Chapter 82: Attention Deficit Hyperactivity Disorder

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KEY CONCEPTS

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1. Untreated or ineffectively treated childhood attention deficit/hyperactivity disorder (ADHD) can lead to poor school performance, poor socialization, and increased risk for traffic accidents, psychiatric comorbidities, unemployment, and involvement with the criminal legal system during adolescence and adulthood.

2. ADHD is 74% genetic in origin and is associated with decreased brain volume, a delay in cortical maturation, and possible dysregulation of the "default mode network," a brain system that regulates attention, prioritization of information, memory, and impulse control.

3. To meet *DSM-5* diagnostic criteria for ADHD, symptoms of inattention or hyperactivity-impulsivity, separately or all together, must be present during childhood and cause functional impairment in two different settings for 6 months. Adult-onset ADHD requires further study.

4. Physical, mental health, and psychiatric comorbidities must be assessed, prior to initiating pharmacotherapy, and the goals of treatment must be set.

5. Preschoolers, school-age children, adolescents, and adults with ADHD all can benefit from nonpharmacologic interventions that include a healthy diet, education on ADHD, and potentially effective educational, cognitive, and behavioral treatments.

6. The stimulants are the most effective pharmacologic treatment option for all ages with a rapid therapeutic effect, typically within 1 or 2 hours of an effective dose. Methylphenidate is recommended as first-line for children and adolescents while amphetamines are first-line treatment for adults based on efficacy and tolerability.

7. Alpha-2 adrenergic agonists such as extended-release preparations of guanfacine and clonidine are less effective than stimulants as monotherapy and are used in combination with stimulants or as monotherapy in youth to improve symptom control, particularly oppositional behaviors and insomnia.

8. When ADHD coexists with other neuropsychiatric conditions, such as anxiety disorders, major depression, autism spectrum disorder (ASD), or Tourette disorder, it is optimal to treat the most functionally impairing disorder first (whether it is ADHD or the co-occurring condition) and then treat the second disorder.

9. When ADHD coexists with bipolar disorder, it is necessary to first stabilize the mood with lithium, an antiseizure medication (or mood stabilizer), or a second generation antipsychotic before adding an ADHD-specific medication such as a stimulant.

10. Atomoxetine is a good option to manage ADHD symptoms in adolescents or adults with substance use disorders or when stimulants are intolerable. It has a delayed onset of effect (2–4 weeks) and has no potential for physical dependence. Viloxazine has similarities with delayed onset and also lacks physical dependence potential, but it requires further study compared to atomoxetine and stimulants to fully assess its place in therapy.

BEYOND THE BOOK

BEYOND THE BOOK

Watch the approximately 7-minute video (Video link) by an ADHD researcher and a child psychiatrist, Dr. Steven R. Pliszka, as he provides an example of a typical interview with a child undergoing evaluation for ADHD and he discusses the clinical assessment of ADHD. An ADHD diagnostic rating tool is used to collect and document information from the child utilized in the diagnostic assessment. Versions of validated diagnostic rating tools for parents and teachers are routinely utilized for diagnostic formulation as well. The video is useful to enhance student understanding regarding the COLLECT and ASSESS steps in the patient care process for managing ADHD.

INTRODUCTION

Once considered primarily a childhood disorder, attention deficit/hyperactivity disorder (ADHD) is now known to persist into adolescence for 75% and into adulthood for approximately 50% of individuals.[1,2] The American Academy of Pediatrics (AAP) considers ADHD a chronic condition that requires ongoing management.[3-5] ADHD has been correlated with neuroanatomical and functional brain changes that functionally result in inattention, impulsivity, and hyperactivity.[6,7] It is unusual for an individual to display signs of the disorder in all settings or even in the same setting at all times; however, there is a persistent pattern of symptoms that continues for 6 months or more.[1,7] Co-occurring anxiety, mood disorders, learning disabilities, medical conditions, and substance use disorders (SUDs) must be considered during assessment and treatment. Behavioral interventions and medications are effective for all ages, but there are special treatment plan considerations when developing and monitoring each age group.[3-5,8]

