JPPT | Review

Diagnosis and Treatment of ADHD in the Pediatric Population

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Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders in childhood with approximately 6 million children (age 3 to 17 years) ever diagnosed based on data from 2016–2019. ADHD is characterized by a constant pattern of inattention and/or hyperactivity-impulsivity symptoms that interferes with development or functioning. Specific criteria from the *Diagnostic and Statistical Manual of Mental Disorders, 5th edition Text Revision* assist with the diagnosis with multiple guidelines available providing non-pharmacologic and pharmacologic recommendations for the treatment of ADHD in the pediatric population. While all guidelines similarly recommend behavioral and/or stimulant therapy as first-line therapy based on age, not all stimulant products are equal. Their differing pharmacokinetic profiles and formulations are essential to understand in order to optimize efficacy and safety for patients. Additionally, new stimulant products and non-stimulant medications continue to be approved for use of ADHD in the pediatric population and it is important to know their differences in formulation, efficacy, and safety to other products currently available. Lastly, due to drug shortages, it is important to understand product similarities and differences to select alternative therapy for patients.

ABBREVIATIONS AAP, American Academy of Pediatrics; ADHD, attention-deficit/hyperactivity disorder; BP, blood pressure; DSM-5-TR, *Diagnostic and Statistical Manual, Fifth Edition, Text Revision*; ER, extended release; FDA, Food and Drug Administration; HR, heart rate; NICE, National Institute for Health and Care Excellence; NSCH, National Survey of Children's Health; PTBM, parent training in behavior management; XR, extended release

KEYWORDS amphetamine; attention deficit disorder with hyperactivity; attention deficit hyperactivity disorder; methylphenidate; off-label use; pediatrics; serotonin and norepinephrine reuptake inhibitors

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Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders in childhood characterized by a constant pattern of inattention and/or hyperactivity-impulsivity symptoms that interferes with development or functioning.[1,2]

Prevalence. Attention-deficit/hyperactivity disorder begins in childhood.[1] Worldwide prevalence in children is approximately 7.2% based on population surveys.[1] Parent-reported data from the 2016–2019 US National Survey of Children's Health (NSCH) estimates that 9.8% (approximately 6 million) of children age 3 to 17 years had ever received a diagnosis of ADHD and 8.7% currently had the disorder.[3,4] By age, adolescents who ever had ADHD are the highest at 13% (3.3 million). Children aged 6 to 11 years are 10% (2.4 million) and 2% (265,000) of children 3 to 5 years follow. State prevalence of ADHD varies. The NSCH found a range of 6.1% to 16.3% (median 10.5%) for children who ever had ADHD and 5.3% to 14.4% for those with a current diagnosis.[3,5] California, Hawaii, Nebraska, Nevada, New Jersey, New York, and South Dakota had estimates significantly lower than the rest of the country while Alabama, Arkansas, Delaware, Georgia, Indiana, Kentucky, Louisiana, Maine, Mississippi, New Hampshire, North Carolina, Ohio, South Carolina, Tennessee, and West Virginia had estimates higher compared with the rest of the country.[5] The prevalence of ADHD in males (13.3%) is more than twice that in females (6.1%).[3] The highest prevalence of ADHD is seen in Black, non-Hispanic (12%) and White, non-Hispanic (10.9%) populations while the lowest prevalence is in the Asian, non-Hispanic (2.6%) and Hispanic (7.5%) populations. ADHD is more common in children in rural areas compared with urban or suburban areas. Patients categorized as being in the lowest federal poverty level and having public insurance also have a higher prevalence of ADHD.

Etiology. The exact cause and risk factors for ADHD are unknown; however, the heritability of ADHD is increased in first-degree relatives of a patient with ADHD with an estimate of 74%.[1,2,6] The involvement of dopaminergic and adrenergic neurotransmitters in ADHD continues to be studied as medication affecting

these neurotransmitters are the most effective first-line pharmacotherapy.[6] Environmental factors may also play a role in ADHD. Prenatal exposure to smoking has been associated with ADHD and patients who have a very low birth weight and degree of prematurity have an increased risk for ADHD.[1]

Diagnosis. There are 3 subtypes of ADHD. Patients are categorized as predominately inattentive, predominately hyperactive/impulsive, or combined (involving symptoms from both inattention and hyperactivity/impulsivity domains). For ADHD diagnosis, per the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision* (DSM-5-TR), patients must have 6 or more of the 9 symptoms in the inattention domain, hyperactivity/impulsivity domain, or both domains for at least 6 months (Table 1).[1] Hyperactivity is the primary symptom in preschool age children with inattention being prominent during ages 5 to 9 years. More subtle signs of hyperactivity are noted in the adolescent population such as fidgeting or feelings of restlessness, impatience, or jitteriness. Despite age, symptoms must negatively affect academic/occupational and social activities and not be consistent with the development level of the patient. Adolescents only require 5 symptoms in a domain for diagnosis. Symptoms should be present before the age of 12 years and occur in 2 or more settings (home, school, work, socially, etc) for diagnosis. Lastly, for diagnosis, symptoms must clearly interfere with or decrease the quality of academic/occupational or social activities and not be better supported by another psychotic or mental disorder diagnoses. Mild ADHD is classified in the DSM-5-TR as the patient having "few, if any, symptoms in excess of those required to make the diagnosis are present, and symptoms result in no more than minor impairments in social or occupational functioning."[1] Severe ADHD is classified "many symptoms in excess of those required to make the diagnosis, or several symptoms that are particularly severe, are present, or the symptoms result in marked impairment in social or occupational functioning." Moderate severity is described as symptoms or impairment between the mild and severe classifications.

