Attention-Deficit/Hyperactivity Disorder

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LEARNING OBJECTIVES

1. Evaluate the signs and symptoms of attention-deficit/hyperactivity disorder (ADHD) in children and adults based on *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* criteria.
2. Distinguish rating scales used for ADHD in children and adults.
3. Evaluate the most updated guideline recommendations for treating ADHD in children and adults.
4. Distinguish the treatment modalities for ADHD including nonpharmacologic and pharmacologic modalities.
5. Evaluate the acute and chronic adverse effects associated with stimulant and nonstimulant medications and strategies to minimize the adverse effects.
6. Synthesize a therapeutic regimen using appropriate agents for management of ADHD symptoms with appropriate goals of therapy.

ABBREVIATIONS IN THIS CHAPTER

ADHD	Attention-deficit/hyperactivity disorder
CBT	Cognitive behavioral therapy
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
NICE	National Institute for Health and Care Excellence
NRI	Norepinephrine reuptake inhibitor
NT	Neurotransmitter(s)

Table of other common abbreviations.

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a clinical diagnosis in pediatrics and adults. It was initially thought to be a hyperkinetic reaction of childhood but is now recognized as a neurodevelopmental condition and results in significant educational, occupational, and social dysfunction (Posner 2020). The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*) criteria for ADHD has evolved since it was first introduced in the second edition of *DSM* (*DSM-II*).

Epidemiology

The prevalence of ADHD in the United States and worldwide has been difficult to estimate because of methodological differences between studies. The consequences of not treating ADHD in children may result in learning impairment, accidents, difficulty with peers and teachers, and failure to achieve full potential. Adults with ADHD may have difficulties in their jobs and personal relationships, as well as engage in substance use and criminal or reckless behaviors (Goodman 2007). Among college students, 2%–8% may have ADHD, and at least 25% of those with a disability diagnosis were reported to have ADHD (DuPaul 2009). Studies among college students with ADHD have reported lower grades, greater social difficulties, and higher alcohol and drug use than their peers without ADHD (Green 2012).

Pathophysiology

The pathophysiology of ADHD is likely multifactorial, consisting of genetic, environmental, structural, and neural components (Figure 1); however, the precise cause of ADHD is not fully understood. Previous

literature suggested specific neural substrates were responsible, but current data suggest the mechanism of ADHD is more supportive of interactions between a variety of neural circuits (Posner 2020).

Genetics have been thought to play a role given the strong heritability factor seen in twin studies (Kieling 2008). To date, neither a single gene nor group of genes have been identified as a major cause; however, multiple genes are recognized to have a moderate effect on ADHD presentation. A meta-analysis established an association in those with ADHD among the genes for dopamine 4 and 5 receptors, as well as the dopamine and serotonin transporters (Bobb 2006). In addition, there is thought to be a relationship between genetic factors and environmental risk factors. Children who were homozygous for the dopamine transport-1 allele with prenatal smoking exposure had a significantly increased risk of developing hyperactivity, impulsivity, and oppositional symptoms; however, when these two factors were independently studied, the risk was not observed (Kahn 2003). Furthermore, there was also a higher risk of ADHD in those with the same dopamine transport-1 gene and exposure to prenatal alcohol (Brookes 2006). When assessing environmental factors alone, toxins such as lead may lead to an increased risk of ADHD (Banerjee 2007).

Alterations in brain structures, including the prefrontal cortex, the basal ganglia, and the cerebellum, may also contribute to ADHD. Findings have consistently shown a volume reduction in these areas and overall brain size in individuals with ADHD into the adolescent years (Kieling 2008). There appears to be a greater reduction in size of the right prefrontal cortex (Hynd 1990), which has been linked to impaired performance in response inhibition tasks (e.g., selection, execution) (Casey 1997) and rapid color naming (Semrud-Clikeman 2000), both of which have been shown to be impaired in ADHD (Willcutt 2005). The basal ganglia have been proposed as a contributor to ADHD. Signals sent from the basal ganglia to the prefrontal cortex are thought to be involved in motor planning, sequencing, learning, and executive function. In addition, correlations between structure size in the basal ganglia and task performance were linked to the right brain hemisphere, emphasizing the role of the right prefrontal connections in relation to ADHD symptomatology (Kieling 2008). Lastly, the cerebellum, although traditionally linked to coordination, has connections involved in cognitive and affective processes. Furthermore, volume reduction in structures of the cerebellum is linked to worse clinical outcomes (Mackie 2007).

When considering the neurotransmitters involved in ADHD presentation, it is important to understand which neurobehavioral concepts are core to ADHD. A meta-analysis evaluated which neuropsychological tasks have deficits in ADHD and found three areas of interest, including vigilance-attention, executive function/cognitive control, and motivation (Nigg 2005). Motivation, specifically as it relates to reinforcement and reward processing, may be altered in ADHD (Tripp 2008). Genetic alterations to the dopamine transporter affecting the clearance of dopamine and dopamine signaling may influence the reward pathway as seen in ADHD. It is postulated that children with ADHD experience a delayed or lack of dopamine signal secondary to predicted reinforcement. This, in turn, leads to behavioral changes such as inattention and some components of hyperactivity and impulsivity. Described alternatively, individuals with ADHD tend to respond to stimuli that provide instantaneous reward as opposed to stimuli that provide a future reward. For example, a patient with ADHD may be less focused and involved in a classroom lecture because the examination is at a future time. However, they may be more invested in a classroom game because of the immediate stimulation of the reward system through the dopamine signaling pathway. Unfortunately, all symptoms, like difficulty organizing tasks and constantly being "on the go," cannot be explained by this dopamine mechanism, and complete understanding of the underlying pathophysiology is still not fully

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- Basic pharmacokinetic and pharmacodynamic principles
- Meaning and interpretation of effect sizes and basic statistical concepts (standard deviations and 95% CI)

Table of common laboratory reference values.

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- National Institute of Mental Health (NIMH). Attention-Deficit/Hyperactivity Disorder. NIMH, 2022.
- Wolraich ML, Hagan JF Jr, Allan C, et al.; Subcommittee on Children and Adolescents with Attention-Deficit/Hyperactivity Disorder. Clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. Pediatrics 2019;144:e20192528.
- National Institute for Health and Care Excellence (NICE). Attention deficit hyperactivity disorder: diagnosis and management. NICE, 2018 [last updated September 13, 2019].
- Canadian ADHD Resource Alliance (CADDRA). Canadian ADHD Practice Guidelines, ed. 4.1. CADDRA, 2020.

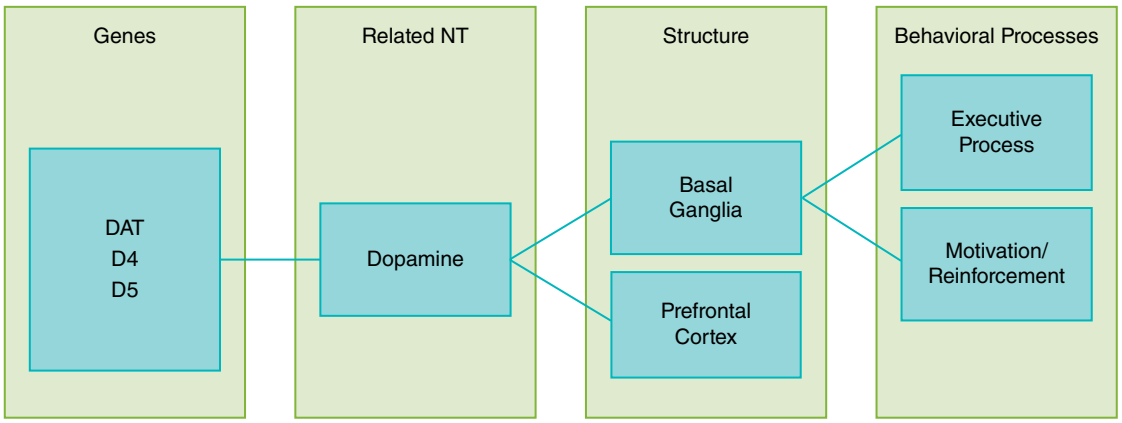

Figure 1. Relationship between genetics, brain structure, and neurotransmitters (NT) as they relate to the executive function and motivation symptomatology of attention-deficit/hyperactivity disorder.

DAT = dopamine transporter; D4 = dopamine 4 receptor; D5 = dopamine 5 receptor.

Information from: Tripp G, Wickens JR. Neurobiology of ADHD. Neuropharmacology 2009;57(7–8):579-89. doi: 10.1016/j.neuropharm.2009.07.026

known (Tripp 2009). Effective treatments, including methylphenidate and amphetamine products, work by inhibiting reuptake and/or facilitating the release of catecholamines, like dopamine, which may reinforce the theorized underlying cause of ADHD.

