CNS SPECTRUMS

CME Review Article

A Clinician's Guide for Navigating the World of ADHD Medications

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- Differentiate the spectrum of medications available for ADHD based on pharmacokinetic and clinical profiles
- Customize ADHD medication selection to the individual needs of pediatric and adult patients with ADHD

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A clinician's guide for navigating the world of attention deficit hyperactivity disorder medications

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Review

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Once considered a condition of hyperactive boys, our knowledge and understanding of attention deficit hyperactivity disorder (ADHD) and has dramatically evolved.[1] Landmark studies by Biederman, Kessler, Faraone, and others have changed and deepened our understanding of ADHD to include a condition which not only affects boys but quite often affects girls.[1–5] The evolution of symptoms across the lifespan and the concomitant neurologic changes which underlie this symptomatic expression has similarly evolved.[6] Studies by Dalsgaard and others have brought to light the significantly increased morbidity and mortality associated with preschoolers, children, and adults struggling with ADHD and associated conditions.[7,8]
This article will help clinicians:

(1) Develop a deeper understanding of the evolution of ADHD symptoms and functional struggles across the age span.
(2) Become familiar with rating scales that evaluate ADHD symptoms, behavioral challenges, and functional difficulties in ADHD.
(3) Learn how to optimize outcomes and manage breakthrough symptoms.
(4) Understand the onset, offset, and duration of action of various ADHD medications.
(5) Develop strategies to adjust or combine medications to address breakthrough symptoms in the morning, afternoon, or evening.

Consequences of ADHD Across the Lifespan

ADHD is a common neurodevelopmental disorder affecting approximately 8% to 11% of school-aged children, both in the United States and throughout the rest of the developed world.[9] ADHD has come to be recognized as a condition which affects both boys and girls and often persists from childhood to adolescence and into adulthood.[10] The classic triad of hyperactivity, impulsivity, and inattention captures many of the core aspects of ADHD but fails to capture some of the difficulties surrounding executive function and emotional reactivity which collectively account for much of the social, educational, occupational, and emotional impairment of the disorder. In early childhood and throughout grade school ADHD is diagnosed more frequently in boys than girls; possibly relating to the higher expression of overt hyperactive symptomatology which is found in preadolescent boys.[5] ADHD patients with predominantly inattentive symptoms are often overlooked, misdiagnosed, or diagnosed 2 to 3 years later in life in that the overt outward marker of hyperactivity has often been used to identify this condition.

Our basic understanding of the neurophysiology of ADHD has advanced dramatically with studies by investigators such as Nora Volkow, who highlighted the differences in dopamine transporter activity in children with ADHD, Philip Shaw who tracked maturation of the prefrontal cortex in children with ADHD, and studies looking at the influence of genetic heritability and environmental factors.[2,11] These studies, taken in total, show that ADHD is a highly genetic neurologic condition which affects numerous cortical and subcortical pathways that coordinate information processing, impulsivity, emotional modulation, and neurochemical pathways that modulate communication between these cortical regions. ADHD has an overall genetic heritability of approximately 75%, that is, three out of four times there will be a genetic family history. There is also an important impact of environmental factors and the influence of the environment upon our genes with epigenetic changes occurring in a number of our children exposed to environmental stressors such as prenatal nicotine exposure, lead exposure, or severe psychosocial trauma.[12,13]

Long-term follow-up longitudinal studies have shown that ADHD children are at greater risk of academic difficulties, emotional dysregulation with oppositional defiant disorder tendencies and emotional volatility. Longitudinal imaging studies have shown a 2 to 3 year delay in maturation of the prefrontal cortex and associated pathways in children with ADHD as compared to non-ADHD controls.[6] It is therefore not surprising that ADHD symptomatology continues to evolve throughout childhood, adolescence, and into early adulthood as the underlying neurophysiology of the brain continues to mature and is influenced by outside environmental demands such as high school, college, employment, and the social demands of adulthood.

By adolescence, there is an increased rate of drug and alcohol abuse, an increased rate of motor vehicle and traffic-related difficulties and a dramatically increased rate of teenage pregnancy for ADHD individuals compared to controls.[9] Followed on into adulthood, ADHD individuals have lower occupational and economic performance, have increased difficulty with financial management, have increased rates of psychiatric comorbidity such as depression, alcohol, and drug abuse, intermittent explosive disorder, and a variety of anxiety disorders.[14] ADHD adults have increased rates of marital dysfunction and divorce, dramatically worsened abilities to maintain ongoing friendships and significantly lower evaluations of self-esteem and self-worth.[15]

Can Treatment Make a Difference?

Although classic ADHD studies have shown that both behavioral and medical interventions can improve core ADHD symptoms, there has been debate about the overall long-term functional impact of ADHD interventions. Studies by Biederman, Wilens, and others have shown that consistent ADHD treatment decreased the rate of drug and alcohol abuse later in life.[15] Numerous studies in analog classroom settings have shown improved performance on task-related activities such as completing math problems and improvement on behavioral tasks measured by rating scales such as the SKAMP (Swanson, Kotkin, Atkins, M-Flynn, and Pelham).[16]

Studies by Dalsgaard and others have shown that ADHD is associated with significantly increased morbidity and mortality.[7,8] These studies have found increased rates of accidental injury requiring medical treatment and injury requiring emergency room intervention. Utilizing the Danish birth registry, Dalsgaard found that on a nationwide basis ADHD individual had dramatically increased mortality rates compared to the general population. ADHD preschoolers had an 86% increased mortality rate, school-aged students had a 58% increased mortality rate, and adults with ADHD had a 325% increased mortality rate relative to non-ADHD individuals within the same population.[5] These studies went on to analyze whether ADHD treatment within the overall population of Denmark impacted these adverse outcomes. They found that ADHD treatment was associated with an overall decrease in accidental injury and medical utilization due to accidents and trauma. On a nationwide basis, they found a 25% to 37% decrease in emergency room utilization among ADHD individuals receiving treatment versus those not receiving treatment.[7]

Similarly, a 2 year follow-up study of ADHD adults in the United States found that women had a 27% reduction and men had 34% reduction in motor vehicle trauma rates in the months where they took their medications as compared to the months where they were unmedicated. Treatment was even more impactful in those with high impulsivity with men who ride motorcycles having a 49% reduction in trauma rates in the months where they took their medications.[17]

Diagnosis and Recognition of Symptoms

ADHD is a pervasive condition with symptoms that start in childhood or adolescence and involve a core of 18 classic symptoms.[10] According to DSM V criteria, children with ADHD must have a persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning with ≥6 of nine inattentive symptoms for an inattentive presentation, ≥ 6 of nine hyperactive/impulsive symptoms for a hyperactive/impulsive presentation or ≥6 inattentive and six hyperactive/impulsive symptoms to meet criteria for a combined presentation. Longitudinal studies of ADHD children followed into adulthood by Barkley found that ADHD adults had difficulty remembering symptoms dating back to early childhood and therefore the DSM V diagnostic criteria have been modified.[14] For a diagnosis in late adolescence or adulthood, several symptoms must have been present before age 12 and there must continue to be ≥5 of nine symptoms in either the inattentive, hyperactive/impulsive, or in both domains for diagnosis.

Improving the Accuracy of ADHD Diagnosis and Treatment

Clinical data and research evidence have highlighted the need to shift from a subjective to a more objective measure of ADHD diagnosis and treatment. A variety of fairly sensitive and specific ADHD rating scales have been developed to better define and measure ADHD symptoms both during initial diagnosis and throughout ongoing treatment. While in no way substituting for a thorough clinical evaluation, these scales help to:

(1) Better quantify and define ADHD impairments during the initial diagnosis.
(2) Measure ADHD symptoms at various time points throughout the day.
(3) Track ADHD symptoms to make sure that overall symptomatic improvement, symptomatic remission, and functional normalization have been optimized for each patient.
(4) Save time by providing an objective measure of symptom severity before meeting with a patient.