Patients with ADHD frequently have comorbid disorders.[1] Half of children with the combined subtype and approximately one-fourth of children with the predominantly inattentive subtype will also present with oppositional defiant disorder. About one-fourth of children and adolescents with combined subtype will have conduct disorder. Autism spectrum disorder, obsessive-compulsive disorder, and tic disorders can occur concomitantly with ADHD. It is recommended by the American Academy of Pediatrics (AAP) to screen for comorbid conditions in a child or adolescent with ADHD.[7]

Rating Scales. Several ADHD clinical questionnaires and rating scales based on the DSM are available to assist clinicians with diagnosis and follow-up assessments after therapy is initiated. The use of parent-reported or teacher-reported behavior-rating scales began in the late 1960s.[6] Today, there are clinician-, parent-, self-, and teacher-reported rating scales. The ADHD Rating Scales, Conners Rating Scales, and National Institute for Children's Health Quality Vanderbilt Assessment Scales are commonly used in practice for preschool-age children to adolescents. Clinicians should ensure they are using the appropriate rating scale for the patient's age, the person completing the scale, and purpose. The scales assist with ADHD diagnosis by converting subjective symptom information into objective data and then allow an objective manner for follow-up. The scale can also identify the subtype of ADHD. Providers can compare the objective outcomes to prior ratings to evaluate for symptom

Table 1. DSM-5-TR Attention-Deficit/Hyperactivity Disorder Symptoms by Domain[1*]

Inattention	Hyperactivity and Impulsivity
Often fails to provide close attention to detail or makes careless errors in schoolwork, at work, or during other activities	Often fidgets with or taps hands/feet or fidgets in seat
Often has difficulty focusing on tasks or activities	Often leaves seat in situations when is it expected to remain seated
Often does not seem to be listening when spoken to directly	Often inappropriately runs around or climbs in situations
Often fails to follow through on instructions and fails to complete schoolwork, chores, or duties	Often cannot play or engage in leisure activities quietly
Often has difficulty organizing and managing tasks and activities	Often is "on the go"
Often avoids, dislikes, or is hesitant to participate in tasks requiring sustained mental effort	Talks excessively often
Often loses items necessary for tasks or activities	Shouts out an answer before a question has been completed often
Easily distracted by extraneous stimuli often	Inability waiting his or her turn often
Forgetful in daily activities often	Interrupts or intrudes on others often

* Six symptoms (5 for adolescents) must be met in each individual domain to be classified as combined subtype.

improvement or worsening over time. Additionally, the provider can objectively evaluate symptoms in different settings if the parent and teacher complete forms.

Guidelines. Several guidelines are available to assist clinicians with the diagnosis and treatment of ADHD in the pediatric population.[7–9] The AAP first begin publishing pediatric guidelines for ADHD in 2000.[7] The most current guideline was released in 2019 and provides incremental updates, a process of care algorithm, and a companion article on systemic barriers to the care of pediatric patients (4 to 18 years of age) with ADHD.[7] The AAP guidelines recommend ADHD diagnosis is based on the DSM-5 criteria. Their recommended first-line treatment for ADHD in preschool-aged children (age 4 years to the sixth birthday) includes evidence-based parent training in behavior management (PTBM) and/or behavioral classroom interventions.[7] Methylphenidate can be initiated if behavioral interventions fail to significantly improve symptoms and functioning continues to be impaired during ages 4 to 5 years. For children ages 6 years to the 12th birthday, first-line treatment for ADHD includes a Food and Drug Administration (FDA)-approved medication and/or PTBM and/or behavioral classroom interventions, with both behavioral therapies being preferred as an adjunct to medication therapy. First-line ADHD therapy for adolescents (age 12 years to the 18th birthday) is treatment with a FDA-approved medication with the patient's assent. Evidenced-based training interventions and/or behavioral interventions are encouraged. Stimulants are the recommended first-line medication therapy due to their efficacy and strength of evidence.

The American Academy of Child and Adolescent Psychiatry first published an ADHD practice parameter in 1997 and issued their most recent parameter in 2007.[8] Treatment recommendations are similar to the AAP guidelines. The Society for Developmental and Behavioral Pediatrics published "Clinical Practice Guideline for the Assessment and Treatment of Children and Adolescents with Complex Attention-Deficit/Hyperactivity Disorder" in 2020.[9] This was the first guideline from the Society of which they described the intention of the work to complement the AAP guidelines. "Complex ADHD" is defined based on age (presentation at <4 years or >12 years), presence or suspicion of coexisting conditions, moderate to severe impairment in daily living function, uncertainty of diagnosis, or inadequate response to treatment. This guideline provides psychosocial (behavioral, educational, and psychological interventions), pharmacological treatment recommendations, and information regarding therapy for ADHD and comorbid conditions.