DSM-5 Criteria

The *DSM-5* criteria for ADHD are divided into symptoms of inattention and hyperactivity/impulsivity (Table 1) (American Psychiatric Association 2013). Children and adolescents up to 16 years of age may be diagnosed with ADHD by meeting six or more symptoms of inattention, hyperactivity/impulsivity, or a combination of the symptoms for at least 6 months. Symptoms must also be present in two or more settings (such as school and home) and must interfere with functioning (e.g., social, school, work). In addition, the symptoms must not be caused by another disorder, such as mood, anxiety, dissociative, or personality disorder. In adults and adolescents 17 years of age or older, only five symptoms are needed to meet criteria for ADHD. Several symptoms of either inattention or hyperactivity/impulsivity must be present before 12 years of age (Figure 2). Patients may be diagnosed with predominantly inattentive, predominantly hyperactive/impulsive, or combined depending on which category of symptoms is present. Symptoms of ADHD may present differently in adults; for example, "squirming in seat" for children may present as restlessness or tapping feet/fingers for adults.

Table 1. Core Symptoms of ADHD in Pediatrics and Adults

Inattention	Hyperactivity/Impulsivity
• Cannot pay attention to details or makes careless mistakes • Cannot focus on tasks or activities • Cannot seem to listen when spoken to directly • Does not complete tasks such as schoolwork, chores, and/or work • Has difficulty organizing tasks or activities • Avoids, dislikes, or is reluctant to do tasks that require mental effort (such as schoolwork or homework) • Often loses objects required for tasks • Easily distracted • Often forgetful in daily activities	• Often fidgets or squirms when seated • Often leaves seat when remaining seated is expected • Often runs about or climbs when not appropriate (in adults, may present as restlessness) • Often unable to play or take part in leisure activities • Is often "on the go" • Talks excessively • Blurts out answer before question has been completed • Has trouble waiting their turn • Interrupts or intrudes on others

Adapted from: American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 5th ed. American Psychiatric Association, 2013.

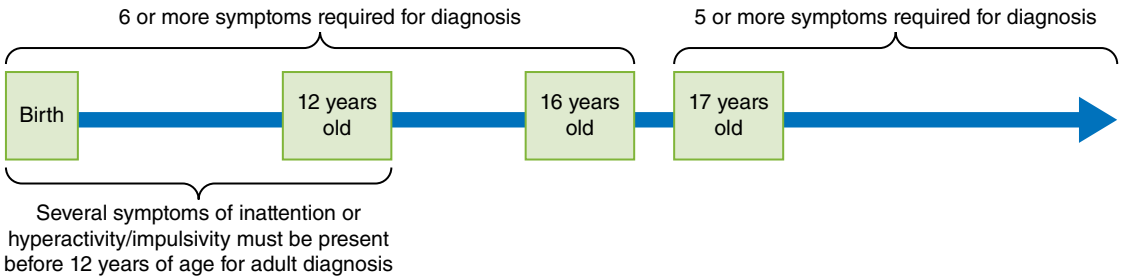

Figure 2. Timeline and number of symptoms required for each age group.

Adapted from: American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 5th ed. American Psychiatric Association, 2013.

Comorbidities

Attention-deficit/hyperactivity disorder commonly presents alongside other conditions, and the necessity of treatment for all conditions must be carefully weighed based on the severity of symptoms, level of dysfunction, and burden of treatment. In a 2016 caregiver survey, 60% of children with ADHD had at least one other mental health condition, such as anxiety, depression, behavior or conduct problems, substance use disorders, or autism spectrum disorder (Danielson 2018); as such, children with ADHD should also be screened for learning disorders. In adults, depression and anxiety are often comorbid and may be caused by longstanding untreated ADHD. In these latter situations, treatment of ADHD alone may provide relief from depression and anxiety symptoms (McIntosh 2009).

RATING SCALES

Children

There are several rating scales that are used to evaluate symptoms of ADHD. The most used scales can be found in Table 2. When completing rating scales in children, reports from caregivers and educators for the presence and severity of symptoms in different settings are essential. For example, the Conners' Rating Scales provides versions to be used by

Table 2. Attention-deficit/hyperactivity disorder (ADHD) Rating Scales for Children and Adults

Children and Adolescents		Adults	
Rating Scales	**Details**	**Rating Scales**	**Details**
ADHD Rating Scale – 5	18 items Observer-rated	Adult ADHD Self-Report Scale Symptom Checklist	18 items Self-report
Conners' Rating Scales – Revised	Parent: Full, 110 items Short, 45 items Teacher: Full, 115 items Short 41 items Self: Full, 99 items Short, 41 items	Conners' Adult ADHD Rating Scales	Self: Long, 66 items Short, 26 items Observer: Long, 66 items Short, 26 items
Vanderbilt ADHD Diagnostic Rating Scale	Parent: 55 items Teacher: 43 items	Wender Utah Rating Scale	Self: 61 items

Information from: Children and adults with Attention-Deficit/Hyperactivity Disorder (CHADD). Clinical Practice Tools. Available at www.chadd.org/for-professionals/clinical-practice-tools/; American Academy of Family Physicians National Research Network. ADHD Screeners and Qualify of Life Assessments. [updated April 21, 2021]. Available at www.aafp.org/dam/AAFP/documents/patient_care/adhd_toolkit/adhd19-assessment-screeners.pdf.

the patient, caregiver, or educator, but is a detailed questionnaire and may not be practical for use in clinical practice.

Adult

In adults, there are many self-reported symptom scales. Often, partners or family members who directly observe the patient in numerous settings and/or situations may be asked to provide supporting information using a rating scale, such as the Conners' Adult ADHD Rating Scales. Common rating scales used in adults are listed in Table 2.

GUIDELINES

Children

American Academy of Pediatrics (AAP) – 2019

The AAP guideline for ADHD provides guidance for diagnosis and evaluation of children 4–18 years of age. These guidelines recommend obtaining information from caregivers, educators, and other school staff, as well as the child or adolescent. In addition, it is important to rule out other medical and/or psychiatric conditions that may resemble ADHD such as anxiety, depression, developmental disorders, and physical conditions. For children 4–6 years of age, nonpharmacologic interventions are recommended as first line (Figure 3). For older children and adolescents, a combination of nonpharmacologic and pharmacologic therapies is most effective. Parent training for management of behavior is critical, especially for young children. Specialized educational plans, such as an Individualized Education Program, should also be requested to aid in the educational success of the child (Wolraich 2019).

National Institute for Health and Care Excellence (NICE) – 2018

Amended in 2019, the NICE guideline provides direction on recognition, diagnosis, and management of ADHD in children, young adults, and adults in the United Kingdom. The NICE guideline describes certain groups that may be at higher risk for ADHD (Figure 4) and adds emphasis on the need to support those with a diagnosis of ADHD, their families, caregivers, educators, and other health care professionals to ensure successful treatment outcomes.

Children under 5 years of age should receive ADHD-focused group parent training program and environmental modification as first line treatment. Medications should only be offered after receiving a second opinion from an ADHD specialist who has expertise in managing ADHD in young children. Among children and adolescents 5–18 years of age, individual or group parent training programs and environmental modifications are first line. Medications may be considered if nonpharmacologic interventions have been trialed but failed, and ADHD symptoms cause significant impairment. Cognitive behavioral therapy (CBT) may also be used for young people who have benefited from medications, but their symptoms still impair social skills with peers, problem-solving, self-control, active listening skills or dealing with and expressing feelings.

In 2019, the NICE guideline was modified to recommend that an ECG was not necessary before starting stimulants, atomoxetine, or guanfacine unless certain conditions exist (Figure 4). Medications should only be initiated in those with

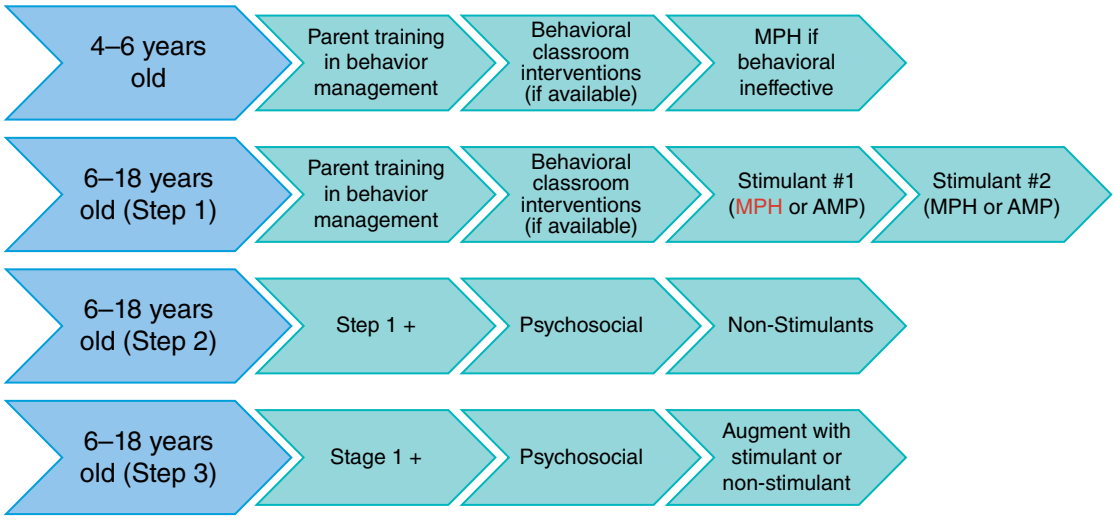

Figure 3. American Academy of Pediatrics summary of recommendations based on age. Red text indicates preferred stimulant.