Why Should a Clinician Use ADHD Rating Scales?

Just as it is helpful for an internist to know an individual's blood pressure or hemoglobin A1c when diagnosing and optimizing treatment for a hypertensive or diabetic patient, ADHD rating scales can be similarly useful in the management of our patients.

The ADHD-Rating Scale (ADHD-RS), the Vanderbilt, and the Conner's are examples of ADHD scales that have been shown to be consistent measures of core ADHD symptoms and are sensitive to treatment effect.[18–21] Various ratings of executive function such as the Behavior Rating Inventory of Executive Function, can be utilized to measure executive function deficits which frequently cause impairment for ADHD individuals.[22]

Another group of scales has been developed to measure ADHD symptoms and how they fluctuate throughout the day. Analog Classroom and Analog Workplace settings have been developed to measure ADHD symptoms and evaluate how long different treatment modalities improve symptoms over the course of the day. In these settings the 13 item SKAMP is used to measure attention, behavior, and deportment in children and the Permanent Product Measure of Performance measures a child or adult's ability to sit and complete a series of basic math equations during 10 minutes and these tests are then repeated at various time points throughout the day.[16,23] The Before School Functioning Questionnaire (BSFQ) has been developed to help clinicians better evaluate ADHD symptoms and functional impairments which cause significant disruption during the morning hours.[24] The Parent Rating of Evening and Morning Behavior (PREMB) evaluates behavioral problems both in the morning (PREMB-AM) and evening (PREMB-PM) in children.[5]

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Rating scales cannot only be used to detect breakthrough symptoms for pharmacotherapeutic adjustment but can also be used to detect symptomatic or functional issues for psychotherapeutic intervention. Family training, daily structure, and behavior modification can all be optimized by using appropriate rating scales to monitor associated struggles throughout the day.

Goals for Treatment

ADHD medications have some of the highest effect sizes of any medical intervention.[25] Studies also demonstrate, however, that response to specific medications is highly individual. Studies show that some patients respond equally well to either class, while other individuals have a preferential response to either a methylphenidate preparation or an amphetamine preparation.[26] Individuals who have experienced adverse effects or have failed stimulants may go on to either tolerate or preferentially respond to non-stimulant medications.[27]

Studies with all three classes of medications, methylphenidates, amphetamines, and non-stimulants, have highlighted that it is all too easy for clinicians to settle for partial improvement while still leaving patients with ongoing symptomatology.[28] Clinical response has often been defined as a 25% to 30% symptom improvement, but this still leaves patients with ongoing significant symptomatic and functional impairment. Interestingly, clinicians interpret 30% symptom improvement as "much" or even "very much improved" on global clinical measures.[29–32]

Patients and clinicians may be tempted to be satisfied with 30% improvement, even though the evidence is clear that such minimal improvement almost inevitably means continued functional impairment. For most patients, further improvement is possible. Long-term trials demonstrate that nearly 75% to 80% of patients can achieve >50% symptom reduction and achieve symptomatic remission with overall Attention Deficit Hyperactivity Disorder Raring Scale- ADHDRS scores of less than 18 (meaning that ADHDRS scores are mild or less on average).[33,34]

Most individuals with ADHD will have moderate to moderately severe symptoms when first presenting for diagnosis or treatment with corresponding ADHD-RS scores in the 30 seconds to low 40 seconds (18 symptoms rated 0 to 3, 0 none, 1 mild, 2 moderate, and 3 severe).[28]

A recent study with MPH DR/ER dosed in the evening for ADHD children demonstrated that ADHD symptoms could be decreased from 42 to 11 after 6 weeks of dose titration, with an average final dose of 60 mg per day. To put this in clinical perspective; these children were highly symptomatic with ADHD scores that were moderate or severe on all 18 items and by the end of 6 weeks their ADHD symptoms were mild or none on average. This and other studies point to the importance of appropriate titration to optimize outcomes in our patients with ADHD[28] (Figure 1).

In addition to overall symptom improvement, our treatments must deliver symptomatic improvement at time points where functional impairment is occurring for our patients. Studies by Sallee, Whalen, Mattingly, and others have shown that clinicians primarily focus on consequences of ADHD during school and work while overlooking impairments that occur at the beginning and end of the day.[35–37] Sallee et al found that 79% of ADHD caregivers have discussed early morning functional impairments such as getting out of bed, getting dressed, self-hygiene, eating breakfast, packing their backpack, and being able to catch the bus as being some of the most impairing issues for their children with ADHD. Nearly half of these caregivers reported getting early to administer ADHD medication before their child's normal wake time to compensate for functional difficulties experienced before their child's medication was otherwise taking effect.[32]

Comorbid Conditions

As now noted in DSM 5, ADHD frequently presents with a constellation of associated emotional, behavioral, and cognitive challenges.[10] Young children with ADHD frequently have associated learning disorders or developmental disabilities such as difficulties with sensory integration, problems with working memory, speech, and language delay, and difficulties with reading comprehension. A baseline battery of neurocognitive testing to detect specific learning challenges should be considered in all school-age children with ADHD. Recognition of specific learning challenges can help to better identify therapeutic interventions and academic accommodations which can be of great benefit for children struggling with ADHD and associated learning difficulties.

Emotional Impulsivity, Oppositional Behavior, and Poor Frustration Tolerance

Many children, adolescents, and adults with ADHD struggle with symptoms associated with poor frustration tolerance. These symptoms can present in childhood as difficulty waiting, impatience with delays, or excessive frustration when asked to shift from a preferred to a nonpreferred task.[36] Such frustration often leads to a sequence of escalating emotional and behavioral dyscontrol, "meltdowns" out of proportion to the task at hand, and emotional fragmentation.[37,38]

Oppositional thoughts and behaviors can trouble ADHD individuals of any age.[39–41] Difficulties shifting from preferred to nonpreferred tasks and impaired recognition of the emotional impact of their behavior on others frequently lead to such oppositional patterns in ADHD individuals.

Appropriate medication selection can improve not just core ADHD symptoms but can also improve morning function, morning behavioral issues, and evening behavior.[38,42] The BSFQ allows clinicians to monitor functional issues that a parent or caregiver are noting to be disruptive for a child or their family in the morning before school. The PREMB allows a clinician to disruptive behaviors in both the morning or evening. Morning behaviors include getting up in the morning, getting ready for school, arguing with siblings, or being late for school or the bus. Evening behaviors include doing homework, eating dinner with the family, getting ready for bed, and falling asleep (Tables 1 and 2; Figure 2).

Immediate-Release, Extended-Release, Delayed-Release, or Combinations; Choosing Between Medication Options

The last several years have seen an explosion in stimulant delivery systems available for ADHD treatment. Stimulants are now considered the first-line pharmacologic treatment option for individuals with ADHD.[85,86] ADHD treatment has progressed from a decision between short-acting methylphenidate (Ritalin, Methylin…) versus short-acting amphetamine (Dexedrine, Adderall…), each of which required dosing several times per day in order to maintain therapeutic efficacy.