The AAP also has a 2014 clinical report regarding ADHD and substance abuse and a world consensus statement was published in 2023 on treating patients with ADHD and substance use disorder.[10,11]

The European National Institute for Health and Care Excellence (NICE) ADHD guidelines were released in 2008 with the most recent update published March 2018.[12] Two additional amendments were released in 2018 and 2019. Group-parent training programs, individual-parent training programs, and cognitive behavioral therapy are recommended for patients and carers depending on the age of the patient. For patients 5 years of age and older, methylphenidate, lisdexamfetamine, and atomoxetine or guanfacine are recommended in this order. The Canadian ADHD Practice Guidelines were first released in 2006 with the current fourth edition released in 2018.[13] A multimodal treatment plan including psychosocial therapy and medications is recommended. Long-acting stimulants are recommended as first-line agents with atomoxetine, guanfacine extended release (XR) and short or intermediate-acting stimulants as second-line. Third-line agents recommended are bupropion, clonidine, imipramine, and modafinil. Both NICE and Canadian guidelines recommend the DSM-5-TR criteria for ADHD diagnosis and also include recommendations for the treatment of adults.[12,13]

Non-Pharmacological Therapies

Behavioral therapy is strongly recommended for parents of and patients with ADHD. Examples of evidence-based behavioral and educational interventions include PTBM, behavioral classroom management, behavioral peer intervention, and individualized instructional support (e.g., instructional and class placement, Individualized Education Program, or rehabilitation plan).[7,9] Many PTBM pre-school programs are group programs.[7] Behavioral classroom interventions are also recommended if the child attends pre-school. Older children can additionally complete organizational skills training.[9] Behavioral parent and classroom training have positive outcomes in preadolescent children.[7] For adolescents with ADHD, PTBM may involve parents and adolescents in sessions and training focusing on school functioning skills is effective. For the adolescent, training that is continued over time, has frequent and constructive feedback, and is targeted at specific behaviors has the greatest benefit.[7] Additionally, in children and adolescents, psychosocial interventions such as behavioral therapy and training interventions have been effective. Training in social skills has not demonstrated benefit for children with ADHD.[7] Outcomes from behavioral therapies tend to continue even after therapy ends.

Digital therapeutics have emerged as a therapy for ADHD. One systematic review and meta-analysis of video game-based therapeutic interventions found that it was effective in decreasing ADHD symptoms and improving cognitive areas.[14] Typically these games focus on cognitive training such as improving attention, memory, reaction time, cognitive flexibility, or motor ability. Patients were found to have a high engagement with

the games as there were low rates of dropouts from the studies. Another systematic review and meta-analysis found that digital therapeutics improved inattention and hyperactivity/impulsivity symptoms compared with control but medication improved inattention and significantly improved hyperactivity/impulsivity better than game-based digital therapeutics.[15] EndeavorRx was the first game-based digital therapeutic device approved by the FDA to improve attention function in children 8 to 12 years of age with ADHD (primarily inattentive or combined-type).[16] This approval in 2020 was the first type of game-based FDA approval for any disease or condition. It is available only via prescription and should be part of a comprehensive patient treatment plan.

Pharmacologic Treatments

US Food and Drug Administration-approved medications for the treatment of ADHD include stimulant and non-stimulant options.[1,7] The stimulants are described in 2 classes, methylphenidate and amphetamine. Atomoxetine, viloxazine, guanfacine, and clonidine represent non-stimulant choices commonly used in the management of ADHD. Stimulants have an effect size of 1 for treating ADHD, while non-stimulants (atomoxetine and extended-released guanfacine and clonidine) have an effect size of 0.7.[7] Bupropion, may be used off-label in patients non-responsive or unable to take an FDA-approved agent, or with a coexisting mental health diagnosis.[17] The initial medication therapy choice depends on several factors. Some general considerations include duration of desired coverage, ability of the patient to swallow solid dosage forms, time(s) of day when target symptoms occur, pharmacokinetic properties of the dosage formulation, desire to avoid administration at school, coexisting disorder or condition, potential adverse effects, history of substance abuse, preference of patient/caregiver, and medication expense and availability.

Stimulants. The stimulant class is recommended first-line in the management of ADHD due to the extensive evidence of efficacy and a known safety profile.[1,7,18] Stimulants work by blocking the presynaptic reuptake of norepinephrine and dopamine, with amphetamine also increasing the presynaptic release of dopamine and serotonin. Some areas of the brain known to show neurotransmitter impact include striatal dopamine transporters and norepinephrine transporters in the frontal lobes.[19] Both methylphenidate and amphetamine improve the core symptoms of ADHD, hyperactivity/impulsivity, and inattention, and have also shown improvements in academic functioning and a decreased risk of unintentional injuries, motor vehicle accidents (among male patients), and criminal acts.[7,18]

The AAP clinical practice guideline does not specify which stimulant class is more effective nor name a preferred starting product as part of the standards of care.[7] Studies have found amphetamines to have better response rates at the group level when compared with methylphenidate and the non-stimulants.[18] Yet, at the patient level, participants had equally good response to both amphetamine and methylphenidate. Another systematic review found amphetamine, as compared with methylphenidate, to be slightly more efficacious in reducing core ADHD symptoms in children and adolescents, yet methylphenidate was better tolerated.[17] Based on both safety and efficacy data in children, and what is commonly seen in practice, it is prudent to start with methylphenidate and reserve amphetamines for future needs.