AMP = amphetamines; MPH = methylphenidate.

Information from: Wolraich ML, Hagan JF, Allan C, et al; Subcommittee on Children and Adolescents with Attention-Deficit/Hyperactive Disorder. Clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. Pediatrics 2019;144:e20192528. doi: 10.1542/peds.2019-2528

Risk factors for ADHD development	Conditions qualifying for ECG prior to medication treatment
• Born preterm • Children diagnosed with oppositional defiant disorder, conduct disorder, or mood disorder • A family history of ADHD diagnosis • Epilepsy diagnosis • Adults with a mental health condition • Those with a history of substance misuse • Those with an acquired brain injury	• History of congenital heart disease or previous cardiac surgery • History of sudden cardiac death in a first-degree relative under 40-years-old • Shortness of breath on exertion compared with peers • Fainting on exertion or in response to fright or noise • Rapid, regular palpitations that start and stop suddenly • Chest pain suggesting cardiac origin • Signs of heart failure • Murmur heard on cardiac examination • Hypertensive blood pressure for adults

Figure 4. Risk factors for attention-deficit/hyperactivity disorder (ADHD) development and conditions qualifying patients for ECG prior to initiating ADHD medications.

Information from: National Institute for Health and Care Excellence (NICE). 2018 [last updated September 2019]. Attention deficit hyperactivity disorder: diagnosis and management. Available at www.nice.org.uk/guidance/ng87/resources/attention-deficit-hyperactivity-disorder-diagnosis-and-management-pdf-1837699732933.

training and expertise in diagnosing and managing ADHD (NICE 2018).

Canadian ADHD Resource Alliance (CADDRA)

The CADDRA guideline recommends treatment objectives for ADHD should follow specific, measurable, attainable, relevant, and timely criteria. Medication selection should be based on individual and medication-related factors, and multimodal treatment should be used when possible. For those who are 6–17 years of age, first line options should include long-acting psychostimulants (e.g., lisdexamfetamine, methylphenidate, amphetamine mixed salts). Second line or adjunctive treatments such as short- and intermediate-acting psychostimulants (e.g., methylphenidate, dexamphetamine) and long-acting nonstimulants (e.g., guanfacine, atomoxetine) should be reserved for individuals who have significant side effects, suboptimal response, or have a contraindication to first line options. An adequate trial of both methylphenidate and amphetamine classes are recommended before trialing second line treatment options. Nonpharmacological treatment, including CBT, behavioral interventions, parent training, cognitive training, and social skills training, should be incorporated and may be preferred by many patients (CADDRA 2020).

Adults

CADDRA

The CADDRA also provides ADHD guidance for adults. Recommendations are similar to children and adolescents with first line options including long-acting psychostimulants (e.g., lisdexamfetamine, methylphenidate, amphetamine mixed salts). Adequate trials of both methylphenidate and amphetamine classes are recommended before trialing second line treatment, such as short- and intermediate-acting psychostimulants (e.g., short-acting methylphenidate or dexamphetamine) and long-acting nonstimulants (e.g., guanfacine, atomoxetine). Use should be reserved for those individuals who have significant side effects, suboptimal response, or have a contraindication to first line options. As with children and adolescents, nonpharmacological treatment should also be incorporated in adult ADHD treatment (CADDRA 2020).

European Consensus Statement

According to the European Consensus Statement, first line treatment should be psychoeducation for both the patient and significant others; this approach improves psychological well-being and improve the quality of relationships among patients. If pharmacologic treatment is deemed necessary, long-acting stimulants are the treatment of choice. Nonstimulants (e.g., atomoxetine) are recommended as a second line treatment. Use of guanfacine, bupropion, and tricyclic antidepressants is limited because of lack of evidence. Whereas CBT reduces the core and associated mood symptoms of ADHD, it is only recommended to be used as an adjunct to medications (Kooij 2019).

NONPHARMACOLOGIC TREATMENT

Nonpharmacologic treatments are first line in the pediatric population, especially in those who may not be eligible for medication management because of side effects or age. In children under 6 years of age, behavioral management should be considered as first line therapy (Posner 2020). Nonpharmacologic modalities are numerous, with varying degrees of evidence and benefit reported. Refer to NICE guidelines for a more extensive evidence-based review of nonpharmacologic treatment modalities (NICE 2018).

Parent training provides "behavioral strategies to modify their children's behavior and reestablish positive relationships within the family" (Sonuga-Barke 2001). In 1999, a psychosocial intervention trial in children 7 to about 10 years of age found a combination of first line pharmacological management and psychosocial treatment (e.g., parent training and child-focused and school-based treatment), yielded similar outcomes as psychosocial treatment alone. However, the combination group had better improvement in functional outcomes, including academic performance, caregiver-child relations, and social skills compared with either therapy alone (The MTA Cooperative Group 1999). Parent training alone in children of preschool age revealed minimal benefit in overall ADHD symptoms but did demonstrate benefit in family functioning and child conduct problems (Rimestad 2019). Similar results were found in a review of parent training in children between 2 and 15 years of age (Daley 2014). Various guidelines (e.g., AAP, NICE) recommend parent training for preschool-aged children as first line. Parent training should be considered up to 17 years of age given the functional benefits to both the child and the family unit (Wolraich 2019; NICE 2018).

Cognitive behavioral therapy has been studied in both children and adults with ADHD. It aims to improve ADHD symptoms by reinforcing positive behaviors and fostering situations in which desirable behaviors occur (Drechsler 2020). Skills included in CBT are verbal self-instruction, problem-solving strategies, and social skills training (Daley 2018). This psychosocial intervention may use caregivers and educators in very young children to engage the CBT principles with the affected patient, whereas older children and adolescents can be taught to use CBT techniques (Drechsler 2020). Evidence suggests that CBT in children and adolescents has a positive effect on parenting, academic performance, social skills, and some behaviors (Daley 2014). Literature does not support CBT alone for core ADHD symptoms (Daley 2018) in children; however, it may be beneficial for symptom reduction when used in combination with medications (Ding 2018).

Comparatively, adults may be more responsive to psychosocial therapy because of multiple factors, including initiating self-referral and greater insight into their difficulties with ADHD symptoms. Several studies have demonstrated that individual and group CBT are effective in the treatment of adults with ADHD in conjunction with medication after partial response, or simply in combination compared with medication alone (Safren 2005; Wilens 1999; Stevenson 2002). In addition, a small randomized controlled study found that adding medication to CBT did not significantly improve the outcomes of CBT therapy. Thus, CBT with or without medication is beneficial in adults (Weiss 2012). Cognitive behavioral therapy is a valuable addition in conjunction with medication therapy in both children and adults, but response in adults appears to be more robust as both a stand-alone treatment and augmentation modality.

Other strategies include neuropsychological treatments and noninvasive brain stimulation (Drechsler 2020). One notable FDA-approved example is a digital game-based device, EndeavorRx, that is indicated for children 8–12 years of age for improvement of attention function. As a digital therapeutic, this device can mitigate some of the limitations, such as medication side effects. EndeavorRx works through video game graphics and reward loops. It incorporates adaptive mechanisms to adjust the difficulty based on the user's ability and progression through the session. Unlike other video games, the length of time the device is used is limited to a certain "dose" per session (EndeavorRx; Kollins 2020). The efficacy of this device has been evaluated by the mean change in the Test of Variables of Attention (TOVA) Attention Performance Index (API). Those in the treatment group had a mean (standard deviation) change from baseline on the TOVA API of 0.93 (3.15) compared with 0.03 (3.16) in the control group. Changes in these scores from preintervention to postintervention were found to be significant in the treatment group ($p<0.0001$), but not in the control group ($p=0.67$). These findings indicate that this device-based treatment was effective at improving attention in children 8–12 years of age with ADHD (Kollins 2020). Although novel nonpharmacologic therapies are promising, pharmacologic modalities remain the gold standard.