Various strategies have been developed by pharmaceutical manufacturers to avoid the mid-day and intraday dosing. Early

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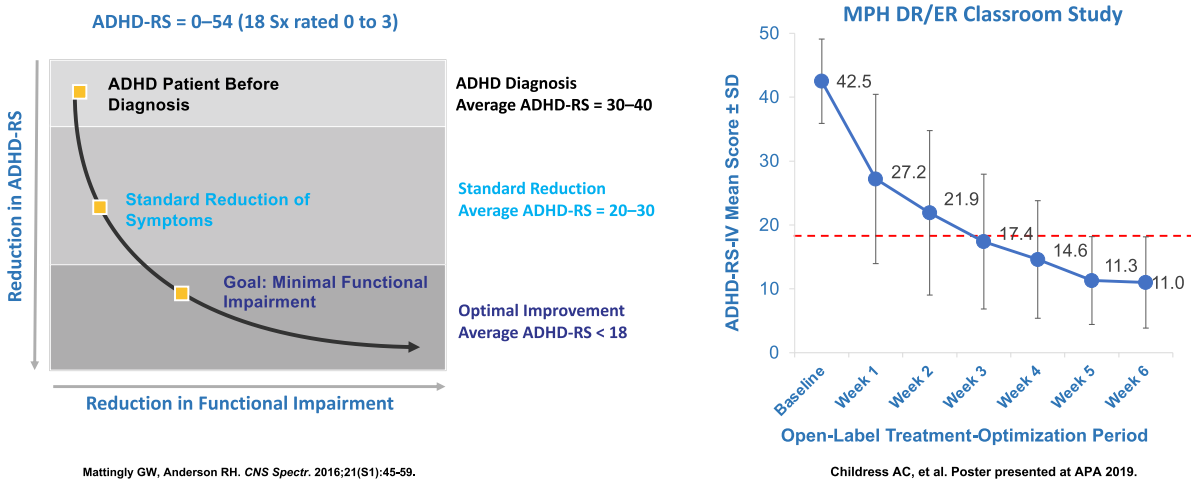

Figure 1. Optimizing symptom reduction results after 6 weeks of treatment.

modifications involved slow-release wax matrix technologies (Ritalin SR…) that while extending the duration of action continued to have difficulties with variable release patterns from day to day and from patient to patient depending on pH-related factors, gastric motility, and meal effects.

The next set of sustained-release medications involved beaded technologies (Adderall XR, Focalin XR…) where a certain percentage of medication was released in short-acting immediate release beads while another percentage of beads were coated with a pH-dependent layer that would begin releasing approximately 4 hours later in the less acidic small intestine providing clinical efficacy for approximately 8 to 10 hours. These beaded technologies allowed for adjustment of the percent immediate-release versus sustained-release beads (30/70, 40/60, or 50/50) in order to have greater delivery in the morning or increased medication delivery in the afternoon. A triple bead mixed amphetamine salt compound has been approved for adolescent and adults with ADHD. This compound (Mydayis) was shown to achieve a 16 hour duration of action in clinical trials.

A more recent adaptation of the beaded technology involves a multi-layered release technology where each bead has an immediate-release outer layer with an extended release inner layer. These pH-dependent layers then dissolve as each bead passes through various points in the intestinal tract. This multilayered release profile results in a biphasic pharmacokinetic curve with an immediate first peak 2 hours post dose and a second peak 8 hours post dose with an MPH compound (Aptensio) achieving 12 hour duration of effect in clinical trials. A longer duration multilayered MPH formulation (Adhansia) has been approved with duration of improvement of 13 hours in pediatric trials and up to 16 hours in adult trials.

Beyond Beads

The OROS capsule (Concerta) provides a novel delivery system with ongoing continuous release. After ingestion, stomach fluid is absorbed through osmotic pores in one end of the capsule causing medication to be excreted through a laser-drilled hole at the other end of the capsule. The release occurs over 10 to 12 hours but many patients experience a shorter duration of action.

A prodrug version of amphetamine was developed by binding lysine to amphetamine. Lisdexamfetamine (Vyvanse) is a hydrophilic "biologically inactive" prodrug which is not able to cross the bi-lipid blood–brain barrier. Lisdexamfetamine is enzymatically cleaved into free amphetamine and free lysine by enzymes in the cytosol of the human red blood cells providing sustained symptomatic improvement for 13 hours in children and 14 hours in adults. Lisdexamfetamine can be dissolved in fluid such as juice and administered in a liquid dose.

Transdermal

The ADHD field has one transdermal methylphenidate (Daytrana) option which provides continuous transdermal release of methylphenidate from the moment the patch is applied with continued efficacy until approximately 2 hours after the patch is removed.[61,87] This allows flexibility of daytime dosing with shorter or longer wear times depending on the individual needs of the patient. Unfortunately, adverse effects such as rash and skin discomfort often hinder the use of this transdermal technology, although it should be noted that a transdermal amphetamine based patch currently in development may minimize some of the associated skin reactions.

Microparticles

A variety of pH based ion-exchange polymers have been developed to allow ion exchange of stimulant molecules with underlying microparticle polymers. These pH based microparticle polymer technologies have allowed the development of sustained-release orally disintegrating tablets (ODT). Sustained release microparticle-based ODTs, MPH (Cotempla ODT) or amphetamine (Adzenys ODT) as well as a liquid suspension amphetamine (Adzenys) are approved for treatment of ADHD. Each ODT has stimulant molecules ionically bound to between 100 000 and 200 000 microparticles. A portion of these microparticles begin releasing stimulant immediately when they encounter ions in gastric lumen and some of these micorparticles are pH coated such that they will not release stimulant until they have passed into the small intestine.

Another microparticle multilayered technology allows liquid suspension or chewable tablets. Methylphenidate (Quillivant and Quilichew) and amphetamine (Dyanavel) preparations are approved for treatment of ADHD. These liquid formulations offer sustained-release preparations that can be titrated in small increments for children that are especially sensitive to side effects.

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Table 1. FDA-Approved Methylphenidate[a] Formulations for ADHD

Delivery Mechanism and Formulation	Generic Name	Brand Name	Approved Ages	Dosing (Per Day)	Onset of Effect	Duration of Effect	Comments	References
Short-acting								
Dexmethylphenidate tablet	Dexmethylphenidate HCL	Focalin	Children ≥6	2	NA	6 h	At least 4 h between doses	43, 44
Methylphenidate tablet	Methylphenidate HCL	Ritalin	Children ≥6, adults	2 to 3	1 to 2 h	4 h		45, 46
Methylphenidate chewable tablet and liquid	Methylphenidate HCL	Methylin	Children ≥6, adults	2 to 3	1 h[b]	4 h[b]	Chewable tablet: take with 8 oz of water 30 to 45 min before meals Oral solution: take 30 to 45 min before meals Last dose before 6 PM	47, 48
Intermediate-acting								
Methylphenidate tablet	Methamphetamine HCL	Methylin ER	Children ≥6, adults	1	NA	NA		49
Methylphenidate tablet	Methamphetamine HCL	Ritalin-SR	Children ≥6, adults	1	1.5 h	8 h	Take after meals for maximum duration of effect	43, 45
Methylphenidate tablet	Methamphetamine HCL	Metadate ER	Children ≥6, adults	1	NA	8 h		50
Methylphenidate capsule	Methamphetamine HCL	Metadate CD	Children 6 to 15	1	1.5 h	8 to 9 h	May be sprinkled on applesauce	51, 52
Long-acting								
Dexmethyl phenidate capsule	Dexmethylphenidate HCL	Focalin XR	Children ≥6, adults	1	30 min	12 h	May be sprinkled	53, 54
Methylphenidate chewable tablet	Methylphenidate HCL	QuilliChew ER	Children ≥6, adults	1	45 min	8 h		55, 56
Methylphenidate chewable tablet	Methylphenidate HCL	Ritalin LA	Children 6 to 12	1	30 min to 1 h	12 h	May be sprinkled	43, 52, 56
Methylphenidate tablet	Methylphenidate HCL	Concerta	Children ≥6, adults	1	1 to 2 h	10 to 12 h		52, 57
Methylphenidate liquid	Methylphenidate HCL	Quillivant XR	Children ≥6, adults	1	45 min	12 h	Shake bottle vigorously for 10 s before dispensing	55, 58
Methylphenidate capsule	Methylphenidate HCL	Aptensio XR	Children ≥6, adults	1	1 h	12 h	May be sprinkled	56, 59
Methylphenidate ODT	Methylphenidate	Cotempla XR-ODT	Children ≥6	1	1 h	12 h	No crushing or chewing Allow to disintegrate in saliva before swallowing	56, 60
Methylphenidate transdermal patch	Methylphenidate	Daytrana	Children ≥6	1	2 h	12 h	Wear for ≤9 h	52, 61
Methylphenidate capsule	Methylphenidate HCL	Adhansia XR	Children ≥6, adults	1	1 h	13 to 16 h	May be sprinkled and consumed within 10 min	62
Methylphenidate capsule	Methylphenidate HCL	Jornay PM	Children ≥6, adults	1	8 to 10 h	12+ h	Take in the evening between 6:30 and 9:30 PM for early morning symptom control may be sprinkled	63, 64

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; FDA, U.S. Food and Drug Administration; HCL, hydrochloride; NA, not available; ODT, orally disintegrating tablet.
[a]The American Academy of Pediatrics recommends utilizing methylphenidate as the first choice for preschool-aged children.[23]
[b]Methylin is bioequivalent to Ritalin,[5] but it has not been tested independently in a classroom study.