When selecting a long-acting stimulant product, the clinician should match the pharmacokinetic profile of the medication dosage form to the needs of the patient. Duration of efficacy should match the duration needed for symptom control. However, based on the pharmacokinetic design of the medication formulation, the drug release profile should be matched to the patient's needs. For example, a patient who has more severe symptoms in the morning may need a product that is 50% immediate release compared with one that is 22% immediate release. It is important to remember that increasing a dose to increase efficacy can increase adverse effects as well; thus, changing products to a different pharmacokinetic profile may provide improved efficacy without additional adverse effects. Additionally, a patient who has more late afternoon/early evening symptoms may do better with a product that 70% to 80% of the dose is released in the second pharmacokinetic release to provide longer lasting efficacy of symptoms compared with a dose that provided 50% for the second release. Tables 2 and 3 provide pharmacokinetic and dosage formulation information for the stimulants.[20–39] Lastly, most stimulant products are not interchangeable on a milligram-for-milligram basis and may require a taper off/on when a change of agents is required. Product medication labeling should always be referenced for guidance regarding equivalence and/or a process for conversion, if available.

Across the stimulant class, proper baseline and periodic monitoring of safety/adverse events are paramount.[7,18,40] Table 4 highlights variables to monitor, frequency of monitoring, and important points to consider.[7,12,18,40] Also, critical to drug selection is the medication adverse effect profile. Table 5 shows common stimulant adverse events and suggested management strategies.[7,18] In the end, stimulant selection within ADHD management is patient-specific with a balance of efficacy, safety, and management of medication adverse events.

A final consideration with the stimulant class is related to serious risks with misuse, abuse, addiction, overdose, and sharing of these medications.[41] The FDA published a drug safety communication in May of 2023 updating warnings to improve the safe use of stimulants

Table 2. Methylphenidate-based Stimulants[20–29]

Medication	Brand Name (US)	Frequency of Dosing	Immediate Release/First Dose Release	Sustained Release/ Second Dose Release	Duration of Action (hr)	Formulation(s)	Available Strengths
Immediate release							
Methylphenidate	Ritalin*	BID-TID	100%	—	3–5	Tablet	5, 10, 20 mg
	Methylin*	BID-TID	100%	—	3–5	Chewable tablet (Grape flavor); solution (Grape flavor)	2.5, 5, 10 mg; 5, 10 mg/5 mL
Dexmethylphenidate	Focalin*	BID	100%	—	3–5	Tablet	2.5, 5, 10 mg
Extended release							
Methylphenidate	Ritalin LA*	Once daily	50%	50%	6–8	Capsule (May open and sprinkle beads on applesauce)	10, 20, 30, 40, 60 mg
	Metadate CD*	Once daily	30%	70%	6–8	Capsule (May open and sprinkle beads on applesauce)	10, 20, 30, 40, 50, 60 mg
	Metadate ER*	Once daily			8	Tablet	10, 20 mg
	QuilliChew ER	Once daily	30%	70%	8	Chewable tablet (Cherry flavor)	20, 30, 40 mg
	Concerta*	Once daily	22%	78%	10–12	Tablet (Swallow whole)	18, 27, 36, 54 mg
	Relexxii*	Once daily	18%	72%	8–12	Tablet (Swallow whole)	18, 27, 36, 45, 54, 63, 72 mg
	Daytrana	Once daily (9 hr wear)			10–12	Patch (Apply 2 hours prior to need for effect)	10, 15, 20, 30 mg
	Quillivant XR	Once daily	20%	80%	12	Suspension (Banana flavor)	25 mg/5 mL
	Cotempla XR-ODT	Once daily	25%	75%	12	Orally disintegrating tablet (Dissolve on tongue; Grape flavor)	8.6, 17.3, 25.9 mg
	Aptensio XR	Once daily	40%	60%	12	Capsule (May open and sprinkle beads on applesauce)	10, 15, 20, 30, 40, 50, 60 mg
	Jornay PM	Once daily in pm (between 6:30–9:30 pm)	<5%	95+%	12 (begins 10 hr after dose)	Capsule (May open and sprinkle beads on applesauce)	20, 40, 60, 80, 100 mg
	Adhansia XR (Discontinued July 20, 2022)	Once daily	20%	80%	16	Capsule	25, 35, 45, 55, 70, 85 mg
Dexmethylphenidate	Focalin XR*	Once daily	50%	50%	8–12	Capsule (May open and sprinkle beads on applesauce)	5, 10, 15, 20, 25, 30, 35, 40 mg
Serdexmethylphenidate/ dexmethylphenidate	Azstarys	Once daily	30%	70%	13	Capsule (May open and sprinkle in 2 oz water or applesauce)	26.1–5.2, 39.2–7.8, 52.3–10.4 mg