PHARMACOLOGIC TREATMENT

Stimulant Therapies

Pharmacologic management can be broken down into two categories: stimulants and nonstimulants. Stimulants are first line therapy in the management of ADHD because of their rapid onset of efficacy and high likelihood of success. Stimulants include methylphenidate, amphetamines, and their respective derivatives. Whereas effect size remains the same between stimulant classes, the mechanism of action does vary slightly. Methylphenidate and its derivatives do not have fully understood mechanisms. They are believed to work by blocking the presynaptic dopamine and norepinephrine transporter, preventing repacking of these neurotransmitters back into the neuron and allowing for continued effects in the brain. Methylphenidate is a racemic mixture, with dexmethylphenidate as the more active *d*-enantiomer, and is available in both long- and short-acting formulations (Table 3). New agents continue to be introduced to the market, one of which is a combination of dexmethylphenidate and its prodrug, serdexmethylphenidate.

Comparatively, amphetamines and derivatives work by promoting release of norepinephrine and dopamine from the presynaptic nerve terminals into the synaptic cleft. To a lesser extent, they are also thought to work similarly to methylphenidate-type drugs by blocking the dopamine and norepinephrine transporters and preventing the reuptake of these catecholamines into the nerve terminals. An example is lisdexamfetamine, a long-acting amphetamine product, which is a prodrug that is converted to dextroamphetamine (*d*-enantiomer of the racemic amphetamine compound) (Table 4).

Table 3. Details of Methylphenidate Products

Individual Drug Details			Class-Wide Effects		
Generic	Brand	FDA Indications and Approved Age for Use	Contraindications	Adverse Effects	Monitoring Parameters
Methylphenidate	Ritalin	ADHD, narcolepsy: ≥6 yr	Hypersensitivity to component Use of MAOI within past 14 days or in combination with MAOIs Concerta, Daytrana Metadate ER, Metadate CD, methylphenidate chewable tablets: • Marked anxiety, tension, and agitation • Glaucoma • Family history or diagnosis of Tourette syndrome or tics Metadate CD: • Severe hypertension • Heart failure • Arrhythmia • Hyperthyroidism or thyrotoxicosis • Recent MI or angina • Concomitant use of halogenated anesthetics • Hereditary fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency	BBW: Abuse/dependence potential Gastrointestinal: • Stomach upset (decreased appetite [2%–26%]/N/V/C/D) CNS: • Insomnia • Headache • Anxiety • Depression • Irritability • Aggression/agitation • Dizziness • Emotional lability/lack of emotion • Fatigue/sedation • Jitteriness/nervousness • Psychotic disorder/mania Nutritional: • Growth retardation • Weight loss Cardiovascular: • Increased BP/HR • Serious cardiac events Dermatologic: • Rash/skin excoriation • Hyperhidrosis Others: • Decreased libido • Tic disorder • Priapism • Fever	Risk for abuse, misuse, or dependence prior to prescribing and throughout treatment ECG (in those with history or exam suggestive of cardiac disease) BP/HR Growth rate (height/weight) and appetite (children) Weight (adults) ADHD symptoms Sleep changes Behavioral changes Psychiatric symptoms Signs of peripheral vasculopathy Transdermal formulation only: skin irritation QuilliChew ER only: total amount of phenylalanine intake in those with phenyl-ketonuria
	Methylin	ADHD, narcolepsy: 6–12 yr			
Dexmethylphenidate	Focalin	ADHD: 6–17 yr			
Methylphenidate extended release	Metadate ER	ADHD: ≥6 yr			
	Metadate CD	ADHD, narcolepsy: ≥6 yr			
	Concerta	ADHD, narcolepsy: ≥6 yr			
	Ritalin LA	ADHD, narcolepsy: ≥6 yr			
	Cotempla-XR-ODT	ADHD: 6–17 yr			
	Daytrana	ADHD: 6–17 yr			
	Quillivant-XR	ADHD, narcolepsy: ≥6 yr			
	QuilliChew ER	ADHD, narcolepsy: ≥6 yr			
	Jornay PM	ADHD, narcolepsy: ≥6 yr			
	Aptensio XR	ADHD, narcolepsy: ≥6 yr			
	Adhansia-XR	ADHD, narcolepsy: ≥6 yr			
Dexmethylphenidate	Focalin XR	ADHD: ≥6 yr			
Serdexmethylphenidate/dexmethylphenidate	Azstarys	ADHD: ≥6 yr			

ADHD = attention-deficit/hyperactivity disorder; BBW = black box warning; BP = blood pressure; C = constipation; CD = extended release; D = diarrhea; ECG = electrocardiogram; ER = extended release; HR = Heart Rate; IR = immediate release; LA = long acting; MAOI = monoamine oxidase inhibitor; MI = myocardial infarction; N = nausea, ODT = orally disintegrating tablet; V = vomiting; XR = extended release.

Information from: Drugs@FDA [internet database]. Available at www.accessdata.fda.gov/scripts/cder/daf/index.cfm.

Table 4. Details of Amphetamine Products

Individual Drug Details			Class-Wide Effects		
Generic	**Brand**	**FDA Indications and Approved Ages**	**Contraindications**	**Adverse Effects**	**Monitoring Parameters**
Mixed amphetamine salts	Adderall	ADHD, narcolepsy: ≥3 yr	Hypersensitivity to amphetamine or component of formulation Use of MAOI within past 14 days or in combination with MAOIs Adderall IR/ER: • Advanced arteriosclerosis • Symptomatic cardiovascular disease • Moderate to severe hypertension • Hyperthyroidism • Glaucoma • Agitated states • History of drug abuse Evekeo IR tablet: • Advanced arteriosclerosis • Symptomatic cardiovascular disease • Moderate to severe hypertension • Hyperthyroidism • Agitated states • History of substance abuse	BBW: Abuse/dependence potential Evekeo, Adderall BBW: Misuse may cause serious cardiovascular events Gastrointestinal: • Stomach upset (decreased appetite/N/V/C/D) CNS: • Insomnia • Headache • Anxiety • Depression • Irritability • Aggression/ agitation • Dizziness • Emotional lability/ lack of emotion • Fatigue/sedation • Syncope • Jitteriness/ nervousness • Psychotic disorder/ mania • Suicidal ideation Cardiovascular: • Increased BP/HR • Serious cardiac events/arrhythmias Nutritional: • Growth retardation • Weight loss Dermatologic: • Pruritis/rash • Hyperhidrosis Others: • Decreased libido • Sexual dysfunction • Tic disorder • Priapism • Serotonin syndrome • Fever • Xerostomia	Risk for abuse, misuse, or addiction prior to prescribing and throughout treatment ECG (in those with history or exam suggestive of cardiac disease) BP/HR Growth rate (height/weight) and appetite (children) Weight (adults) ADHD symptoms Sleep changes Behavioral changes Psychiatric symptoms Signs of peripheral vasculopathy
Amphetamine sulfate (d- and l-amphetamine)	Evekeo	ADHD: ≥3 yr Narcolepsy: ≥6 yr Exogenous obesity: ≥12 yr			
	Evekeo-ODT	ADHD: 6–17 yr			
Dextroamphetamine sulfate	Zenzedi	ADHD: 3–16 yr Narcolepsy: ≥6 yr			
	ProCentra	ADHD: 3–16 yr Narcolepsy: ≥6 yr			
Methamphetamine	Desoxyn	ADHD: ≥6 yr			
Amphetamine	Adzenys XR-ODT	ADHD: ≥6 yr			
	Dyanavel XR	ADHD: ≥6 yr			
Mixed amphetamine salts	Adderall XR	ADHD: ≥6 yr			
Mixed amphetamine salts	Mydayis	ADHD: ≥13 yr			
Dextroamphetamine	Dexedrine Spansule	ADHD, narcolepsy: ≥6 yr			
Lisdexamfetamine	Vyvanse	ADHD: ≥6 yr; Binge Eating Disorder (adults)			
	Vyvanse chews	ADHD ≥ 6 yr; Binge Eating Disorder (adults)			

ADHD = attention-deficit/hyperactivity disorder; BBW = black box warning; BP = blood pressure; C = constipation; D = diarrhea; ECG = electrocardiogram; ER = extended release; HR = Heart Rate; IR = immediate release; LA = long acting; MAOI = monoamine oxidase inhibitor; N = nausea; ODT = orally disintegrating tablet; V = vomiting; XR = extended release.

Information from: Drugs@FDA [internet database]. Available at www.accessdata.fda.gov/scripts/cder/daf/index.cfm.