Table 2. FDA-Approved Amphetamine Formulations for ADHD

Delivery Mechanism and Formulation	Generic Name	Brand Name	Approved Ages	Dosing (Per Day)	Onset of Effect	Duration of Effect	Comments	References
Short-acting								
Amphetamine tablet	Amphetamine mixed salts	Adderall	Children ≥3	1 to 3	1.5 h	4 to 6 h	Elimination half-life 9.77 to 11 h for the D-isomer and 11.5 to 13.8 h for L-isomer	65–68
Dextroamphetamine tablet	Dextroamphetamine sulfate	Dexedrine	Children 3 to 16	1 to 2	NA	4 to 6 h		67, 69
Dextroamphetamine tablet	Dextroamphetamine sulfate	Zenzedi	Children 3 to 16	1 to 3	NA	4 to 6 h		70
Dextroamphetamine liquid	Dextroamphetamine sulfate	ProCentra	Children 6 to 16	1 to 2	NA	6 to 10 h	Plasma half-life of approximately 12 h	71
Methamphetamine tablet	Methamphetamine HCL	Desoxyn	Children ≥6	1 to 2	NA	NA	Not readily available	72
Intermediate-acting								
Amphetamine tablet and ODT	Racemic amphetamine sulfate	Evekeo	Children ≥3 (tablet) Children 6 to 17 (ODT)	1 to 2	45 min	9.25 h	Elimination half-life 10.0 to 11.7 h	73–75
Dextroamphetamine capsule	Dextroamphetamine sulfate	Dexedrine spansule	Children 6 to 16	1 to 2	NA	6 to 10 h	Plasma half-life of approximately 12 h	67, 69
Long-acting								
Amphetamine capsule	Amphetamine mixed salts	Adderall XR	Children ≥6, adults	1	1.5 h	10.5 to 12 h	May be sprinkled on applesauce	76, 77
Amphetamine liquid	Amphetamine	Adzenys ER	Children ≥6, adults	1	1.5 h[a]	10 to 12 h[a]	Do not add to food or other liquids	78
Amphetamine ODT	Amphetamine	Adzenys XR-ODT	Children ≥6, adults	1	1.5 h[a]	10 to 12 h[a]	Allow tablet to disintegrate in saliva before swallowing	79
Amphetamine liquid	Amphetamine	Dyanavel XR	Children ≥6	1	1 h	12		80
Amphetamine capsule	Amphetamine mixed salts	Mydayis	Children ≥13, adults	1	2 h	14 h	May be sprinkled on applesauce	81, 82
Amphetamine prodrug capsule and chewable tablet	Lisdexamfetamine dimesylate	Vyvanse	Children ≥6, adults	1	1.5 to 2 h	12 to 14 h	Capsule: may be sprinkled in water, orange juice, or yogurt Chewable tablet: chew thoroughly before swallowing	83, 84

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; FDA, U.S. Food and Drug Administration; HCL, hydrochloride; NA, not available; ODT, orally disintegrating tablet.
[a]Adzenys XR-ODT and Adzenys ER are bioequivalent to extended-release mixed amphetamine salts (ie, Adderall XR),[42, 85] but have not been tested independently in a classroom study.

- Morning function on Before School Functioning Questionnaire (BSFQ)
- Morning behavior on Parents Rating of Evening and Morning Behavior- Morning Subscale (PREMB-R AM)
- Evening behavior on Parents Rating of Evening and Morning Behavior- Evening Subscale (PREMB-R PM)
- 94%, 98%, and 84% of participants achieved scores below screening risk (ie, <80th percentile cut-off) on the BSFQ, PREMB-R AM, and PREMB-R PM, respectively, after 6 weeks of MPH DR/ER treatment

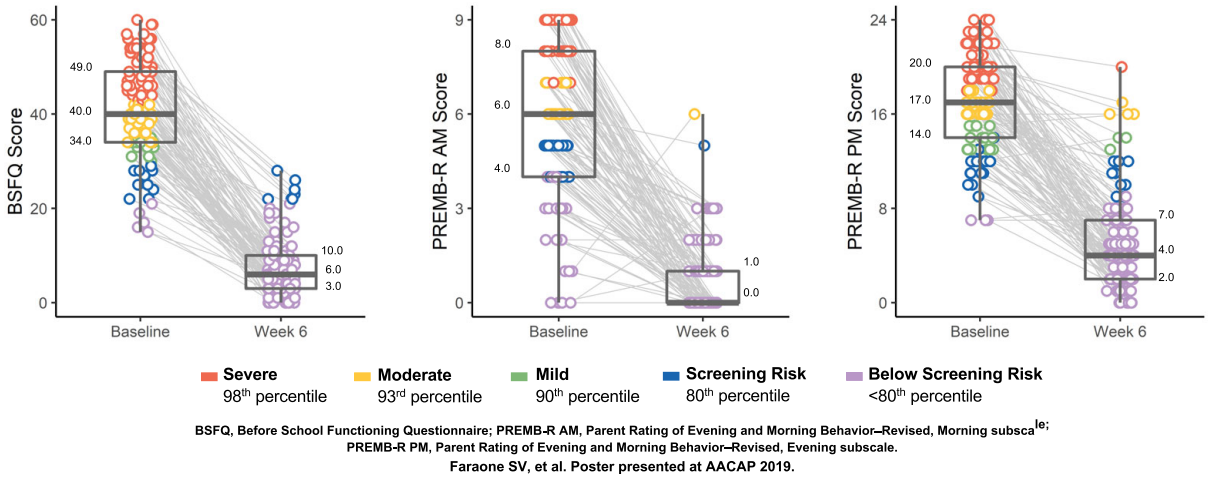

Figure 2. Improving function and behavior.

Nighttime Dosing

A unique microparticle MPH medication (Jornay PM) has been developed to improve ADHD symptoms both in the morning upon awakening yet also provide sustained duration to improve ADHD symptoms throughout the day until bedtime. This delayed release extended release "DR/ER" ADHD medication is designed to be taken around 8 pm in the evening. The outer delayed release layer does not allow the medication to begin absorption until 5 to 6 am. The inner extended release layer provides gradual stimulant release into the early evening. This technology demonstrated improvement in morning behavior, before school functioning, reduction in core ADHD symptoms, and improvement in evening behavior.

Nonstimulants

Three noradrenergic non-stimulants are currently approved in the United States for treatment of ADHD. The options either block reuptake of norepinephrine transporters (atomoxetine, Strattera) or directly stimulate the norepinephrine alpha 2a receptor (guanfacine-XR, Intuniv, and clonidine-XR, Kapvay). These options may be utilized for individuals who cannot tolerate the dopaminergic side effects of stimulants, require 24 hour symptomatic coverage or who have significant concerns about abuse or diversion of stimulants. In addition, both guanfacine-XR and clonidine-XR are approved for use in combination with a stimulant for children who have break through symptoms on a stimulant alone.

