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 2017).
  - 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 2017a). Common comorbid psychiatric disorders include oppositional defiant disorder, conduct disorder, depression, anxiety disorder, and learning disabilities (Krull 2017b). 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 2017c).
  - 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 2017).
- 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 2017d).
  - 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 2017e).
- 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 alpha2-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, Dexamethylphenidate, Methylphenidate, Selective Alpha Adrenergic Agonists, Selective Norepinephrine Reuptake Inhibitor

Table 1. Medications Included Within Class Review

<table>
<thead>
<tr>
<th>Drug</th>
<th>Generic Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimulants</td>
<td></td>
</tr>
</tbody>
</table>

Data as of September 20, 2017 AVD/CME

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<table>
<thead>
<tr>
<th>Drug</th>
<th>Generic Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evekeo (amphetamine sulfate)</td>
<td>-</td>
</tr>
<tr>
<td>Adderall (mixed amphetamine salts)</td>
<td>✔</td>
</tr>
<tr>
<td>Focalin (dexamethylphenidate hydrochloride [HCl])</td>
<td>✔</td>
</tr>
<tr>
<td>ProCentra (dextroamphetamine sulfate)</td>
<td>✔</td>
</tr>
<tr>
<td>Zenzedi (dextroamphetamine sulfate)</td>
<td>✔</td>
</tr>
<tr>
<td>Desoxyn (methamphetamine HCl)</td>
<td>✔</td>
</tr>
<tr>
<td>methylphenidate HCl chewable tablets</td>
<td>✔</td>
</tr>
<tr>
<td>Methylin Oral Solution (methylphenidate HCl)</td>
<td>✔</td>
</tr>
<tr>
<td>Ritalin (methylphenidate HCl)</td>
<td>✔</td>
</tr>
<tr>
<td>Dexedrine Spansule (dextroamphetamine sulfate sustained-release)</td>
<td>✔</td>
</tr>
<tr>
<td>Metadate ER (methylphenidate HCl ER)</td>
<td>✔</td>
</tr>
<tr>
<td><strong>Adzenys ER (amphetamine ER)</strong></td>
<td>✔</td>
</tr>
<tr>
<td>Adzenys XR-ODT (amphetamine ER)</td>
<td>-</td>
</tr>
<tr>
<td>Dyanavel XR (amphetamine ER)</td>
<td>✔</td>
</tr>
<tr>
<td>Adderall XR (mixed amphetamine salts ER)</td>
<td>✔</td>
</tr>
<tr>
<td>Mydayis (mixed amphetamine salts ER)</td>
<td>-</td>
</tr>
<tr>
<td>Focalin XR (dexamethylphenidate HCl ER)</td>
<td>✔</td>
</tr>
<tr>
<td>Vyvanse (lisdexamfetamine dimesylate)</td>
<td>-</td>
</tr>
<tr>
<td>Aptensio XR (methylphenidate HCl ER)</td>
<td>-</td>
</tr>
<tr>
<td>Concerta (methylphenidate HCl ER)</td>
<td>✔</td>
</tr>
<tr>
<td>Cotempla XR-ODT (methylphenidate ER)</td>
<td>-</td>
</tr>
<tr>
<td>methylphenidate HCl ER (CD)</td>
<td>✔</td>
</tr>
<tr>
<td>methylphenidate HCl ER</td>
<td>✔</td>
</tr>
<tr>
<td>QuilliChew ER (methylphenidate HCl ER)</td>
<td>-</td>
</tr>
<tr>
<td>Quillivant XR (methylphenidate HCl ER)</td>
<td>-</td>
</tr>
<tr>
<td>Ritalin LA (methylphenidate HCl ER)</td>
<td>✔</td>
</tr>
<tr>
<td>Daytrana (methylphenidate transdermal system)</td>
<td>-</td>
</tr>
</tbody>
</table>

**Non-stimulants**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Generic Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strattera (atomoxetine HCl)</td>
<td>✔</td>
</tr>
<tr>
<td>Kapvay (clonidine HCl ER)</td>
<td>✔</td>
</tr>
<tr>
<td>Intuniv (guanfacine HCl ER)</td>
<td>✔</td>
</tr>
</tbody>
</table>