* Generic available in certain strengths.

in the management of ADHD and other conditions. The FDA is requiring updates to the boxed warnings and prominent wording across this medication class. Health care professionals are urged to assess a patient's risk of misuse, abuse, and addiction before prescribing stimulant medications and throughout therapy. Refill requests should also be evaluated for appropriate timing. It is important to counsel patients to take their

Table 3. Amphetamine-based Stimulants[20–22,30–39]

Medication	Brand Name (US)	Frequency of Dosing	Immediate Release/ First Dose Release	Sustained Release/ Second Dose Release	Duration of Action (hr)	Formulation(s)	Available Strengths
Immediate release							
Mixed amphetamine salts	Adderall*	Once daily-TID	100%		4–6	Tablet	5, 7.5, 10, 12.5, 15, 20, 30 mg
Amphetamine	Evekeo*	Once daily-TID	100%		4–6†	Tablet (Slightly bitter taste)	5, 10 mg
	Evekeo-ODT	Once daily-TID	100%		4–6	Orally dissolving tablet (Slightly bitter taste)	5, 10, 15, 20 mg
Dextroamphetamine	Dexedrine/ DextroStat*	BID-TID	100%		4–6	Tablet	5, 10 mg
	Zenzedi*	BID-TID	100%		4–6	Tablet	2.5, 5, 7.5, 10, 15, 20, 30 mg
	ProCentra*	BID-TID	100%		4–6	Solution (Bubblegum flavor)	5 mg/5 mL
Extended release							
Mixed amphetamine salts	Adderall XR*	Once daily	50%	50%	10–12	Capsules (May open and sprinkle beads on applesauce)	5, 10, 15, 20, 25, 30 mg
	Mydayis	Once daily	33.3%†	33.3%†	16	Capsules (May open and sprinkle beads on applesauce)	12.5, 25, 37.5, 50 mg
Amphetamine	Adzenys ER (3 dextro- to 1 levo-isomer)	Once daily	50%	50%	10–12	Suspension (Orange flavor)	1.25 mg/mL
	Adzenys XR-ODT	Once daily	50%	50%	10–12	Orally disintegrating tablet (Dissolve on tongue; Orange flavor)	3.1, 6.3, 9.4, 12.5, 15.7, 18.8 mg
	Dyanavel XR (3.2 dextro- to 1 levo-isomer)	Once daily			13	Suspension (Bubblegum flavor)	2.5 mg/mL
	Dyanavel XR (3.2 dextro- to 1 levo-isomer)	Once daily			13	Tablet (Bubblegum flavor)	5, 10, 15, 20 mg
Dextroamphetamine	Dexedrine Spansule*	Once daily-BID			6–8	Capsule (May open and mix with soft food)	5, 10, 15 mg
	Xelstrym	Once daily (9 hr wear)			9	Patch (Apply 2 hours prior to need for effect)	4.5, 9, 13.5, 18 mg
Lisdexamfetamine	Vyvanse	Once daily			10–12§	Capsule (May open and mix with orange juice, water, or yogurt)	10, 20, 30, 40, 50, 60, 70 mg
	Vyvanse	Once daily			10–12	Chewable tablet (Strawberry flavor)	10, 20, 30, 40, 50, 60 mg

ODT, oral dissolving tablet

* Generic available in certain strengths.
† 3 bead system: 33.3% at each release.
‡ BID dosing resulted in efficacy for a 10-hour duration.[30]
§ Adult study determined efficacy for up to 14 hours duration.[39]

Table 4. Recommended Monitoring for Stimulant Medications[7,12,18,40]

Monitoring Variable	Frequency of Monitoring	Comments
Blood pressure (BP)	Baseline (prior to stimulant initiation), each follow-up visit (every 3–6 months), and after any dose change	Further evaluation and/or therapy modifications needed with a systolic BP ≥ 95th percentile or BP ≥ 130/80 on 2 or 3 occasions
Heart rate	Baseline (prior to stimulant initiation), each follow-up visit (every 3–6 months), and after any dose change	Therapy modifications needed with a sustained resting tachycardia (> 120 beats per minute) or arrhythmia
Height, weight, body mass index	Baseline (prior to stimulant initiation) and each follow-up visit (every 3–6 months)	Options to assist with weight loss or poor growth include administer medication at or after meal, offer additional meals or snacks early in the morning or late in evening after stimulants effects have worn off, consume high-calorie dense foods of good nutritional value, obtain dietary advice from a dietician, consider a drug holiday, change medication
Electrocardiogram (ECG)	Not routinely recommended	ECG and cardiology referral recommended if any of the following apply: history of congenital heart disease or previous cardiac surgery, history of sudden death in first-degree relative before age 40 yr, shortness of breath or fainting on exertion, palpitations that are rapid, regular and start and stop suddenly, chest pain, signs of heart failure, murmur on cardiac exam, hypertension

medication as prescribed, not to share their medications with others, how to properly store and dispose of unused medication, and on signs and symptoms of non-medical use, addiction, and drug diversion. Signs and symptoms of stimulant overdose should also be reviewed with the patient and caregivers including when to seek emergency care.