A fourth novel nonstimulant (viloxazine XR) is set for tentative approval by the FDA in early 2021. Viloxazine, considered a "multimodal agent" in that it both blocks the norepinephrine reuptake pump and directly modulates several serotonin receptors with elevation of intrasynaptic serotonin levels. Viloxazine will likely initially be approved for children and adolescents with positive adult ADHD studies reported in December 2020 (Table 3).

Adjusting Medication to Optimizing Outcomes

Quite often a patient will return stating that "I'm doing better" after starting an ADHD treatment. The question is are they normalized, are they partially better but still symptomatic, are their symptoms still causing functional difficulties at various points throughout the day or in certain areas of their life. Are they partially better but not well?

Studies around the world have demonstrated the need to gradually adjust the dose and titrate for optimal effect. Many consumer databases have shown that quite often ADHD medications are being prescribed at doses below what was shown to be the optimal effective dose. The rule of thumb is to titrate until there are no breakthrough symptoms or residual functional difficulties or one encounters a dose-limiting side effect or has reached the maximum dose. One should then consider trying an alternative molecule-MPH, amphetamine, or nonstimulant or an alternative formulation of the same molecule that may address breakthrough symptoms at the beginning, the middle, or the end of the day.

Breakthrough Symptoms

End of the day breakthrough symptoms one should consider:

(1) Increase dose of current medication to see if it will provide longer coverage.
(2) Change to a formulation with a longer duration-
    a. short acting to intermediate-MPH to MPH XR, AMPH to AMPH XR
    b. intermediate to long-MPH XR to OROS MPH, AMPH XR to Lisdexamphetamine
    c. long to longer-OROS MPH to MPH XXR or MPH DR/ER, Lisdexamphetamine to AMPH XXR
(3) Consider adding a nonstimulant-atomoxetine, guanfacine, clonidine, viloxazine.
(4) Consider using a long-acting stimulant and adding a short-acting stimulant at the end of the day.

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Table 3. FDA-Approved Nonstimulant Medications for ADHD

Delivery Mechanism and Formulation	Generic Name	Brand Name	Approved Ages	Dosing (Per Day)	Onset of Effect[a]	Duration of Effect	Comments	References
Long-acting								
Norepinephrine transporter reuptake inhibitor capsule	Atomoxetine	Strattera	Children ≥6, adults	1 to 2	3 to 4 wk	NA[b]	Dosed by body weight	88, 89
Alpha$_2$-adrenergic receptor agonist tablet	Clonidine HCL	Kapvay	Children ≥6	2	2 wk	NA	An antihypertensive agent may be prescribed in addition to a stimulant Discontinuation must be gradual	90, 91
Alpha$_2$-adrenergic receptor agonist tablet	Guanfacine	Intuniv	Children ≥6	1	3 wk	Up to 24 h per dose	An antihypertensive agent may be prescribed in addition to a stimulant Dosed by body weight	92, 93
Serotonin norepinephrine modulating agent capsule	Viloxazine HCL	SPN-812[c]	Children 6 to 17	1	1 wk	24 h		94–96

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; FDA, U.S. Food and Drug Administration; HCL, hydrochloride; NA, not available.
[a]Time to onset of the full effect of nonstimulant medications is extended compared to stimulant medications due to long titration periods.[43, 86, 97]
[b]The duration of effect of atomoxetine has not been formally measured as in studies of stimulation medications. Evidence from clinical studies suggests that one-daily dosing of atomoxetine is associated with efficacy into the evening.[48]
[c]Pending FDA approval.[49]

(5) Consider layering 2 doses of long-acting stimulant-one in the morning and one around noon.

Beginning of the day breakthrough symptoms one should consider:

(1) Give the morning dose as early as possible.
(2) Adding a bit of short-acting stimulant in the morning with the long-acting stimulant.
(3) Using a long-acting stimulant that releases more medication in the IR component.
(4) Adding a nonstimulant with 24 hour coverage-atomoxetine, viloxazine.
(5) Switching to 8 pm dosing of MPH DR/ER to allow blood level ascendency to coincide with morning awakening.

Summary

Our knowledge and understanding of the underlying neurobiology and symptomatic expression of ADHD has advanced dramatically over the past decade. Associated with these advances has been a similar explosion of new formulations for individualization of treatment based on our patient's needs. Optimized treatment is enhanced by measuring and tracking ADHD symptoms with the goal of treating to symptomatic remission with minimal functional impairment. Individual clinical presentation and patient response guide a clinician's choice between chemical classes of medications: methylphenidate, amphetamine, or non-stimulant. Within both classes of stimulant, we now have delivery systems that tailor the release kinetics to each individual patient with immediate-release, 8-hour sustained-release, 12 hour sustained-release, and 13 to 16 hour sustained-release. In addition, we now have an evening dosed DR/ER methylphenidate that captures morning symptoms with sustained symptom control throughout the day and into the evening. A deeper understanding of the functional difficulties encountered by ADHD patients throughout their lives, coupled with more consistent use of ADHD rating scales enables clinicians to choose between a wide variety of medication delivery systems in order to optimize the outcome for each of their patients.[98–103]

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References

1. Biederman J, Mick E, Faraone SV. Age-dependent decline of symptoms of attention deficit hyperactivity disorder: impact of remission definition and symptom type. *Am J Psychiatry*. 2000;**157**(5):816–818.
2. Faraone SV, Mick E. Molecular genetics of attention deficit hyperactivity disorder. *Psychiatr Clin North Am* 2010;**33**(1):159–180.
3. Kessler RC, Adler L, Barkley R, *et al.* The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication. *Am J Psychiatry*. 2006;**163**(4):716–723.
4. Adler LA, Goodman DW, Kollins SH, *et al.* On behalf of the 303 study group: double-blind, placebo-controlled study of the efficacy and safety of

https://doi.org/10.1017/S1092852921000146 Published online by Cambridge University Press