*Note: Brand Metadate CD has been discontinued, but generics are available.*

( Drugs@FDA 2017, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2017, Facts & Comparisons 2017)
### INDICATIONS

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

<table>
<thead>
<tr>
<th>Indication</th>
<th>Evekeo (amphetamine sulfate)</th>
<th>Adzenys ER, Adzenys XR-ODT, Dyaneal XR</th>
<th>Adderall, Mydayis (mixed amphetamine salts ER)</th>
<th>Strattera (atomoxetine HCl)</th>
<th>Kapvay (clonidine HCl ER)</th>
<th>Focalin (dexmethylphenidate IR), Focalin XR</th>
<th>ProCentra, Zelzali (dextroamphetamine sulfate IR), Doxerametamine sulfate SR</th>
<th>Intuniv (guanfacine HCl ER)</th>
<th>Vyvanse (lisdexamfetamine dimesylate)</th>
<th>Desoxyn (methylphenidate HCl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHD*</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>☑</td>
<td>☑</td>
</tr>
</tbody>
</table>

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 is made.
### Indication

<table>
<thead>
<tr>
<th>Indication</th>
<th>Adderall (amphetamine ER)</th>
<th>Adderall XR, Mydayis (mixed amphetamine salts ER)</th>
<th>Strattera (atomoxetine HCl)</th>
<th>Kapvy (clonidine HCl ER)</th>
<th>ProCentra, Zened (dextroamphetamine sulfate SR)</th>
<th>Intuniv (guanfacine HCl ER)</th>
<th>Vyvanse (lisdexamfetamine dimesylate)</th>
<th>Desoxyn (methamphetamine HCl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysfunction may or may not be warranted.*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment of ADHD as monotherapy and as adjunctive therapy to stimulant medications</td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Narcolepsy**</td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>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).†</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Moderate to severe BED in adults</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
</tbody>
</table>

* Adderall, Evekeo, ProCentra, and Zenzedi are approved for use in children 3 years of age and older. Daytrana, Desoxyn, Dexedrine, Dyanavel, Evekeo, and Kavpy are approved for use in children 6 years of age and older. Adderall XR, Adderens ER, Adderens XR-ODT, Aptensio XR, Focalin, Focalin XR, methylphenidate ER (CD), Metadate ER, Methylin Oral Solution, methylphenidate, Quillivant XR, Quillivant XR, Ritalin, Ritalin LA, Strattera, and Vyvanse are approved for use in patients 6 years of age and older. Cotempra XR-ODT is 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:

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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 alpha2-adrenergic agonists to be more efficacious than placebo in reducing the core symptoms of ADHD in children and adolescents.
- Adzenys ER, a new 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.
- Cotempla XR-ODT, a new methylphenidate ER orally disintegrating tablet formulation, was approved based on a randomized, double-blind (DB), multi-center (MC), placebo-controlled (PC) laboratory classroom study (Childress et al 2017) (N = 87) which found that the average Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP)-Combined score was significantly better for Cotempla XR-ODT than for placebo (least squares [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).
- Mydayis, a new 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-Rating Scale [ADHD-RS] score, Permanent Product Measure of Performance [PERMP] score) (Mydayis Prescribing Information 2017, Weisler et al 2017) (see results below in Table 3 below).