Despite the efficacy of stimulant medications, side effects from these agents can be cause for discontinuation and/or contraindication for their use. A systemic review was conducted on the comparative efficacy and tolerability of various medications for the management of ADHD in children, adolescents, and adults (Cortese 2018). First, when evaluating the efficacy on core ADHD symptoms in children and adolescents, the study found that there was a moderate to large effect size for methylphenidate (standardized mean difference [SMD] −0.78; 95% CI, −0.93 to −0.62) compared with placebo. Comparatively, only a moderate effect was seen with use of methylphenidate in adults (SMD −0.49; 95% CI, −0.64 to −0.35). Tolerability was based on proportion of patients who dropped out of the included studies because of side effects. Methylphenidate was inferior to placebo in tolerability only in adult patients. Efficacy for amphetamines in children and adolescents revealed superiority to placebo, with a large effect size (SMD −1.02; 95% CI, −1.19 to −0.85). For tolerability, amphetamines were found to be inferior to placebo in children, adolescents, and adults. Common side effects included weight loss and blood pressure changes. Weight was significantly decreased by amphetamines and methylphenidate in children and adolescents (amphetamines: SMD −0.71; 95% CI, −1.15 to −0.27; methylphenidate: SMD −0.77; 95% CI, −1.09 to −0.45) and adults (amphetamines: SMD −0.60; 95% CI, −1.03 to −0.18; methylphenidate: SMD −0.74; 95% CI, −1.20 to −0.28). Systolic (SBP) and diastolic blood pressure (DBP) increases were significant in children and adolescents with amphetamine use, whereas SBP and DBP increases were seen in adults secondary to methylphenidate use. Weight loss and increases in blood pressure are important to consider when prescribing stimulants.

Side effects of stimulant medications to consider prior to initiation include growth delay in children and cardiac sequelae in both children and adults. Proper patient evaluation, monitoring, and education are essential. Growth suppression encompasses height deficits and weight loss, both of which are thought to be secondary to decreased appetite. Height deficits are also thought to be secondary to the underlying pathophysiology of ADHD, resulting in alterations of brain catecholamines and leading to altered neuroendocrine function (Spencer 1998). Data are conflicting regarding the effects of stimulant medications on the overall growth of children. Some data suggest stimulant use is linked to decreased height and weight (Poulton 2005; Rapport 2002), whereas other studies have suggested that long term growth is not impacted by stimulant use and should not impede the use of stimulants for the management of ADHD symptoms (Zachor 2006). Despite the mixed results, providers should monitor growth and, if necessary, use drug holidays (such as skipping medication on weekends) to aid in growth catch up. A randomized clinical trial looking at drug holidays (limited to nonschool days), caloric supplementation, and weight/height monitoring for growth suppression found that all three led to an increase in weight velocity but none led to an increase in height velocity (Waxmonsky 2020). Drug holidays can also be beneficial for confirming the benefits of medications, assessing the need for continued medication therapy, and establishing nonpharmacologic coping mechanisms (Ibrahim 2015). An additional consideration with stimulants is the black box warning for abuse and dependence, which can be monitored through drug use and refills. It is important to account for false positives and how these medications should appear on urine screening (Table 5). In addition, counseling patients of the possibility of positive drug tests is prudent in those who may encounter drug testing (i.e., job applications).

Guidelines have historically recommended the requirement of a thorough cardiac workup, such as an ECG. In 2011, a large retrospective cohort study which included over one million children and young adults, showed no evidence that current use of ADHD medication was associated with increased cardiovascular events (Cooper 2011). Additional studies have found there is no convincing evidence of serious cardiac events in children or adults secondary to stimulant use. While concerns exist given the minor, though statistically significant, increases in blood pressure and heart rate, evidence does not strongly support development of serious cardiac events. Thus, although an ECG can be helpful in identifying potential cardiac anomalies that might put a patient at higher risk for cardiac events, it is not strongly supported by the evidence. Guidelines recommend conducting a thorough medical history to ascertain cardiac risk factors and conduct ECGs only if needed on an individual patient basis (Martinez-Raga 2013).

Table 5. Urine Drug Screen Immunoassay Results for ADHD Treatments

Agents	Drug Screening Immunoassay Result
Amphetamines/ lisdexamfetamine	Positive for amphetamines
Methylphenidate	Possible false positives for amphetamines
Atomoxetine	Possible false positives for amphetamines
Clonidine	No reported cross reactivity with immunoassay
Guanfacine	No reported cross reactivity with immunoassay

Information from: Jensen, C.M., Breindahl, T. Patients in medical treatment for attention-deficit/hyperactivity disorder (ADHD): are they at risk in drug screening? Atten Def Hyp Disord 2019;11:333-40. doi: 10.1007/s12402-018-0282-9

Nonstimulant Therapies

Nonstimulant medications are considered second line for management of ADHD (Table 6). Nonstimulants include the norepinephrine reuptake inhibitors atomoxetine and viloxazine, and the extended-release formulations of alpha-2 adrenoreceptor agonists, guanfacine and clonidine. Norepinephrine reuptake inhibitors work by increasing free norepinephrine in the brain by blocking its reuptake from the synapse. The alpha-2 receptor agonists are believed to work by acting on the postsynaptic receptors in the prefrontal cortex and improving delay-related neuron firing.

In a systematic review by Cortese et al., the efficacy of atomoxetine, clonidine and guanfacine were all found to be superior to placebo in children and adolescents (atomoxetine:

Table 6. Details of Nonstimulant Products

Generic	Brand	FDA Indications and Approved Age for Use	Contraindications	Adverse Effects	Monitoring Parameters
Atomoxetine	Strattera	ADHD: ≥6 yr	Hypersensitivity to component Use of MAOI within past 14 days or in combination with MAOIs Narrow angle glaucoma Current or history of pheochromocytoma Cardiac or vascular condition that could be expected to deteriorate with clinically important increases in BP or HR	Gastrointestinal: • Stomach upset (decreased appetite [15%–23%]/N/V/C/D) Cardiovascular: • Increased BP/HR • Serious cardiac events/arrhythmias (rare) • Orthostasis/syncope CNS: • Insomnia • Drowsiness/fatigue • Headache • Irritability • Emotional lability/hostility Dermatologic: • Hyperhidrosis Nutritional: • Weight loss (2%–7%) Others: • Decreased libido • Sexual dysfunction • Hepatotoxicity/hepatic failure • Priapism (rare) • Xerostomia	AST/ALT ECG (in those with history or exam suggestive of cardiac disease) BP, HR Height (in children) Weight Appetite (in children) Sleep changes Behavioral changes
Viloxazine	Qelbree	ADHD: 6–17 yr	Hypersensitivity to components Use of MAOI within past 14 days or in combination with MAOIs Concomitant use of sensitive CYP 1A2 substrates or CYP 1A2 substrates with narrow therapeutic index	Gastrointestinal: • Stomach upset (decreased appetite [5%–8%]/N/V/C/D) Cardiovascular: • Increased diastolic blood pressure • Increased heart rate CNS: • Insomnia • Drowsiness/fatigue • Increased risk of suicidal ideation/tendencies • Headache • Irritability	ECG (in those with history or exam suggestive of cardiac disease) Mental status changes BP, HR SCr (renally excreted) AST/ALT (metabolized via liver)

(*continued*)

Table 6. Details of Nonstimulant Products (*continued*)

Generic	Brand	FDA Indications and Approved Age for Use	Contraindications	Adverse Effects	Monitoring Parameters
Guanfacine XR	Intuniv	ADHD: ≥6 yr (monotherapy and adjunct)	Hypersensitivity to components	Gastrointestinal: • Stomach upset (decreased appetite [5%–15%]/N/V/C/D) CNS: • Insomnia • Drowsiness/fatigue • Increased risk of suicidal ideation/ tendencies • Headache • Irritability • Emotional lability • Dizziness Cardiovascular: • Orthostasis • Hypotension • Increased heart rate Others: • Xerostomia	BP, HR Mental status changes
Clonidine XR	Kapvay	ADHD: 6–17 yr (monotherapy and adjunct)	Hypersensitivity to components	Gastrointestinal: • Stomach upset (N/V/C/D) CNS: • Insomnia/restless sleep • Drowsiness/fatigue • Headache • Aggression/irritability • Dizziness • Night terrors/ nightmares Cardiovascular: • Bradycardia • Orthostasis • Hypotension • Increased heart rate Others: • Xerostomia	BP, HR Mental status changes

ADHD = attention-deficit/hyperactivity disorder; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BP = blood pressure; C = constipation; CYP = cytochrome P450; D = diarrhea; ECG = electrocardiogram; HR = Heart Rate; IR = immediate release; MAOI = monoamine oxidase inhibitor; N = nausea; SCr = serum creatinine; V = vomiting; XR = extended release.