lisdexamfetamine dimesylate in adults with attention-deficit/hyperactivity disorder. *J Clin Psychiatry*. 2008;**69**(9):1364–1373.
5. Greene RW, Biederman J, Faraone SV, *et al.* Social impairment in girls with ADHD: patterns, gender comparisons, and correlates. *J Am Acad Child Adolesc Psychiatry*. 2001;**40**:704–710.
6. Shaw P, Eckstrand K, Sharp W, *et al.* Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. *Proc Natl Acad Sci USA*. 2007;**104**:19649–19654.
7. Dalsgaard S, Østergaard SD, Leckman JF, *et al.* Mortality in children, adolescents, and adults with attention deficit hyperactivity disorder: a nationwide cohort study. *Lancet*. 2015;**385**(9983):2190–2196.
8. Dalsgaard S, *et al.* Effect of drugs on the risk of injuries in children with attention deficit hyperactivity disorder: a prospective cohort study. *Lancet Psychiatry*. 2015;**2**(8):702–709.
9. Cortese S. Pharmacologic treatment of attention-deficit disorder. *N Engl J Med*. 2020;**383**(11):1050–1056.
10. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-5*. Washington, DC: American Psychiatric Association; 2013.
11. Volkow ND, Wang GJ, Newcorn JH, *et al.* Motivation deficit in ADHD is associated with dysfunction of the dopamine reward pathway. *Mol Psychiatry*. 2011;**16**(11):1147–1154.
12. Banerjee TD, Middleton F, Faraone SV. Environmental risk factors for attention-deficit hyperactivity disorder. *Acta Paediatr*. 2007;**96**:1269–1274.
13. Zhu J, Lee KP, Spencer TJ, Biederman J, Bhide PG. Transgenerational transmission of hyperactivity in a mouse model of ADHD. *J Neurosci*. 2014;**34**(8):2768–2773.
14. Barkley RA, Murphy KR, Fischer M. *ADHD in Adults: What the Science Says*. New York, NY: Guilford Press; 2010.
15. Wilens TE, Biederman J. Alcohol, drugs and attention-deficit/hyperactivity disorder: a model for the study of addictions in youth. *J Psychopharmacol*. 2006;**20**(4):580–588.
16. Wigal SB, Gupta S, Guinta D, *et al.* Reliability and validity of the SKAMP rating scale in a laboratory school setting. *Psychopharmacol Bull*. 1998;**34**:47–53.
17. Chang Z *et al.* Association between medications use for attention-deficit/hyperactivity disorder and risk of motor vehicle accidents. *JAMA Psychiatry*. 2019;**74**(6):597–603.
18. DuPaul GJ, Power TJ, Anastopoulos AD, *et al. ADHD Rating Scale-IV: Checklists, Norms, and Clinical Interpretation*. New York, NY: Guilford Press; 1998.
19. Barbaresi WJ. Improving care for children with ADHD: the information is just a rating scale away. *Pediatrics*. 2016;**137**(3):e20154450. Epub 2016 Feb 29.
20. Chang LY, Wang MY, Tsai PS. Diagnostic accuracy of attention-deficit/hyperactivity disorder: a meta-analysis. *Pediatrics*. 2016;**137**(3):2015–2749.
21. Culpepper L, Mattingly G. A practical guide to recognition and diagnosis of ADHD in adults in the primary care setting. *Postgrad Med*. 2008;**120**(3):16–26. doi:10.3810/pgm.2008.09.1904**.**
22. Guy SC, Isquith PK, Gioia GA. *Behavior Rating Inventory of Executive Function—Self Report Version*. Lutz, FL: Psychological Assessment Resources; 2004.
23. Wigal SB, Wigal TL. The laboratory school protocol: its origin, use, and new applications. *J Atten Disord*. 2006;**10**:92–111.
24. Wilens TE, Hammerness P, Martelon M, *et al.* A controlled trial of the methylphenidate transdermal system on before-school functioning in children with attention-deficit/hyperactivity disorder. *J Clin Psychiatry*. 2010a;**71**:548–556.
25. Faraone SV, Glatt SJ. A comparison of the efficacy of medications for adult attention-deficit/hyperactivity disorder using meta-analysis of effect sizes. *J Clin Psychiatry*. 2010;**71**(6):754–763.
26. Arnold LE. Methylphenidate vs. amphetamine: comparative review. *J Atten Disord*. 2000;**3**:200–211.
27. Cutler AJ, Brams M, Bukstein O, et al: Response/remission with guanfacine extended-release and psychostimulants in children and adolescents with attention-deficit/hyperactivity disorder. *Am Acad Child Adolesc Psychiatry*. 2014;**53**(10):1092–1101.
28. Mattingly G, Anderson R. Optimizing outcomes in ADHD treatment: from clinical targets to novel delivery systems. *CNS Spectr*. 2016;**21**(S1):45–59.
29. Guy W. Clinical global impressions. ECDEU Assessment Manual for Psychopharmacology. 1976, Rockville, MD: US Department of Health, Education, and Welfare; Public Health Service, Alcohol, Drug Abuse and Mental Health Administration, NIMH Psychopharmacology Research Branch, 218–222.
30. Goodman D, Faraone SV, Adler LA, et al: Interpreting ADHD rating scale scores: linking ADHD rating scale scores and CGI levels in two randomized controlled trials of lisdexamfetamine dimesylate in ADHD. *Primary Psychiatry*. 2010;**17**(3): 44–52.
31. Steele M, Jensen PS, Quinn DMP. Remission versus response as the goal of therapy in ADHD: a new standard for the field? *Clin Ther*. 2006;**28**(11):1892–1908.
32. Mattingly G, Culpepper L, Babcock T, *et al.* Aiming for remission in adults with attention deficit/hyperactivity treatment: the primary care goal. *Postgrad Med*. 2015;**127**(3):323–329.
33. Mattingly GW, Weisler RH, Young J, *et al.* Clinical response and symptomatic remission in short and long term trials of lisdexamfetamine dimesylate. *BMC Psychiatry*. 2013;**13**:39.
34. Mattingly G, Childress A, Nordbrock, *et al.* Clinical response and symptomatic remission with Aptensio XR (methylphenidate extended release) in children and adolescents with ADHD. Poster. American Psychiatry Association Meeting; 2016 Atlanta.
35. Sallee FR. Early morning functioning in stimulant-treated children and adolescents with attention-deficit/hyperactivity disorder, and it's impact on caregivers. *J Child Adolesc Psychopharmacol*. 2015;**25**(7):558–565.
36. Mattingly GW, Wilson J, Ugarte L, et al: Individualization of attention deficit hyperactivity disorder treatment: pharmacotherapy considerations by age and co-occurring conditions. *CNS Spectr*. 2020:1–20.
37. Whalen CK, Henker B, Jamner LD, et al: Toward mapping daily challenges of living with ADHD: maternal and child perspectives using electronic diaries. *J Abnorm Child Psychol*. 2006;**34**:115–130.
38. Mattingly G, Surman CB, Mao AR, *et al.* Improving communication in ADHD care: results from in-office linguistic research. *CNS Spectr*. 2011;**16**(4):85–94.
39. Campbell SB, Shaw DS, Gilliom M. Early externalizing behavior problems: toddlers, preschoolers at risk for later maladjustment. *Develop Psychopathol*. 2000;**12**:467–488.
40. Luman M, Oosterlaan J, Sergeant JA. The impact of reinforcement contingencies on AD/HD: a review and theoretical appraisal. *Clin Psychol Rev*. 2005;**25**:183–213.
41. Lahey B, Applegate B, Barkley RA, *et al.* DSM-IV field trials for oppositional defiant disorder and conduct disorder in children and adolescents. *Am J Psychiatry*. 1994;**151**(11):1673–1685.
42. Faraone SV, *et al.* Poster presented at AACAP 2019.
43. Childress AC. Methylphenidate HCL for the treatment of ADHD in children and adolescents. *Expert Opin Pharmacother*. 2016;**17**(8):1171–1178. doi:10.1080/14656566.2016.1182986.
44. FOCALIN Dexmethylphenidate hydrochloride tablets, CII Prescribing Information. Novartis Pharmaceuticals Corporation; 2017. Accessed April 3, 2019. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021278s023lbl.pdf.
45. Ritalin Hydrochloride methylphenidate hydrochloride USP tablets & Ritalin-SR methylphenidate hydrochloride USP sustained-release tablets, CII Full Prescribing Information. Novartis Pharmaceuticals Corporation; 2017. Accessed April 3, 2019. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/018029s055lbl.pdf.
46. Swanson J, Gupta S, Lam A, *et al.* Development of a new once-a-day formulation of methylphenidate for the treatment of attention-deficit/hyperactivity disorder: proof-of-concept and proof-of-product studies. *Arch Gen Psychiatry*. 2003;**60**(2):204–211. doi:10.1001/archpsyc.60.2.204.
47. METHYLIN Chewable Tablets (Methylphenidate HCl Chewable Tablets), CII Full Prescribing Information. Shionogi Inc; 2013. Accessed April