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

<table>
<thead>
<tr>
<th>Study Number (Age range)</th>
<th>Primary Endpoint</th>
<th>Treatment Group</th>
<th>Mean Baseline Score (SD)</th>
<th>LS Mean Change from Baseline</th>
<th>Placebo-subtracted Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adult Studies</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Study 1 (18 to 55 years)</td>
<td>ADHD-RS</td>
<td>Mydayis 12.5 mg/day§</td>
<td>39.8 (6.38)</td>
<td>-18.5 (-11.7 to -4.4)</td>
<td>-8.1 (-13.4 to -9.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mydayis 37.5 mg/day§</td>
<td>39.9 (7.07)</td>
<td>-23.8</td>
<td>-13.4 (-17.1 to -9.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>40.5 (6.52)</td>
<td>-10.4</td>
<td></td>
</tr>
<tr>
<td>Study 2 (18 to 55 years)</td>
<td>Average PERMP</td>
<td>Mydayis 50 mg/day§</td>
<td>239.2 (75.6)†</td>
<td>293.23*</td>
<td>18.38 (11.28 to 25.47)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>249.6 (76.7)†</td>
<td>274.85*</td>
<td></td>
</tr>
<tr>
<td>Study 3 (18 to 55 years)</td>
<td>Average PERMP</td>
<td>Mydayis 25 mg/day§</td>
<td>217.5 (59.6)†</td>
<td>267.96*</td>
<td>19.29 (10.95 to 27.63)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>226.9 (61.7)†</td>
<td>248.67*</td>
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</tr>
<tr>
<td><strong>Pediatric Studies</strong></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Study 4 (13 to 17 years)</td>
<td>ADHD-RS-IV</td>
<td>Mydayis 12.5 to 25 mg/day§</td>
<td>36.7 (6.15)</td>
<td>-20.3</td>
<td>-8.7 (-12.6 to -4.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>38.3 (6.67)</td>
<td>-11.6</td>
<td></td>
</tr>
<tr>
<td>Study 5 (13 to 17 years)</td>
<td>Average PERMP</td>
<td>Mydayis 25 mg/day§</td>
<td>214.5 (87.8)‡</td>
<td>272.67*</td>
<td>41.26 (32.24 to 50.29)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>228.7 (101)‡</td>
<td>231.41*</td>
<td></td>
</tr>
</tbody>
</table>

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 (Punjia 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 (Hirotia et al 2014) (N = 2276) in pediatric patients with ADHD found that alpha2-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 alpha2-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 a 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 alpha2-adrenergic agonists). However, there is insufficient evidence to definitively conclude that one stimulant is more efficacious than another (Krull 2017e, AAP 2011).

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.

Alpha2-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.
Several clinical guidelines have provided recommendations on the treatment of ADHD in children and adolescents.

According to the American Academy of Pediatrics (AAP) guidelines (2011), 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 (2015) 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 is not recommended in adults with ADHD as there is no evidence that it improves efficacy or treatment satisfaction. For patients who are not responsive to an initial stimulant, clinicians should discuss the risks and benefits of switching to a non-stimulant medication with the patient.

CLINICAL GUIDELINES

ADHD

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The Medical Letter (2015) 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 is not recommended in adults with ADHD as there is no evidence that it improves efficacy or treatment satisfaction. For patients who are not responsive to an initial stimulant, clinicians should discuss the risks and benefits of switching to a non-stimulant medication with the patient.
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.

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.

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.