Methylphenidate Formulations. Methylphenidate-based stimulants represent a common starting point for the medication management of ADHD in younger children. The AAP recommends it for preschool children after behavioral therapy.[7] The NICE recommends starting with this class of stimulants when ADHD symptoms persist after environmental modifications in children and young people.[12] Methylphenidate products are listed in Table 2.[20–29] US Food and Drug Administration approval for each product varies per age. Medication formulations range from immediate release (3- to 5-hour duration of action) to extended release (8- to 13-hour duration of action). Brand name products fall into the methylphenidate, dexmethylphenidate, and serdexmethylphenidate categories. Product formulations include tablets, capsules, chewable tablets, orally dissolving tablets, solutions, suspensions, and a transdermal patch. Generic product options are available for several agents in this class, representing more cost-effective options. Patient education regarding unique dosage forms is imperative. For example, Concerta has an osmotic-controlled release methylphenidate tablet shell that allows for a slow, controlled release.[42] Yet, the tablet shell does not dissolve completely and may be seen intact in the stool. Additionally, the tablet does not change shape and thus, should not be used in patients with preexisting severe gastrointestinal narrowing.[24] Another important note is that most products are not interchangeable due to pharmacokinetic properties and dosage formulations and require a taper off/on when a shift of agents is necessary. Lastly, it is important to verify therapeutic equivalence with the FDA Orange Book for generic stimulant products.

A published pharmacological review has detailed characteristics of earlier products available for ADHD treatment.[42] Since 2018, at least 3 new medications have joined the methylphenidate class. These new dosage forms seek to increase the functionality of the class. They include a first-in-class prodrug formulation, another multilayer beaded long-acting formulation, and a distinctive delayed-release/extended-release product design. All 3 are capsules with a long duration of action allowing for once-daily dosing.

Approved in March 2021, Azstarys capsules contain dexmethylphenidate and serdexmethylphenidate in a fixed molar ratio of 30%/70%, respectively.[21,29] The prodrug component, serdexmethylphenidate, undergoes bioactivation in the lower GI tract. The unique formulation allows for continuous conversion to dexmethylphenidate providing extended concentrations (up to 13 hours) of active drug throughout the course of therapy. The capsules are offered in 3 distinctive strengths. The medication can be taken with or without food and

Table 5. Stimulant Adverse Events and Management[7,18]

Adverse Event	Potential Management Options
Sleep disturbance	Behavioral measures (sleep hygiene), dosage reduction, administer dose earlier in day, alternative stimulant formulation or class, change to or add-on a non-stimulant option
Decreased appetite	See weight monitoring in Table 4
Increased blood pressure (BP) or heart rate (HR)	See BP and HR monitoring in Table 4
Dizziness	Monitor BP and HR, ensure adequate fluid intake, consider longer-acting preparation
Rebound ADHD symptoms	Increase dose of long-acting agent or add smaller dose of short-acting medication before when rebound symptoms appear
Tics	Dosage reduction, change to non-stimulant option, stop offending medication
Suicidality and psychosis	Verify appropriate dose is administered as prescribed, reduce dose, discontinue stimulant, screen for safety/refer to specialist
Diversion and misuse	Monitor prescription refills, open discussions with patient/caregiver, avoid co-use with alcohol, tobacco, marijuana, and other illicit substances, proper medication storage and disposal

is FDA-approved for patients ≥6 years of age. Capsules can be consumed whole, opened onto applesauce, or mixed with 50 mL water. Opened capsules must be taken within 10 minutes of mixing. Due to its prolonged duration of action, Azstarys is given once daily in the morning. Adverse effects are like other products in the class, with the most common being insomnia and suppressed appetite.

Adhansia XR was FDA-approved in February 2019, yet was discontinued by the manufacturer in July 2022.[21,27] Per the manufacturer, the product discontinuation was a business decision and not based on efficacy or safety concerns.[43] Authorized for patients ≥ 6 years, the product represented another encapsulated beaded long-acting methylphenidate formulation.[27] The significant advantage for Adhansia XR was its lengthy duration of action (roughly 16 hours). This formulation represented the longest interval product in the methylphenidate class.

Jornay PM represents a new methylphenidate formulation, a delayed-release/extended-release capsule.[28] Approved by the FDA in August 2018, Jornay PM is recommended for patients ≥6 years of age.[21] The product is manufactured in 5 unique strengths ranging from 20 to 100 mg.[28] Like other ADHD medications, capsules may be opened for administration, without crushing or chewing the capsule contents. Of importance, transitioning between Jornay PM and other methylphenidate products is not on a milligram-to-milligram exchange based on formulation and release mechanism differences. Jornay PM is unique in that it is taken in the evening, representing the first and only product in the stimulant class with this specific time of administration. Timing of the evening dose (6:30 to 9:30 pm) is recommended to optimize the efficacy and tolerability of the medication for the subsequent day. In children 6 to 12 years of age, 8 pm was found to be the optimal timing of administration. Pharmacokinetic properties of Jornay PM show that ≤5% of the total drug dose is released within the first 10 hours after dosing. Following this time, methylphenidate absorption occurs with a single peak and a median maximum concentration time of 14 hours. Jornay PM is marketed to improve the morning routine in patients with ADHD and subsequently to continue control for the dosing duration. Another potential benefit of this product is to assist patients who struggle with morning medication adherence. Due to its long duration, insomnia is the most common adverse effect (33%–41%) of this product in pediatric patients.[28]