Information from: Drugs@FDA [homepage on the internet]. Available at www.accessdata.fda.gov/scripts/cder/daf/index.cfm.

SMD −0.56; 95% CI, −0.66 to −0.45; clonidine: SMD −0.6; 95% CI −0.85 to −0.50; guanfacine: SMD −0.71; 95% CI, −1.17 to −0.24). Atomoxetine, however, was the only agent that was found to be superior to placebo (SMD −0.45; 95% CI, −0.58 to −0.32) in adults. In comparing these agents to stimulants, amphetamines were found to be significantly superior to atomoxetine in children (SMD −0.46; 95% CI, −0.65 to −0.27) and adults (SMD −0.34; 95% CI, −0.58 to −0.10), whereas methylphenidate was superior to atomoxetine in children only (SMD 0.22; 95% CI, 0.05 to 0.39) (Cortese 2018). Of note, the data for these comparators, as well as guanfacine and clonidine, were of low quality based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach for network meta-analyses. With respect to tolerability,

guanfacine was the only studied nonstimulant found to be inferior to placebo in children and adolescents, and atomoxetine was found to be inferior to placebo in adults. Given the superiority of stimulants over nonstimulants, nonstimulants are typically reserved as second line treatment options as adjunct or for those who are unable to tolerate or are contraindicated to receive stimulant medications.

There are some patient-specific factors that may indicate the need for using second line agents over stimulants. Based on several case reports in the 1970s and 1980s, there were concerns that stimulants may worsen tics in those with a tic disorder (Lowe 1982; Golden 1974). About 50% of patients with tic disorders have co-occurring ADHD (Banaschewski 2007). However, recent evidence found that stimulants have not been shown to worsen tics in most patients. In some cases, though, stimulants may exacerbate symptoms, so the use of atomoxetine or alpha-2 receptor agonists could be considered as alternative agents (Osland 2018). Atomoxetine is indicated as a monotherapy agent for treatment in children, adolescents, and adults. Clonidine is indicated for use alone or as adjunct therapy to stimulants in children and adolescents, and guanfacine is indicated as alone or as adjunct in children, adolescents, and adults. A new product, viloxazine, was FDA approved in April 2021, but comparative studies with other ADHD agents are not yet available.

Bupropion, although not FDA indicated for use in ADHD, has been used off-label for this indication, but is typically reserved as a last line agent. In addition, it could be considered in patients who have comorbid mental health diagnoses, such as major depression with ADHD. However, stimulants and other nonstimulant medications, as previously discussed, are preferred and have more robust evidence for their use.

Navigating Different Formulations

There are numerous options available to help accommodate a variety of patient needs. For instance, in patients who have difficulty swallowing pills, a liquid formulation, orally disintegrating tablet, chewable tablet, or patch formulation may be preferred. It is important to monitor patients regularly to determine medication tolerability and adjust dosing or dosage forms as appropriate. When determining the appropriateness of treatment options for various patient preferences and symptom presentations, differences in formulations (immediate vs. long-acting) or dosage forms (tablets, solutions, or patches), should be considered. Some agents are formulated

Table 7. Formulation and Pharmacokinetic and Dosing Information for ADHD Pharmacotherapy

Generic	Brand	Elimination Half-Life (hours)	CYP pathway (if applicable) & Metabolite (major)	Dosing	Max Daily Dose (mg/day)	Dosage Forms
Methylphenidate Products (Short-Acting)						
Methylphenidate	Ritalin	3–4	PPAA/ritalinic acid	5–10 mg daily or BID	60	C, L, T, chewable
	Methylin	3–4	PPAA	10 mg BID-TID	60	L, chewable
Dexmethylphenidate	Focalin	2	PPAA	2.5–5 mg BID	20	T
Methylphenidate Products (Intermediate-Acting)						
Methylphenidate	Metadate ER	3–7	PPAA	10–20 mg daily	60	T
Methylphenidate Products (Long-Acting)						
Methylphenidate	Metadate CD	3–7	PPAA	20 mg daily	60	C (30% IR/70% ER)
	Concerta	3	PPAA	18 or 36 mg daily	72	T (OROS)
	Ritalin LA	3–7	PPAA	10–20 mg daily	60	C (50% IR/50% DR)
	Daytrana	3–4	PPAA	10 mg daily	30	Patch
	Quillivant-XR	5–6	PPAA	20 mg daily	60	Suspension (20% IR/80% ER)

(*continued*)

Table 7. Formulation and Pharmacokinetic and Dosing Information for ADHD Pharmacotherapy (*continued*)

Generic	Brand	Elimination Half-Life (hours)	CYP pathway (if applicable) & Metabolite (major)	Dosing	Max Daily Dose (mg/day)	Dosage Forms
	QuilliChew ER	5	PPAA	20 mg daily	60	Chewable tablet
	Aptensio XR	7	PPAA	10 mg daily	60	C (40% IR/60% CR)
	Cotempla-XR-ODT	4	PPAA	17.3 mg daily	51.8	T (25% IR/75% ER)
	Jornay PM	6	PPAA	20 mg QPM	100	C
	Adhansia-XR	7	PPAA	25 mg daily	100	C (20% IR/80% CR)
Dexmethylphenidate	Focalin XR	3	PPAA	10 mg daily	40	C (50% IR/50% DR)
Serdexmethylphenidate/dexmethylphenidate	Azstarys	5.7/11.7	Dexmethylphenidate PPAA	39.2 mg/7.8 mg daily	52.3/10.4	C
Amphetamine Products (Short-Acting)						
Mixed amphetamine salts	Adderall	10–13	CYP2D6, 4-hydroxy-amphetamine, norephedrine	2.5–5 mg daily	40	T
Amphetamine sulfate (d- and l-amphetamine)	Evekeo	7–34	CYP2D6, 4-hydroxy-amphetamine, norephedrine, alpha-hydroxy-amphetamine	3–5 yr: 2.5 mg daily ≥6 yr: 5 mg daily or BID	60	T
	Evekeo-ODT	11–14	CYP2D6, 4-hydroxy-amphetamine, norephedrine, alpha-hydroxy-amphetamine	5 mg daily or BID	40	ODT
Dextroamphetamine sulfate	Zenzedi	12	4-hydroxynorephedrine, norephedrine	5 mg daily or BID	40	T
	ProCentra	11–15	4-hydroxynorephedrine, norephedrine	5 mg daily or BID	40	Solution
Methamphetamine	Desoxyn	4–5	CYP2D6; *para*-hydroxymethamphetamine, amphetamine	5 mg daily to BID	25	T
Amphetamine Products (Long-Acting)						
Amphetamine	Adzenys XR-ODT	11–15	4-hydroxy-amphetamine, norephedrine, alpha-hydroxy-amphetamine	3.1 mg daily	18.8	T (50% IR/50% DR)
	Dyanavel XR	11–15	4-hydroxy-amphetamine, norephedrine, alpha-hydroxy-amphetamine	2.5–5 mg daily	20	Suspension
Mixed amphetamine salts	Adderall XR	10–13	CYP 2D6; 4-hydroxy-amphetamine, norephedrine	10 mg daily	30	C
Mixed amphetamine salts	Mydayis	10–13	CYP 2D6; 4-hydroxy-amphetamine, norephedrine	12.5 mg daily	50	C

(*continued*)

Table 7. Formulation and Pharmacokinetic and Dosing Information for ADHD Pharmacotherapy (*continued*)

Generic	Brand	Elimination Half-Life (hours)	CYP pathway (if applicable) & Metabolite (major)	Dosing	Max Daily Dose (mg/day)	Dosage Forms
Dextroamphetamine	Dexedrine Spansule	12	4-hydroxynorephedrine, norephedrine	5 mg daily or BID	60	C
Lisdexamfetamine	Vyvanse	<1 for parent; 12 for active metabolite	Dextroamphetamine	30 mg daily	70	C
	Vyvanse Chews	<1 for parent; 12 for active metabolite	Dextroamphetamine	30 mg daily	70	Chewable tablet
Nonstimulants						
Atomoxetine	Strattera	5–8	CYP2D6, 4-hydroxyatomoxetine	≥6 yr old (≤70 kg): 0.5 mg/kg daily, increase after 3 days to 1.2 mg/kg daily or in two divided doses ≥6 yr old (≥70 kg) or adults: 40 mg/day, increase after 3 days to 80 mg daily or in two divided doses	100	C
Viloxazine	Qelbree	7–11	No active metabolites	100–200 mg daily	400	C
Guanfacine XR	Intuniv	17	CYP3A4, inhibitor of MATE1, OCT1	1 mg daily	6	T
Clonidine XR	Kapvay	12–16	P-hydroxy-clonidine and others	0.1 mg daily	0.4	T

BID = twice daily; C = capsule; CD = extended release; CR = controlled release; CYP = cytochrome P450; DR = delayed release; ER = extended release; IR = immediate release; L = liquid; LA = long acting; MATE = multidrug and toxin extrusion; OCT = 3-oxoacid CoA-transferase; ODT = orally disintegrating tablet; OROS = osmotic-release oral system; PPAA = Alpha-phenyl-2-piperidine acetic acid; QPM = every evening; T = tablet; TID = three times daily; XR = extended release.