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- 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.
- Atomoxetine is contraindicated for use in patients with glaucoma, pheochromocytoma, severe CV disorders, hypersensitivity to any component of the product, and in those taking MAOIs. It carries a boxed warning for 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 alpha2-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>
<thead>
<tr>
<th>Drug</th>
<th>Duration of action*</th>
<th>Available Formulations</th>
<th>Route</th>
<th>Usual Recommended Frequency</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stimulants</strong></td>
<td></td>
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<tr>
<td>Evekeo (amphetamine)</td>
<td>4 to 6 h</td>
<td>Tablets</td>
<td>Oral</td>
<td>ADHD, narcolepsy: Daily up to divided doses daily</td>
<td>ADHD and narcolepsy</td>
</tr>
<tr>
<td>Adzenys ER (amphetamine ER)</td>
<td>10 to 12 h</td>
<td>Suspension</td>
<td>Oral</td>
<td>Daily in the morning</td>
<td></td>
</tr>
<tr>
<td>Adzenys XR-ODT (amphetamine ER)</td>
<td>10 to 12 h</td>
<td>Orally disintegrating tablets</td>
<td>Oral</td>
<td>Daily in the morning</td>
<td>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.</td>
</tr>
<tr>
<td>Dyanavel XR (amphetamine ER)</td>
<td>Up to 13 h</td>
<td>Suspension</td>
<td>Oral</td>
<td>Daily in the morning</td>
<td>The bottle should be shaken before administration.</td>
</tr>
<tr>
<td>Adderall (mixed amphetamine salts)</td>
<td>4 to 6 h</td>
<td>Tablets</td>
<td>Oral</td>
<td>ADHD, narcolepsy: Daily up to divided doses daily</td>
<td>The first dose should be given on awakening, then additional doses at intervals of 4 to 6 hours.</td>
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<td>Drug</td>
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<tr>
<td>Adderall XR (mixed amphetamine salts ER)</td>
<td>10 to 12 h</td>
<td>Capsules</td>
<td>Oral</td>
<td>Daily in the morning</td>
<td>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.</td>
</tr>
<tr>
<td>Mydayis (mixed amphetamine salts ER)</td>
<td>16 h</td>
<td>Capsules</td>
<td>Oral</td>
<td>Daily in the morning</td>
<td>Dosage adjustment is needed for severe renal impairment. Use in end stage renal disease (ESRD) is not recommended. Capsules may be 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.</td>
</tr>
<tr>
<td>Focalin (dextmethylphenidate)</td>
<td>5 to 6 h</td>
<td>Tablets</td>
<td>Oral</td>
<td>Twice daily</td>
<td></td>
</tr>
<tr>
<td>Focalin XR (dextmethylphenidate ER)</td>
<td>10 to 12 h</td>
<td>Capsules</td>
<td>Oral</td>
<td>Daily in the morning</td>
<td>ER capsules may be taken whole, or the capsule may be opened and the entire contents sprinkled on applesauce.</td>
</tr>
<tr>
<td>ProCentra, Zenzedi (dextroamphetamine)</td>
<td>4 to 6 h</td>
<td>Solution (ProCentra) Tablets (Zenzedi)</td>
<td>Oral</td>
<td>ADHD, narcolepsy: Daily up to divided doses daily</td>
<td>The first dose should be given upon awakening; additional doses at intervals of 4 to 6 hours.</td>
</tr>
<tr>
<td>Drug</td>
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<tr>
<td>Dexedrine Spansule (dextroamphetamine SR)</td>
<td>6 to 8 h</td>
<td>Capsules</td>
<td>Oral</td>
<td>ADHD, Narcolepsy</td>
<td>Dosage adjustment is needed for renal impairment/ESRD. 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. The chewable tablets must be chewed thoroughly before swallowing. A single dose should not be divided.</td>
</tr>
<tr>
<td>Vyvanse (lisdexamfetamine)</td>
<td>10 to 12 h</td>
<td>Capsules, chewable tablets</td>
<td>Oral</td>
<td>ADHD, BED: Daily in the morning</td>
<td>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. The chewable tablets must be chewed thoroughly before swallowing. A single dose should not be divided.</td>
</tr>
<tr>
<td>Desoxyn (methamphetamine)</td>
<td>3 to 5 h</td>
<td>Tablets</td>
<td>Oral</td>
<td>ADHD: Daily to twice daily</td>
<td>The chewable tablets should be taken with at least 8 ounces (a full glass) of water or other fluid. The ER tablets may be used in place of</td>
</tr>
<tr>
<td>Methylin, Ritalin (methylphenidate)</td>
<td>3 to 5 h</td>
<td>Chewable tablets, tablets (Ritalin), solution (Methylin)</td>
<td>Oral</td>
<td>Twice daily to 3 times daily</td>
<td>The chewable tablets should be taken with at least 8 ounces (a full glass) of water or other fluid. The ER tablets may be used in place of</td>
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<tr>
<td>Methylphenidate ER</td>
<td>3 to 8 h</td>
<td>Tablets</td>