3, 2019. http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=09f13452-8f90-426e-9687-d30be75db9d7.
48. METHYLIN Oral Solution (Methylphenidate HCl Oral Solution), *CII Full Prescribing Information*. Shionogi, Inc; 2013. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021419s014lbl.pdf. Accessed April 3, 2019.
49. Methylphenidate Hydrochloride Extended-Release Tablets USP. For Oral Use, CII Prescribing Information. SpecGx LLC; 2017. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=b1b0f2ff-d9df-42ab-b471-226ecf97e075. Accessed June 24, 2019.
50. METADATE ER Tablets (Methylphenidate Hydrochloride Extended-Release Tablets, USP), CII Prescribing Information. Upstate Pharma, LLC; 2014. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=739bbd64-d9e1-4771-967b-a2cd08f4eaf5. Accessed April 3, 2019.
51. METADATECD (Methylphenidate HCl, USP) Extended-Release Capsules, CII Full Prescribing Information. UCB, Inc; 2014. http://www.ucb.com/_up/ucb_com_products/documents/Metadate_CD_COL_02_2015.pdf. Accessed April 3, 2019.
52. Frolich J, Banaschewski T, Dopfner M, *et al.* An evaluation of the pharmacokinetics of methylphenidate for the treatment of attention-deficit/hyperactivity disorder. *Expert Opin Drug Metab Toxicol*. 2014;**10**(8):1169–1183. doi:10.1517/17425255.2014.922542.
53. Focalin XR. (Dexmethylphenidate hydrochloride) extended-release capsules for oral use, CII Full Prescribing Information. Novartis Pharmaceuticals Corporation; 2015. https://www.pharma.us.novartis.com/product/pi/pdf/focalinXR.pdf. Accessed April 3, 2019.
54. Quillichew ER. (Methylphenidate hydrochloride) extended-release chewable tablets for oral use, CII Full Prescribing Information. NextWave Pharmaceuticals, Inc.; 2015. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/207960s005lbl.pdf. Accessed April 3, 2019.
55. Cortese S, D'Acunto G, Konofal E, Masi G, Vitiello B. New formulations of methylphenidate for the treatment of attention-deficit/hyperactivity disorder: pharmacokinetics, efficacy, and tolerability. *CNS Drugs*. 2017;**31**(2):149–160. doi:10.1007/s40263-017-0409-0.
56. Ritalin LA. (Methylphenidate hydrochloride) extended-release capsules, CII Full Prescribing Information. Novartis Pharmaceuticals Corporation; 2015. https://www.pharma.us.novartis.com/product/pi/pdf/ritalin_la.pdf. Accessed April 3, 2019.
57. Concerta (Methylphenidate HCl) extended-release tablets, CII Full Prescribing Information. Janssen Pharmaceuticals Inc.; 2017. http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=1a88218c-5b18-4220-8f56-526de1a276cd. Accessed June 24, 2019.
58. Quillivant XR (Methylphenidate hydrochloride) for extended-release oral suspension, CII Full Prescribing Information. NextWave Pharmaceuticals, Inc.; 2015. https://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=e0157005-6e3e-4763-b910-9eb0937608c9. Accessed June 4, 2019.
59. Aptensio XR (Methylphenidate hydrochloride extended-release) capsules or oral use, CII Full Prescribing Information. Rhodes Pharmaceuticals L. P.; 2017. http://aptensioxr.com/resources/full-prescribinginformation.pdf. Accessed April 3, 2019.
60. Cotempla XR-ODT. (Methylphenidate extended-release orally disintegrating tablets), CII, Full Prescribing Information. Neos Therapeutics, Inc.; 2017. http://www.neostxcontent.com/Labeling/Cotempla/Cotempla_PI.pdf. Accessed April 3, 2019.
61. Daytrana. (Methylphenidate transdermal system) full prescribing information. Noven Pharmaceuticals, Inc.; 2017. http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=2c312c31-3198-4775-91ab-294e0b4b9e7f. Accessed April 3, 2019.
62. Adhansia XR. (Methylphenidate hydrochloride) extended-release capsules, for oral use, CII Full Prescription Information. Purdue Pharma LP; 2019. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212038Orig1s000lbl.pdf. Accessed June 20, 2019.
63. Childress A, Mehrotra S, Gobburu J, *et al.* Single-dose pharmacokinetics of HLD200, a delayed-release and extended-release methylphenidate formulation, in healthy adults and in adolescents and children with attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol*. 2018;**28**(1):10–18. doi:10.1089/cap.2017.0044.
64. Jornay PM (Methylphenidate hydrochloride) extended-release capsules, for oral use, CII Full Prescription Information. Ironshore Pharmaceuticals & Development, Inc.; 2018. Accessed June 24, 2019. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=d95dede0-b1ff-4489-8f91-3bbe122852bf.
65. Wolraich M, Brown L, Brown RT, *et al.* ADHD: clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. *Pediatrics*. 2011;**128**(5):1007–1022. doi:10.1542/peds.2011-2654.
66. Adderall (Dextroamphetamine saccharate, amphetamine aspartate, dextroamphetamine sulfate and amphetamine sulfate tablets), CII Prescribing Information. Teva Select Brands; 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/011522s043lbl.pdf. Accessed April 3, 2019.
67. Hodgkins P, Shaw M, McCarthy S, Sallee FR. The pharmacology and clinical outcomes of amphetamines to treat ADHD: does composition matter? *CNS Drugs*. 2012;**26**(3):245–268. doi:10.2165/11599630-000000000-00000.
68. Swanson JM, Wigal S, Greenhill LL, *et al.* Analog classroom assessment of Adderall in children with ADHD. *J Am Acad Child Adolesc Psychiatry*. 1998;**37**(5):519–526.
69. Dexedrine (Dextroamphetamine sulfate) SPANSULE sustained-release capsules and tablets, CII Full Prescribing Information. Amedra Pharmaceuticals LLC; 2015. http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=a37b6ef9-78b4-4b18-8797-ecb583502500. Accessed April 3, 2019.
70. Zenzedi (Dextroamphetamine sulfate, USP), CII Prescribing Information. Arbor Pharmaceuticals, LLC; 2017. http://zenzedi.com/docs/PIandMedicationGuide.pdf. Accessed April 3, 2019.
71. Procentra (Dextroamphetamine sulfate) oral solution, CII Full Prescribing Information. Independence Pharmaceuticals, LLC; 2015. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=1548cce2-fb6b-4f17-8a3b-868933f6c9d6. Accessed April 3, 2019.
72. Desoxyn (Methamphetamine hydrochloride tablets, USP), CII Prescribing Information. Recordati Rare Diseases Inc.; 2013. https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/005378s028lbl.pdf. Accessed April 3, 2019.
73. Evekeoodt (Amphetamine sulfate) orally disintegrating tablets, CII Full Prescribing Information. Arbor Pharmaceuticals, LLC; 2019. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/209905s000lbl.pdf. Accessed April 3, 2019.
74. Childress AC, Brams M, Cutler AJ, *et al.* The efficacy and safety of Evekeo, racemic amphetamine sulfate, for treatment of attention-deficit/hyperactivity disorder symptoms: a multicenter, dose-optimized, double-blind, randomized, placebo-controlled crossover laboratory classroom study. *J Child Adolesc Psychopharmacol*. 2015;**25**(5):402–414. doi:10.1089/cap.2014.0176.
75. EVEKEO. (Amphetamine sulfate tablets, USP), CII Prescribing Information. Arbor Pharmaceuticals, LLC; 2016. https://www.evekeo.com/pdfs/evekeo-pi.pdf?v=1496932091614. Accessed April 3, 2019.
76. Adderall XR. (Mixed salts of a single-entity amphetamine product) dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate monohydrate, amphetamine sulfate capsules, CII full Prescribing Information. Shire US, Inc.; 2018. http://pi.shirecontent.com/PI/PDFs/AdderallXR_USA_ENG.PDF. Accessed April 3, 2019.
77. McCracken JT, Biederman J, Greenhill LL, *et al.* Analog classroom assessment of a once-daily mixed amphetamine formulation SLI381 (Adderall XR), in children with ADHD. *J Am Acad Child Adolesc Psychiatry*. 2003;**42**(6):673–683. doi:10.1097/01.CHI.0000046863.56865.FE.
78. Adzenys ER (Amphetamine) extended-release oral suspension, CII Full Prescription Information. Neos Therapeutics LP; 2017. http://www.neostxcontent.com/Labeling/AdzenysER/AdzenysER_PI.pdf. Accessed June 24, 2019.
79. Adzenysxr-ODT (Amphetamine extended-release orally disintegrating tablets), CII Full Prescription Information. Neos Therapeutics LP; 2015. http://www.neostxcontent.com/Labeling/Adzenys/Adzenys_PI.pdf. Accessed April 3, 2019.
80. Dyanavel XR (Amphetamine) extended-release oral suspension, CII Full Prescribing Information. Tris Pharma, Inc; 2019. http://www.trispharma.com/DXRUSPI.pdf. Accessed April 3, 2019.