Information from: Briars L, Todd T. A review of pharmacological management of attention-deficit/hyperactivity disorder. J Pediatr Pharmacol Ther 2016;21:192-206. doi: 10.5863/1551-6776-21.3.192; Information from: Drugs@FDA [homepage on the internet]. Available at www.accessdata.fda.gov/scripts/cder/daf/index.cfm; Wagner DJ, Sager JE, Duan H, et al. Interaction and transport of methamphetamine and its primary metabolites by organic cation and multidrug and toxin extrusion transporters. Drug Metab Dispos 2017;45:770-8.

as combination products with immediate and extended-release components in one pill (Table 7).

GOALS OF THERAPY

Goals of ADHD treatment are symptomatic control and a return to full functionality in the individual's life, including school, work, and family. Examples for measuring improvement in these various functional areas include grades and teacher input, project efficiency or number of projects completed at work, and familial relationships. In providing care for ADHD patients, it is important to monitor patients regularly to determine medication tolerability and adjust dosing

Patient Care Scenario

A 20-year-old man is returning to your clinic for medication management of his ADHD. He has been seen in clinic for his ADHD, combined type diagnosis, since 10 years of age. His medical history is significant for hypotension. His family has been continuously engaged in his therapy. He allowed his mother to share the following details; she has noticed that ADHD symptoms have been worsening over the past 2 years. She is especially concerned because she suspects that her son may be using illicit drugs. He took the semester off from college because he was easily distracted and unable to focus, which led to failing grades. He has also been instructed numerous times to leave class because of being overly disruptive with uncontrolled talkativeness, fidgeting, blurting out answers, and interrupting others while they are talking. Over the past 3 months, the patient reports that he has only been getting about 3 hours of sleep per night and has lost 10 pounds because of decreased appetite. He is not currently taking any prescribed medication but does admit to you that he has been using intravenous methamphetamine for 3 months. What is best to recommend as an initial ADHD medication with the above patient-specific factors in mind, and what is the best rationale for why other therapies may be inappropriate for this patient?

ANSWER:

The first step would be to assess the patient's need for treatment for ADHD given his concomitant substance use disorder. The patient is experiencing an impairment in functioning, as evidenced by the need to drop out of school and his distractibility and inability to focus. Additionally, examples of poor symptom control include being asked to leave class because of talkativeness, fidgeting, blurting out answers and interrupting others while they are talking. Therefore, given the impact that the symptoms are having on his education, it would be prudent to consider medication therapy in this patient. Nonpharmacologic therapies like CBT could be considered; however, these take time to implement, and are not recommended as first line therapy in adults.

In considering which treatment option is best for this patient, some key points are important to note. First, he is reporting that he has been experiencing weight loss and poor sleep. These factors limit the use of stimulant medications, which may further cause weight loss/appetite suppression and if dosed too close to bedtime, poor sleep. A more significant consideration is his methamphetamine use disorder. Both classes of stimulants, methylphenidate and amphetamines, have a black box warning for abuse/dependence potential. Given this patient is already experiencing methamphetamine dependence, it would be ill advised to initiate another product with similar effects that could prolong or exacerbate his substance use disorder. The patient should abstain from methamphetamine and any other substances prior to initiating treatment for his ADHD. If treatment is then warranted, a nonstimulant would be recommended for this patient. Thus, a nonstimulant would be recommended for this patient. Clonidine extended release has little evidence for use in the adult population, thus may not be optimal for this patient. Guanfacine extended release, although indicated in adults, would not be ideal for this patient given his history of hypotension. Other FDA approved ADHD therapies include the norepinephrine reuptake inhibitor class of medications, which includes atomoxetine and viloxazine. Viloxazine is not indicated for patients over 17 years of age. Therefore, atomoxetine is the best treatment option for this patient because there is no abuse potential and minimal appetite changes compared with other first line pharmacologic treatment options.

1. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 5th ed. American Psychiatric Association, 2013.
2. Canadian ADHD Resource Alliance (CADDRA). Canadian ADHD Practice Guidelines, ed. 4.1. CADDRA, 2020.
3. Kooij JJ, Bijlenga D, Salerno L, et al. Updated European consensus statement on diagnosis and treatment of adult ADHD. Eur Psychiatry 2019;56:14-34. doi: 10.1016/j.eurpsy.2018.11.001
4. Cortese S, Adamo N, Del Giovane C, et al. Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: a systematic review and network meta-analysis. Lancet Psychiatry 2018;5:727-38. doi: 10.1016/S2215-0366(18)30269-4

or dosage forms as appropriate. Patients should also be monitored for response to therapy to assess the need for continuation. Discontinuation of therapy may be considered in patients who do not require ongoing dose increases for symptom management as they enter adulthood, and/or do not experience a return of symptoms after missed doses. If ADHD symptoms return, pharmacotherapy can be reinitiated.

When providing patient education for mental health diagnoses, it is important to provide thorough but concise information to ensure medication adherence while allaying patient fear of side effects that may lead to medication discontinuation. In instances where side effects of ADHD treatment are present, they may be mitigated by specific strategies (Table 8) and should be reviewed with the patient and/or family. Special considerations for comorbid disorders should also be emphasized during patient education. Refer to individual drug tables for comprehensive monitoring recommendations (Tables 3, 4, and 6).

Table 8. Review of Select Side Effects and Mitigation Strategies

Side effect	Medication Adjustment or Intervention
Insomnia	Ensure long-acting formulation is not taken near bedtime based on half-life information; consider switching to intermediate acting agent Avoid dosing supplemental doses too late in the day; dosing later than 2:00 p.m. or 3:00 p.m. could interfere with sleep
Wearing off effects	Several options available: 1. Transition to long-acting formulation 2. Adjust long-acting formulation to provide coverage when needed 3. Provide supplemental immediate release pill for coverage (i.e., supplemental dose at homework time in afternoon)
Growth suppression/weight loss/ appetite suppression	Set alarms for snacking/eating meals Eat breakfast prior to stimulant administration Drug holidays to minimize drug exposure during times that would be least disruptive and allow for return to normal dietary intake Consider nutritional supplements (i.e., shakes) to allow child to obtain necessary nutrients
Stomach upset	Dose medication with food when possible
Jitteriness/anxiety/tremors	Consider a dose reduction Reduce or eliminate caffeinated products Transition to extended-release formulations, which may help to reduce drug peaks and overall feelings of anxiety
Orthostasis (most common with guanfacine and clonidine)	Ensure adequate hydration Stand up slowly from a lying or seated position Monitor blood pressure
Blood pressure and heart rate elevation	Monitor blood pressure Avoid other substances that can increase blood pressure (i.e., caffeine) If intolerable blood pressure or heart rate changes, consider changing to nonstimulant product
Worsening of tics	Consider switching to a nonstimulant product In cases when a stimulant product is necessary, consider a lower dose

Practice Points

- **Attention-deficit/hyperactivity disorder is a neurodevelopmental condition that can significant impact educational, occupational, and social functioning in children and adults.**
- **First line treatments for children include nonpharmacological treatment, such as parent training.**
- **Stimulants remain the gold standard for treatment of ADHD in children, who remain symptomatic despite behavioral interventions, and first line in adults.**
- **Patients who fail one type of stimulant (methylphenidate or amphetamine / dextroamphetamine) may try an alternative class.**
- **Numerous formulations of stimulants are available to allow convenient dosing and increase tolerability.**
- **Patients and caregivers should be engaged to improve adherence.**
- **Nonstimulants such as atomoxetine, viloxazine, clonidine, and guanfacine should be trialed in those who have failed two types of stimulants and/or have intolerances or contraindications to stimulant use.**

CONCLUSION

ADHD is a neurodevelopmental condition that can impact educational, occupational, and social functioning in children, adolescents, and adults. Psychosocial interventions, like parent training, are considered first line in children, with the addition of pharmacologic therapy if symptoms are not controlled and continue to persist. Within pharmacologic management, stimulants remain the gold standard, with high efficacy and fast symptom response. Alternative treatments are reserved for those who have failed two or more types of stimulants or have intolerances and/or contraindications to use. As always, caregivers play an important role in the management of ADHD in younger patients to assist with adherence and monitoring treatment response. Treatment of ADHD should be individualized for each patient. Adjustments to regimens should be considered based on tolerability and convenience for the patient and/or family, as applicable.