<td></td>
<td></td>
<td>the IR tablets when the 8-hour dosage of the ER product corresponds to the titrated 8-hour dosage of the IR products. The ER tablets must be swallowed whole and never crushed or chewed.</td>
</tr>
<tr>
<td>Aptensio XR (methylphenidate ER)</td>
<td>12 h</td>
<td>Capsules</td>
<td>Oral</td>
<td>Daily in the morning</td>
<td>The capsules may be taken whole or they can be opened and sprinkled onto applesauce; the applesauce should be consumed immediately and it should not be chewed. The dose of a single capsule should not be divided.</td>
</tr>
</tbody>
</table>
| Concerta (methylphenidate ER) | 10 to 12 h          | Tablets                | Oral  | Daily in the morning        | The tablets should not be chewed or crushed. 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
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<td>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).</td>
</tr>
<tr>
<td>Cotempla XR-ODT (methylphenidate ER)</td>
<td>12 h</td>
<td>Orally disintegrating tablets</td>
<td>Oral</td>
<td>Daily in the morning</td>
<td>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.</td>
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<td>Methylphenidate ER (CD)</td>
<td>8 to 12 h</td>
<td>Capsules</td>
<td>Oral</td>
<td>Daily in the morning</td>
<td>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.</td>
</tr>
<tr>
<td>QuilliChew ER (methylphenidate ER)</td>
<td>12 h</td>
<td>Chewable tablets</td>
<td>Oral</td>
<td>Daily in the morning</td>
<td>The bottle of Quillivant XR should be shaken</td>
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<tr>
<td>Quillivant XR (methylphenidate ER)</td>
<td>12 h</td>
<td>Suspension</td>
<td>Oral</td>
<td>Daily in the morning</td>
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<tr>
<td>Ritalin LA (methylphenidate ER)</td>
<td>8 to 12 h</td>
<td>Capsules</td>
<td>Oral</td>
<td>Daily in the morning</td>
<td>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.</td>
</tr>
<tr>
<td>Daytrana (methylphenidate transdermal system)</td>
<td>10 to 12 h</td>
<td>Transdermal system</td>
<td>Transdermal</td>
<td>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.</td>
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<tr>
<td>Non-stimulants</td>
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<tr>
<td>Strattera (atomoxetine)</td>
<td>24 h</td>
<td>Capsules</td>
<td>Oral</td>
<td>Daily in the morning or divided dose in the morning and late/afternoon early evening</td>
<td>Dosage adjustment is recommended for patients with moderate or severe hepatic insufficiency. The capsules are not intended to be opened and should be taken whole.</td>
</tr>
<tr>
<td>Kapvay (clonidine ER)</td>
<td>12 h</td>
<td>Tablets</td>
<td>Oral</td>
<td>Daily at bedtime or twice daily divided doses.</td>
<td>With twice daily dosing, either an equal or higher split dosage should be given at bedtime. The tablets should not be crushed.</td>
</tr>
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</table>
**Drug** | **Duration of action** | **Available Formulations** | **Route** | **Usual Recommended Frequency** | **Comments**
--- | --- | --- | --- | --- | ---
Intuniv (guanfacine ER) | 8 to 24 h | Tablets | Oral | Daily in the morning or evening | chewed, or broken prior to swallowing. The initial dosage should be based on the degree of renal impairment. It may be necessary to reduce the dosage in patients with significant renal and hepatic impairment.

See the current prescribing information for full details


**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 alpha2-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 alpha2-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 2011).
  
- 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 alpha2-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 2017e).
  
- 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 2017).
  
- 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.

**REFERENCES**

- Adderall [package insert], Horsham, PA: Teva Select Brands; December 2016.
- Adzenys ER [package insert], Grand Prairie, TX: Neos Therapeutics, Inc.; September 2017.


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• ProCentra [package insert], Newport, KY: Independence Pharmaceuticals, LLC; February 2017.
• Quillivant XR [package insert], New York, NY: Pfizer, Inc.; June 2017.
• Strattera [package insert], Indianapolis, IN: Lilly USA, Inc.; May 2017.
• Zanxedi [package insert], Atlanta, GA: Arbor Pharmaceuticals, LLC; February 2017.