Amphetamine Formulations. Amphetamine-based stimulants represent a preferred ADHD treatment option for children, adolescents, and adults. NICE recommends this class as a second-line agent in children, behind methylphenidate.[12] In contrast, the AAP does not differentiate among stimulant classes, thus including amphetamine formations as a first-line option.[7] Comparing the two stimulant classes, amphetamines are associated with greater adverse effects and adverse events.[17] Amphetamine products are listed in Table 3.[20–22,30–39] Medication formulations range from immediate release (4- to 5-hour duration of action) to extended release (8- to 16-hour duration of action). Brand name products fall into the mixed amphetamine salts, amphetamine, dextroamphetamine, and lisdexamfetamine categories. Product formulations include tablets, capsules, chewable tablets, orally disintegrating tablets, solutions, suspensions, and a newly approved transdermal patch. Generic product options are available for several agents in this class, once again representing more cost-effective options.

Xelstrym (dextroamphetamine) was FDA-approved in March 2022.[37] Indicated for patients ≥ 6 years, this product represents the only transdermal amphetamine patch formulation. Xelstrym was studied in children < 6 years, yet long-term weight loss was an undesirable

adverse event. The patch formulation is available in 4 strengths (4.5 mg/9 hr, 9 mg/9 hr, 13.5 mg/9 hr, and 18 mg/9 hr). Xelstrym must be applied 2 hours before the anticipated effect is necessary and subsequently removed within 9 hours. Patch site rotation is also imperative. The external application of heat will increase drug absorption, and counseling needs to be provided to avoid heat usage. Xelstrym should not be exchanged for other amphetamine formulations based on dosing. Decreased appetite, headache, insomnia, and abdominal pain are a few adverse effects found with Xelstrym treatment.

In September 2017, Adzenys ER extended-release amphetamine suspension was FDA-approved for patients ≥6 years with ADHD.[34] The suspension contains a mixture of 50%/50% uncoated immediate-release microparticles to film-coated microparticles that delays the absorption of amphetamine. Unlike other stimulant preparations, Adzenys has published equivalent conversion doses to and/or from Adderall XR (mixed amphetamine salts). For illustration, an Adderall XR dose of 20 mg would be analogous with an Adzenys ER suspension dose of 12.5 mg based on medication pharmacokinetic properties. The Adzenys ER suspension is distributed in a 1.25-mg/mL concentration and holds a duration of action of approximately 10 to 12 hours. A key advantage of Adzenys ER is the suspension delivery formulation, which allows for ease of administration in patients unable to swallow a tablet or capsule.

Mydayis, as mixed amphetamine salts, was FDA-approved in June 2017.[33] This long-acting formulation includes 3 forms of drug-releasing beads, an immediate-release and 2 separate delayed-release beads that represent a 3:1 ratio of *d*-amphetamine and *l*-amphetamine. Like other capsule preparations, the contents can be mixed in applesauce for delivery, taking caution to not crush or chew. Mydayis is authorized for adolescents (≥13 years of age) and adults only. In studies with children <13 years at comparable doses, elevated plasma levels were found that equated to higher rates of insomnia and decreased appetite. Mydayis is formulated in 4 dosage concentrations. Due to the long duration of action (up to 16 hours), early morning medication administration is imperative. When contrasted with other mixed amphetamine salts formulations, a single dose of Mydayis 37.5 mg supplied similar plasma concentration profiles to the blend of a 25-mg mixed amphetamine salts extended-release capsule followed by a 12.5-mg immediate release dosage form 8 hours after. Mydayis extended-release capsules are the lengthiest duration amphetamine-based formulation on the market and have a longer duration than any currently available methylphenidate product.

Non-stimulants. There are 4 non-stimulant medications, 2 unique drug classes, with FDA approval for the management of ADHD (Table 6).[20–22,44–46] The AAP guidelines include both classes in their treatment recommendations for both children 6 to 11 years and adolescents 12 to 17 years of age.[7] Additionally, NICE includes the use of the non-stimulants as treatment options for pediatric patients ≥ 5 years and adults.[12] The non-stimulant agents are recommended in patients whose symptoms do not respond to either stimulant compound or in situations of concern regarding abuse or diversion with the stimulant class.[7]