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Self-Assessment Questions

Questions 1-3 pertain to the following case.

S.R. is a 32-year-old woman presenting to clinic for medication management. She reports experiencing bothersome symptoms daily that interfere with her ability to complete daily tasks. She was reprimanded at work by her supervisor for not paying attention during meetings and turning in assigned tasks with obvious mistakes. S.R. notes that she is often very distracted by external noises and conversations during meetings. She has difficulty starting projects, and even with the help of a to-do list, she cannot seem to prioritize tasks effectively. It is determined that this patient needs to be referred to an appropriate prescriber for a proper diagnostic workup.

1. Which one of the following questions is most likely to indicate a probable diagnosis of attention-deficit/hyperactivity disorder (ADHD) per the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5)?

   A. Were any of these symptoms present for you prior to age 12?
   B. Have you trialed therapy to help manage these symptoms?
   C. How bothersome are these symptoms?
   D. Do you have a family history of mental health diagnoses?

2. S.R. is diagnosed with ADHD. Based on her symptom presentation, which one of the following specifiers best fit her symptoms?

   A. Primarily hyperactive/impulsive type
   B. Primarily inattentive type
   C. Combined type
   D. Primarily hyperactive/inattentive type

3. The prescriber would like to evaluate S.R. using a rating scale during their next visit. Which one of the following is the most appropriate scale to use?

   A. Vanderbilt ADHD Diagnostic Rating Scale
   B. ADHD Rating Scale-5
   C. Wender Utah Rating Scale
   D. Conners' Rating Scale - Revised

4. A 45-year-old physician has been struggling with long-standing ADHD symptoms. He is having difficulty at work with finishing his patient encounters and notes on time and spends long nights at home catching up with work. His personal life has also suffered because he is unable to help with household chores and has minimal engagement with his children. He trialed methylphenidate extended-release tablets 54 mg per day for 4 weeks, but it has not been effective. Which one of the following is best to recommend for this patient?

   A. Switch to dextroamphetamine 5 mg by mouth twice daily.
   B. Switch to atomoxetine 80 mg by mouth daily.
   C. Switch to clonidine extended release 0.1 mg by mouth daily.
   D. Implement a drug holiday to reduce tolerance.

5. Which one of the following best describes the benefits attained from engaging in parent training?

   A. Parent training provides similar efficacy for overall ADHD symptoms as stimulant medication.
   B. Parent training improves family functioning and childhood conduct issues.
   C. Parent training provides little benefit and should not be used in ADHD.
   D. Parent training improves core ADHD symptoms in combination with medication.

6. A 26-year-old man comes to your clinic for assistance managing his ADHD symptoms. He would like to avoid medication therapy and reports hearing good things about cognitive behavioral therapy (CBT). Which one of the following would be the most appropriate response?

   A. CBT is most effective by starting medication after psychotherapy has been initiated.
   B. CBT has better evidence for use in children and therefore may not be effective for this patient.
   C. CBT must be used in conjunction with medications in order to see clinical improvement.
   D. CBT has shown benefits in its use for ADHD, with and without medication management.

7. A 6-year-old boy (weight: 35 kg) with ADHD, hyperactive/impulsive type, has been receiving behavioral interventions for the past 6 months. His caregivers are concerned about his continued difficulties focusing on tasks both at home and at school, which is interfering with his academic progress. Which one of the following is best to recommend for this patient?

   A. Methylphenidate immediate release 5 mg by mouth twice daily
   B. Methylphenidate extended-release tablets 18 mg by mouth once daily
   C. Atomoxetine 40 mg by mouth twice daily
   D. Lisdexamfetamine 20 mg by mouth twice daily

8. You are educating a caregiver whose 7-year-old will be receiving methylphenidate extended-release tablets osmotic-release oral system (OROS) tablet for their ADHD symptoms. Which one of the following statements is most accurate?

A. You should open the capsule and sprinkle the contents into your child's breakfast.
B. Your child will have a 1-inch decline in height per year of treatment.
C. Your child should eat breakfast in the morning and then take the medication.
D. Your child should take the medication at bedtime so that it will start working the following morning.

9. You are working with a primary care physician who will be seeing a 25-year-old patient who may possibly have ADHD. They would like a recommendation for a rating scale that can be completed quickly in the office. Which one of the following rating scales would be most appropriate?

A. Conners' Rating Scale
B. Vanderbilt ADHD Rating Scale
C. Wender Utah Rating Scale
D. ADHD Self-Report Symptom Checklist

10. A 28-year-old man with history of ADHD and opioid use disorder presents to clinic for management of his ADHD symptoms (inability to focus, lacking motivation, procrastination). He tried ADHD coaching and psychotherapy for the past 2 years but is still struggling. Which one of the following is best to recommend for this patient?

A. Start methylphenidate at low dose.
B. Start dextroamphetamine at low dose.
C. Start atomoxetine at low dose.
D. Start clonidine extended release at low dose.

11. A 15-year-old non-binary patient has been on mixed amphetamine salts extended-release capsules 30 mg daily for 2 years. They reported immediate improvement in their ability to focus during classes and in their grades. However, over the past few visits, you note that they have not been filling their medication as regularly. Upon questioning, they note that they often forget to take their dose and so do not need refills as often as would be expected. Despite missing doses, they report ongoing success in school. Which one of the following is best to recommend for this patient?

A. Initiate a drug holiday plan to assess for ongoing need of medication.
B. Switch the patient to clonidine given the risk for diversion.
C. Switch to atomoxetine given the mixed amphetamine salts is no longer being used.
D. Switch to lisdexamfetamine, to minimize risk of abuse of excess medication.

Questions 12-14 pertain to the following case.

J.T. is a 19-year-old woman, currently in her second year of college, who presents to clinic for assistance in managing her ADHD symptoms. Her chart reveals that she has a history of binge eating disorder in addition to her ADHD diagnosis. She has not been previously treated with any medication for ADHD treatment.

12. Which one of the following is the best recommendation for J.T. for managing her ADHD?

A. Start parent training to target symptoms without medication.
B. Start lisdexamfetamine 30 mg daily.
C. Start atomoxetine 40 mg daily.
D. Start methylphenidate immediate release 5 mg daily, at time of day when her ADHD symptoms are most severe.

13. J.T. has been on treatment for several months and reports good control of her ADHD symptoms. However, she has been noticing some jitteriness recently and wonders if there is anything she can do to manage this side effect. Which one of the following is best to recommend for J.T.?

A. Stop treatment.
B. Switch to nonstimulant therapy to avoid severe jitteriness from stimulants.
C. Advise her to limit her caffeine intake to see if that reduces jitteriness.
D. Switch her to the immediate release form of her medication to limit drug exposure.

14. J.T. returns after 3 months for re-evaluation of her ADHD symptoms. Which one of the following objective measures is best to determine treatment efficacy?

A. Grades
B. Purging episodes
C. Substance use pattern
D. Weight

15. A new provider in your clinic is seeing a 20-year-old patient with ADHD symptoms. The patient has a history of cardiac abnormalities as a young child (8 years of age) but has not experienced symptoms since that time. On baseline exam, the provider could not appreciate any abnormal arrhythmias. They consult you on whether sending the patient for electrocardiogram (ECG) is necessary given the negative exam. Which one of the following is the best recommendation?

A. Yes, all patients less than 24 years of age require an ECG prior to starting a stimulant medication.
B. No, an ECG is not required if the patient is not symptomatic at the time of stimulant initiation
C. Yes, an ECG should be done, given the history of cardiac abnormalities.
D. No, as guidelines say ECGs do not provide any reasonable benefit for ADHD patients.

Learner Chapter Evaluation: Attention-Deficit/Hyperactivity Disorder

As you take the posttest for this chapter, also evaluate the material's quality and usefulness, as well as the achievement of learning objectives. Rate each item using this 5-point scale:

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

1. The content of the chapter met my educational needs.
2. The content of the chapter satisfied my expectations.
3. The author presented the chapter content effectively.
4. The content of the chapter was relevant to my practice and presented at the appropriate depth and scope.
5. The content of the chapter was objective and balanced.
6. The content of the chapter is free of bias, promotion, and advertisement of commercial products.
7. The content of the chapter was useful to me.
8. The teaching and learning methods used in the chapter were effective.
9. The active learning methods used in the chapter were effective.
10. The learning assessment activities used in the chapter were effective.
11. The chapter was effective overall.
12. The activity met the stated learning objectives.
13. If any objectives were not met, please list them here.

OTHER COMMENTS

14. Please provide any specific comments related to any perceptions of bias, promotion, or advertisement of commercial products.
15. Please expand on any of your above responses, and/or provide any additional comments regarding this chapter: