. The tablet will disintegrate in saliva so that it can be swallowed. |
| Dyanavel XR (amphetamine ER) | Up to 13 h | Suspension | Oral | Daily in the morning | The bottle should be shaken before administration. |
| Adderall (mixed amphetamine salts) | 4 to 6 h | Tablets | Oral | *ADHD, narcolepsy*: Daily up to divided doses daily | The first dose should be given on awakening, then additional doses at intervals of 4 to 6 hours. |
| Adderall XR (mixed amphetamine salts ER) | 10 to 12 h | Capsules | Oral | Daily in the morning | Capsules may be taken whole, or the capsule may be opened and the entire contents sprinkled on applesauce and consumed immediately. The dose of a single capsule should not be divided. |
| Mydayis (mixed amphetamine salts ER) | 16 h | Capsules | Oral | Daily in the morning | Dosage adjustment is needed for severe renal impairment. Use in end stage renal disease (ESRD) is not recommended.<br><br>Capsules may be |

| Drug | Duration of action* | Available Formulations | Route | Usual Recommended Frequency | Comments |
|---|---|---|---|---|---|
| | | | | | taken whole, or the capsule may be opened and the entire contents sprinkled on applesauce and consumed immediately in its entirety without chewing. The dose of a single capsule should not be divided. |
| Focalin (dexmethylphenidate) | 5 to 6 h | Tablets | Oral | Twice daily | |
| Focalin XR (dexmethylphenidate ER) | 10 to 12 h | Capsules | Oral | Daily in the morning | ER capsules may be taken whole, or the capsule may be opened and the entire contents sprinkled on applesauce. |
| ProCentra, Zenzedi (dextroamphetamine) | 4 to 6 h | Solution (ProCentra)<br>Tablets (Zenzedi) | Oral | *ADHD, narcolepsy*: Daily up to divided doses daily | The first dose should be given upon awakening; additional doses at intervals of 4 to 6 hours |
| Dexedrine Spansule (dextroamphetamine SR) | 6 to 8 h | Capsules | Oral | *ADHD*<br>Daily or twice daily<br><br>Narcolepsy<br>Daily | |
| Vyvanse (lisdexamfetamine) | 10 to 12 h | Capsules, chewable tablets | Oral | *ADHD, BED*: Daily in the morning | Dosage adjustment is needed for renal impairment/ESRD.<br><br>The capsules may be swallowed whole or can be opened, emptied, and mixed with yogurt, water, or orange juice and consumed immediately. A single capsule should not be divided.<br><br>The chewable tablets must be chewed |

| Drug | Duration of action* | Available Formulations | Route | Usual Recommended Frequency | Comments |
|---|---|---|---|---|---|
| | | | | | thoroughly before swallowing. A single dose should not be divided. |
| Desoxyn (methamphetamine) | 3 to 5 h | Tablets | Oral | Daily to twice daily | |
| Methylin, Ritalin (methylphenidate) | 3 to 5 h | Chewable tablets, tablets (Ritalin), solution (Methylin) | Oral | Twice daily to 3 times daily | The chewable tablets should be taken with at least 8 ounces (a full glass) of water or other fluid.<br><br>The liquid should be given 30 to 45 minutes before meals.<br><br>The ER tablets may be used in place of the IR tablets when the 8-hour dosage of the ER product corresponds to the titrated 8-hour dosage of the IR products.<br><br>The ER tablets must be swallowed whole and never crushed or chewed. |
| Methylphenidate ER | 3 to 8 h | Tablets | | | |
| Adhansia XR (methylphenidate ER) | 13 to 16 h | Capsules | Oral | Daily in the morning | The capsules may be taken whole or they can be opened and sprinkled onto applesauce or yogurt; the entire contents of the mixture should be consumed within 10 minutes, and should not be chewed.<br><br>The dose of a single capsule should not be divided. |
| Aptensio XR (methylphenidate ER) | 12 h | Capsules | Oral | Daily in the morning | The capsules may be taken whole or they can be opened and |

| Drug | Duration of action* | Available Formulations | Route | Usual Recommended Frequency | Comments |
|---|---|---|---|---|---|
| | | | | | sprinkled onto applesauce; the applesauce should be consumed immediately and it should not be chewed.<br><br>The dose of a single capsule should not be divided. |
| Concerta (methylphenidate ER) | 10 to 12 h | Tablets | Oral | Daily in the morning | The tablets should not be chewed or crushed.<br><br>Note: An FDA analysis of methylphenidate ER products manufactured by UCB/Kremers (formerly Kudco) and Mallinckrodt indicated that in some individuals, they may deliver the drug in the body at a slower rate during the 7- to 12-hour range. As a result, the FDA changed the therapeutic equivalence of these products from AB to BX. Because these manufacturers have subsequently failed to demonstrate that their products are bioequivalent to the brand-name reference drug, the FDA proposes to withdraw their approval (*FDA 2016*). |
| Methylphenidate ER | | | | | |
| Cotempla XR-ODT (methylphenidate ER) | 12 h | Orally disintegrating tablets | Oral | Daily in the morning | As soon as the blister pack is opened, the tablet should be placed on |

| Drug | Duration of action* | Available Formulations | Route | Usual Recommended Frequency | Comments |
|---|---|---|---|---|---|
| | | | | | the patient's tongue and allowed to disintegrate without chewing or crushing. The tablet will disintegrate in saliva so that it can be swallowed. |
| Jornay PM (methylphenidate ER) | Peak concentration occurs 14 hours after dose with gradual decline thereafter. | Capsules | Oral | Daily in the evening | The capsule may be swallowed whole or it may be opened and the contents sprinkled onto applesauce and given immediately. The capsule contents must not be crushed or chewed, the dose of a single capsule should not be divided, and the contents of the entire capsule should be taken at the same time. |
| Methylphenidate ER (CD) | 8 to 12 h | Capsules | Oral | Daily in the morning | The capsule may be swallowed whole or it may be opened and the contents sprinkled onto a small amount (tablespoon) of applesauce and given immediately. The capsule contents must not be crushed or chewed. |
| QuilliChew ER (methylphenidate ER) | 12 h | Chewable tablets | Oral | Daily in the morning | A 10 mg or 15 mg dose can be achieved by breaking in half the functionally scored 20 mg and 30 mg tablets, respectively. |
| Quillivant XR (methylphenidate ER) | 12 h | Suspension | Oral | Daily in the morning | The bottle of Quillivant XR should be shaken vigorously for 10 seconds prior to administration. |

| Drug | Duration of action* | Available Formulations | Route | Usual Recommended Frequency | Comments |
|---|---|---|---|---|---|
| | | | | | The suspension is stable for up to 4 months once reconstituted. |
| Ritalin LA (methylphenidate ER) | 8 to 12 h | Capsules | Oral | Daily in the morning | The capsule may be swallowed whole or may be administered by sprinkling the capsule contents on a small amount of applesauce; the contents should not be crushed, chewed, or divided. The mixture should be consumed immediately. |
| Daytrana (methylphenidate transdermal system) | 10 to 12 h | Transdermal system | Transdermal | The patch should be applied 2 hours before an effect is needed and removed within 9 hours. It may be removed earlier than 9 hours if a shorter duration of effect is desired or late day side effects appear. | |
| **Non-stimulants** | | | | | |
| Strattera (atomoxetine) | 24 h | Capsules | Oral | Daily in the morning or divided dose in the morning and late/afternoon early evening | Dosage adjustment is recommended for patients with moderate or severe hepatic insufficiency.<br><br>The capsules are not intended to be opened and should be taken whole. |
| Kapvay (clonidine ER) | 12 h | Tablets | Oral | Daily at bedtime or twice daily divided doses. | With twice daily dosing, either an equal or higher split dosage should be given at bedtime.<br><br>The tablets should not be crushed, chewed, or broken prior to swallowing. |

| Drug | Duration of action* | Available Formulations | Route | Usual Recommended Frequency | Comments |
|---|---|---|---|---|---|
| | | | | | The initial dosage should be based on the degree of renal impairment. |
| Intuniv (guanfacine ER) | 8 to 24 h | Tablets | Oral | Daily in the morning or evening | The tablets should not be crushed, chewed, or broken prior to swallowing; they should not be administered with high fat meals, due to increased exposure<br><br>It may be necessary to reduce the dosage in patients with significant renal and hepatic impairment. |

See the current prescribing information for full details
*References: Prescribing information for individual products, *Medical Letter 2020, Pharmacist's Letter 2016, Krull 2020a*

## CONCLUSION

- Both CNS stimulants and non-stimulants may be used for the treatment of ADHD. In general, stimulants are first-line treatment due to their superior efficacy. Clinical evidence suggests that methylphenidate and amphetamines are equally efficacious, but some patients may respond to one stimulant and not the other. Various short-, intermediate- and long-acting formulations (eg, tablets/capsules, chewable/orally disintegrating tablets, solution/suspension, transdermal patch) are available to provide a range of dosing options. Although non-stimulants such as atomoxetine and alpha$_2$-adrenergic agonists have smaller effect sizes, they may be used in patients who have failed or are intolerant to stimulants or when there is concern about possible abuse or diversion. The alpha$_2$-adrenergic agonists are approved both as monotherapy and as adjunctive therapy to stimulants, and they have been shown to improve both tic and ADHD symptoms in patients with comorbid tic disorder.
  - Current consensus clinical guidelines for the treatment of children and adolescents with ADHD recommend that stimulants are highly effective for reducing core symptoms of ADHD in children (*AACAP 2007*; *AAP 2019*).
- Ultimately, the choice of the initial agent for treatment of ADHD depends upon various factors such as: duration of desired coverage; ability of the child to swallow pills; coexisting tic disorder (use of alpha$_2$-adrenergic agonists may be warranted); potential AEs, history of substance abuse in the patient or household member (eg, avoid stimulants or use stimulants with less potential for abuse [eg, lisdexamfetamine, osmotic-release preparation, methylphenidate patch]); and preference of the patient and parent/guardian (*Krull 2020a*).
- Various stimulants are indicated for treatment of narcolepsy and are generally considered to be second-line agents after modafinil/armodafinil due to their sympathomimetic AEs (*Scammell 2020*).
- Lisdexamfetamine is the only FDA-approved drug indicated for the treatment of moderate to severe BED, with demonstrated efficacy in reduction of mean binge days per week vs placebo. Direct comparison trials between lisdexamfetamine and other drugs used off-label to treat BED are lacking.

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