Norepinephrine Reuptake Inhibitors. Atomoxetine and viloxazine selectively inhibit norepinephrine transporters, thus increasing extracellular synaptic concentrations of norepinephrine and dopamine in the prefrontal cortex.[18,21,22] Unlike the stimulant class, these agents take approximately 1 to 2 weeks to see an initial benefit with 4 to 6 weeks to see the maximal effect on core ADHD symptoms. Atomoxetine is manufactured as a capsule in 7 strengths, available in generic form, and is dosed once daily.[45] Similarly, viloxazine is delivered once daily in a capsule formulation.[46] Both agents hold a boxed warning for suicidal ideation in children and adolescents and use within 14 days of a monoamine oxidase inhibitor is contraindicated. Atomoxetine is metabolized by CYP2D6.[45] Patients who are poor metabolizers of CYP2D6 may have a 5-fold increase in peak plasma concentrations, 10-fold higher area under the curve, and half-life of 24 hours, thus slower elimination of the drug. While atomoxetine is not a CYP2D6 inducer or inhibitor, dose adjustments may be warranted in extensive and poor metabolizer when administered with CYP2D6 inhibitors. Blood pressure and heart rate should also be monitored in patients taking atomoxetine and antihypertensives and pressor agents or systemic albuterol due to cardiovascular effects. Viloxazine is a strong inhibitor of CYP1A2 and weak inhibitor of CYP2D6, and CYP3A4.[46] Sensitive CYP1A2 substrates and CYP1A2 substrates with a narrow therapeutic index are contraindicated with viloxazine use, and moderately sensitive CYP1A2 substrates are not recommended for coadministration. Patients who are poor CYP2D6 metabolizers have higher peak concentrations and area under the curve of viloxazine compared with extensive metabolizers. Pharmacogenomic testing of patients may be considered prior to use of this medication class.

Alpha-2 Agonists. Guanfacine and clonidine extended-release formulations have FDA approval for the management of ADHD in children and adolescents as either monotherapy or in combination with another FDA-approved medication class.[18,21,22] The immediate-release formulations of guanfacine and clonidine may also be used off-label. These agents work by stimulating postsynaptic alpha-2-adrenergic receptors. The extended-release agents are both in tablet formulation, available in generic formulation, and are dosed once daily in the morning. Both agents hold warnings for hypotension, bradycardia, syncope, sedation, somnolence, and dry mouth. It is also

Table 6. Non-stimulant Treatment Options[20–22,44–46]

Medication	Brand Name (US)	Frequency of Dosing	Formulation(s)	Available Strengths	Warnings/Precautions
Norepinephrine reuptake inhibitors					
Atomoxetine	Strattera*	Once daily	Capsule (Swallow whole, do not open)	10, 18, 25, 40, 60, 80, 100 mg	Suicidal ideation in children/adolescents Severe liver injury Serious cardiovascular events
Viloxazine	Qelbree	Once daily	Capsule (May open and sprinkle on pudding or applesauce; do not chew)	100, 150, 200 mg	Suicidal ideation in children/adolescents Blood pressure and heart rate changes Activation of mania/hypomania Somnolence/fatigue
Alpha-2 agonists					
Guanfacine ER	Intuniv*	Once daily	Tablet	1, 2, 3, 4 mg	Hypotension, bradycardia, syncope Sedation/somnolence
Clonidine ER	Kapvay*	Once daily	Tablet	0.1 mg	Hypotension, bradycardia, syncope Vascular disease, cardiac conduction disease, or chronic renal failure Sedation/somnolence Abrupt discontinuation concerns

ER, extended release

* Generic available in certain strengths.

important to educate the patient/caregiver that these agents should not be stopped abruptly to the risk of rebound hypertension. If a patient encounters repeated orthostasis or fainting, a reduction in dose or therapy change is warranted. As with the norepinephrine reuptake inhibitors, clinical response may be delayed with a maximal effect seen at 2 to 4 weeks of therapy.

Off-Label Pharmacologic Treatment Options

Off-label treatment options for the management of ADHD in children have been studied. One agent investigated in both children and adults is bupropion. It holds a parallel mechanism of action and is structurally similar to the stimulant class.[47] However, the medication is contraindicated in patients with a seizure disorder or in patients with a coexisting condition that may put them at risk for seizures (e.g., bulimia nervosa).[21,22] Bupropion also carries the antidepressant-class warning of suicidal ideation in children and adolescents. Another agent studied off-label for ADHD is modafinil. The current labeled use for modafinil is excessive daytime sleepiness related to narcolepsy, obstructive sleep apnea, or shift work sleep disorder.[22] The exact mechanism of modafinil is unclear, but it maintains links to dopamine similar to amphetamine. A network meta-analysis looked at the efficacy and tolerability of various medications for children, adolescents, and adults with ADHD.[17] Both bupropion and modafinil were found to be more efficacious than placebo. Yet the authors note a large confidence interval in relation to the efficacy and tolerability of both agents and recommend caution with interpreting the data. In the end, more information is needed with these agents in the treatment of pediatric ADHD.

Conclusion

ADHD is a common disease practitioners encounter in the pediatric population. Behavioral therapy and/or stimulant medication remain the first-line treatment recommendations. Stimulant products differ based on pharmacokinetic profile and dosage formulation. Additionally, new stimulant products as well as non-stimulants continue to receive approval for use in the pediatric population and drug shortages can impact prescribing. Pharmacists can educate other health care providers on the similarities and differences of ADHD medication to improve the efficacy and safety of therapy for the patient.

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