81. Mydayis (Mixed salts of a single-entity amphetamine product) extended-release capsules, for oral use, CII, Full Prescribing Information. Shire US, Inc; 2017. http://www.shirecontent.com/PI/PDFs/Mydayis_USA_Eng.pdf. Accessed April 3, 2019.
82. Wigal S, Lopez F, Frick G, *et al.* A randomized, double-blind, 3-way crossover, analog classroom study of SHP465 mixed amphetamine salts extended-release in adolescents with ADHD. *Postgrad Med*. 2019;**131**(3):212–224. doi:10.1080/00325481.2019.1574402.
83. Vyvanse. (Lisdexamfetamine dimesylate) capsules and chewable tablets for oral use, CII Full Prescribing Information. Shire US, Inc; 2017. http://pi.shirecontent.com/PI/PDFs/Vyvanse_USA_ENG.pdf. Accessed April 3, 2019.
84. Ermer JC, Pennick M, Frick G. Lisdexamfetamine dimesylate: prodrug delivery, amphetamine exposure and duration of efficacy. *Clin Drug Investig*. 2016;**36**(5):341–356. doi:10.1007/s40261-015-0354-y.
85. Mattingly GW, Wilson J, Rostain AL. A clinician's guide to ADHD treatment options. *Postgrad Med*. 2017;**129**(7):657–666.
86. Briars L, Todd T. A review of the pharmacological management of attention-deficit/hyperactivity disorder. *J Pediatric Pharmacologic Ther*. 2016;**21**(3):192–206.
87. Mattingly G. Lisdexamfetamine dimesylate; a prodrug stimulant for the treatment of ADHD in children and adults. *CNS Spectr*. 2010;**15**(5):315–325.
88. Dickson RA, Maki E, Gibbins C, *et al.* Time courses of improvement and symptom remission in children treated with atomoxetine for attention-deficit/hyperactivity disorder: analysis of Canadian open-label studies. *Child Adolesc Psychiatry Ment Health*. 2011;**5**:14. doi:10.1186/1753-2000-5-14.
89. Strattera. (Atomoxetine hydrochloride) capsules for oral use, Full Prescribing Information. Eli Lilly and Company; 2017. http://pi.lilly.com/us/strattera-pi.pdf. Accessed April 3, 2019.
90. Jain R, Segal S, Kollins SH, *et al.* Clonidine extended-release tablets for pediatric patients with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*. 2011;**50**(2):171–179. doi:10.1016/j.jaac.2010.11.005.
91. Kapvay (Clonidine hydrochloride) extended-release tablets oral, full prescribing information. Concordia Pharmaceuticals Inc.; 2016. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=aa7700e2-ae5d-44c4-a609-76de19c705a7. Accessed April 3, 2019.
92. Biederman J, Melmed RD, Patel A, *et al.* A randomized, double-blind, placebo-controlled study of guanfacine extended release in children and adolescents with attention-deficit/hyperactivity disorder. *Pediatrics*. 2008;**121**(1):e73–e84. doi:10.1542/peds.2006-3695.
93. INTUNIV (Guanfacine) extended-release tablets for oral use, Full Prescribing Information. Shire US, Inc; 2016. http://pi.shirecontent.com/PI/PDFs/Intuniv_USA_ENG.pdf. Accessed April 3, 2019.
94. Nasser A, Liranso T, Adewole T, *et al.* A phase III, randomized, placebo-controlled trial to assess the efficacy and safety of once-daily SPN-812 (viloxazine extended-release) in the treatment of attention-deficit/hyperactivity disorder in school-age children. *Clin Ther*. 2020;**42**(8):1452–1466. doi:10.1016/j.clinthera.2020.05.021.
95. Yu C, Garcia-Olivares J, Candler S, *et al.* New insights into the mechanism of action of viloxazine: serotonin and norepinephrine modulating properties. *J Exp Pharmacol*. 2020;**12**:285–300. doi:10.2147/JEP.S256586.
96. Johnson JK, Liranso T, Saylor K, *et al.* A phase II double-blind, placebo-controlled, efficacy and safety study of SPN-812 (extended-release viloxazine) in children with ADHD. *J Atten Disord*. 2020;**24**(2):348–358. doi:10.1177/1087054719836159.
97. Goodman DW, Starr HL, Ma YW, Rostain AL, Ascher S, Armstrong RB. Randomized, 6-week, placebo-controlled study of treatment for adult attention-deficit/hyperactivity disorder: individualized dosing of osmotic-release oral system (OROS) methylphenidate with a goal of symptom remission. *J Clin Psychiatry*. 2017;**78**(1):105–114.
98. Faraone SV, Childress A, Wigal SB, *et al.* Reliability and validity of the daily parent rating of evening and morning behavior scale. *J Attention Disord*. 2018;**22**(11):1066–1073.
99. Wigal SB, Greenhill LL, Nordbrock E, *et al.* A randomized placebo-controlled double-blind study evaluating the time course of response to methylphenidate hydrochloride extended-release capsules in children with attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol*. 2014;**24**(10):562–569.
100. Sikes C, Stark JG, McMahen R, *et al.* A single-dose, two-way crossover, open-label bioequivalence study of an amphetamine extended-release oral suspension in healthy adults. *J Atten Disord*. 2020;**24**(3):414–419. doi:10.1177/1087054717743329.
101. Stark JG, Engelking D, McMahen R, *et al.* Pharmacokinetics of a novel amphetamine extended-release orally disintegrating tablet in children with attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol*. 2017;**27**(3):216–222. doi:10.1089/cap.2016.0119.
102. Michelson D, Allen AJ, Busner J, *et al.* Once-daily atomoxetine treatment for children and adolescents with attention deficit hyperactivity disorder: a randomized, placebo-controlled study. *Am J Psychiatry*. 2002;**159**(11):1896–1901. doi:10.1176/appi.ajp.159.11.1896.
103. Supernus announces FDA acceptance for review of new drug application for SPN-812 for the treatment of ADHD. Supernus Pharmaceuticals, Inc; 2020. https://www.globenewswire.com/news-release/2020/01/21/1973384/0/en/Supernus-Announces-FDA-Acceptance-for-Review-of-New-Drug-Application-for-SPN-812-for-the-Treatment-of-ADHD.html. Accessed October 8, 2020.

Optional Posttest and CME Certificate

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1. Kim is a 9-year-old patient with ADHD who is having breakthrough symtoms early in the day with guanfacine. Which of the following treatment changes would be most appropriate to improve her symptoms?
   A. Increase the dose of guanfacine
   B. Change to a formulation with longer duration
   C. Use a long-acting stimulant that releases more medication in the immediate release component
   D. None of these changes are appropriate

2. Jenny is a 15-year-old patient who was recently diagnosed with ADHD. In addition to early morning tennis practice, Jenny participates in several after-school activities that keep her busy into the late afternoon, after which she begins her homework. Which of the following treatments is most appropriate for a patient like Jenny who needs all-day symptom relief?
   A. Jornay PM
   B. Ritalin
   C. Adderall
   D. Dexedrine

3. Samson is a 24-year-old patient with comorbid ADHD and sustance use disorder. He wants to avoid ADHD medication that has abuse potential. Which of the following treatments may be most appropriate for Samson?
   A. Viloxazine
   B. Atomoxetine
   C. Methylphenidate
   D. None of these treatments are appropropriate

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