1 The psychiatric assessment of a child requires obtaining information from the child, parents, caregivers, and teachers.[1,5,9] Treating children with psychotropic medications requires a different approach than treating adults. Children undergo neurologic, physiologic, and psychosocial changes throughout development. Age-related pharmacodynamic and pharmacokinetic differences can alter drug disposition and response. Psychotropic medication treatment of children is intended to control symptoms or behaviors that impair learning and development.[1,5,9] Children may not be able to articulate symptom response or adverse effects of a medication. Adolescents and adults with ADHD may not have been diagnosed and treated during childhood, putting them at greater risk for the psychosocial consequences of ADHD, including unemployment, unstable relationships, substance abuse, and incarceration.[1,2,5,10,11]

EPIDEMIOLOGY

ADHD is the most well-known and researched neurodevelopmental disorder of childhood and occurs in approximately 5% to 10% of children and approximately 2.5% to 5% of adults.[12-14] Non-Hispanic Caucasian and African-American children are more likely diagnosed with ADHD compared with children of Hispanic or Asian descent according to CDC and National Children's Health survey data.[12,15] It is more prevalent in males than females with a ratio of 2:1 in children and 1.6:1 in adults.[1] In 2016, 6.1 million children in the United States or 9.4% of those aged 2 to 17 years were diagnosed with ADHD: almost twice the actual rate according to worldwide prevalence studies and the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-5*).[1,5,16] Methodological inconsistencies in diagnostic assessments likely contribute to increasing diagnosis and differences in prevalence rates internationally. Investigators evaluating 135 ADHD prevalence studies representing seven regions (North America, South America, Europe, Asia, Africa, Oceania, and the Middle East) found when consistent diagnostic criteria from the *DSM-5* are applied, the prevalence of ADHD for children and adolescents is similar among countries globally, at approximately 5.5%.[5,13,14,16] There is increasing concern among healthcare professionals and the public regarding the overdiagnosis of ADHD leading to stigmatization and potentially inappropriate treatment.[5]

Increasing rates of ADHD diagnosis in the United States is likely a factor associated with the observed increased prescribing of ADHD medications. In 2016, the US Centers for Disease Control (CDC.gov) reported that 2 million of the 6.1 million children with ADHD were first diagnosed at 2 to 5 years of age.[12,16] Of concern is the mode of treatment for these toddlers, as CDC data showed three out of four 2- to 5-year-olds with ADHD were prescribed medications and only one out of two were prescribed behavioral interventions. The AAP recommends a 6-month trial of behavioral classroom interventions and parent training in behavioral management prior to pharmacotherapy in children less than 6 years old.[12,16] In addition to young

children, adolescents and young adults are increasingly being diagnosed with ADHD. A large US pharmacy benefits management company, Express Script's, analysis of pharmacy claims representing 400,000 privately insured individuals younger than 65 years, showed that ADHD medication use increased by 35.5% for all age groups between 2008 and 2012. In addition, while the number of adults using ADHD medications was up 53.4% from 2008 to 2012, children still received a higher percentage of ADHD prescriptions compared to adults and 80% of these were stimulants.[17] In 2015, 4% of privately insured females ages 15 to 44 filled a prescription for an ADHD medication, most often a stimulant such as amphetamine salts or methylphenidate. This represents a 344% increase in ADHD medication prescribing in 2015 compared to 2003. Over the same time period, filled prescriptions for nonstimulant ADHD medications did not increase.[18]

Therefore, healthcare professionals and teachers should recommend a thorough assessment of ADHD by an experienced clinician using standardized criteria and investigating all possible causes of inattention, impulsivity, and hyperactivity in order to avoid overdiagnosis and potentially inappropriate treatment.

ETIOLOGY AND PATHOPHYSIOLOGY

2 There has been substantial progress in understanding the role of both genetics and the environment, as well as their interaction, in the pathophysiology of ADHD. An extensive review of twin studies over the past 40 years has shown that the heritability of ADHD (the amount of variance in ADHD symptoms attributable to genetics) averages around 74%.[19] The most extensive genome-wide association study (GWAS) to date was a meta-analysis of 12 studies comparing 20,183 persons with ADHD and 35,191 controls.[20] This study discovered 12 regions that achieved genome-wide significance with *none* of the genes identified in previous candidate gene studies (ie, dopamine transporter) being significant.[19] It remains to be seen exactly how the newly identified genes might be involved in ADHD. Despite the size of the study, all 12 loci identified accounted for only 22% of the genetic variance as the remaining ~50% of the heritability is "missing."[19]

Some of the missing heritability may occur because patients have copies or deletions in the genome that cover multiple genes called copy number variants (CNVs). Current CNV studies have implicated a number of systems in ADHD: cholinergic receptors and genes for central nervous system (CNS) development[21] and an area of chromosome 15q13.[22] The CNVs affecting the metabotropic glutamatergic receptor 5 gene were enriched in cohorts of patients with ADHD relative to controls.[23]

Increasingly, there is clear evidence that genes involved in ADHD are also involved in other major psychiatric disorders, including schizophrenia, and affective (mood) disorders.[25] A significant genetic correlation has been found between ADHD and autism spectrum disorder (ASD) in a large GWAS of individuals with ASD.[26] Thus, genes for neurodevelopmental disorders are not specific to ADHD and may show considerable pleiotropy (one gene influences two or more seemingly unrelated phenotypic traits).[27]

Since gene by environment interaction may also be important, it is critical to examine environmental factors. Twin studies can estimate the amount of variance related to the environment and further subdivide environmental effects into "shared" (an event both twins experience, such as neighborhood) and "non-shared" (one twin has a head injury, the other does not). Surprisingly, shared environmental factors do not appear to have a relationship to ADHD symptoms.[28] In an Australian population-based control study, over 12,000 children with ADHD were compared to over 30,000 controls on maternal, pregnancy, and birth data.[29] Mothers of children with ADHD were significantly more likely to be younger, single, or to have smoked in pregnancy. Additionally, they had a higher level of induced labor, preterm labor, preeclampsia, or early term delivery. Antidepressant use in pregnancy is not related to ADHD,[30] and in an extensive review of prenatal factors in ADHD, Sciberras et al.[31] noted that carefully done prospective studies are needed to determine causality of these factors.

2 Genetics and environment work together to shape the brain, and there is an emerging picture of differences in brain structure, function, and connectivity that occur across the life span in individuals with ADHD. Cortical surface area is reduced in ADHD versus controls in both childhood and adulthood; in addition, the age of peak thickness occurs later in ADHD, with the most pronounced delay occurring in the prefrontal cortex.[32] Cortical thickness is also reduced in children with ADHD relative to controls, but when adults with ADHD remit, their cortical thickness is not different from controls.[33] There is evidence that the continued use of stimulants for the treatment of ADHD is associated with greater normalization of cortical thickness.[34] Reduced cerebellar volume is the most pronounced difference in ADHD versus controls.[35] The ENIGMA ADHD study obtained structural

MRI in 1,713 individuals with ADHD and 1,529 controls, both children and adults.[36] Subcortical structures (accumbens, amygdala, caudate, hippocampus, and putamen) were reduced in those with ADHD relative to controls, with effect sizes of around 0.2. Effects were larger in children than adults. In totality, the structural imaging data suggest ADHD is caused by a wide scale process affecting many regions of the brain.

2 Functional MRI has shown that the brains of children with ADHD fail to activate a network of regions involved in attention and impulse control relative to controls.[37] During inhibitory tasks, children with ADHD fail to activate the right inferior frontal cortex and anterior cingulate cortex. When performing attention tasks, children with ADHD have reduced activation in the basal ganglia, prefrontal cortex, and parietal lobe, while they have increased activation of cuneus. There is increasing interest in the role of the default mode network (DMN) in many psychiatric disorders.[38] The DMN consists of the medial prefrontal cortex, medial parietal lobe, or precuneus, as well as the posterior cingulate. These areas are active during the "resting state" when attention is not engaged; this system is actively suppressed during active attention. A lack of connectivity between the prefrontal cortex and precuneus is associated with failure of suppression of the DMN, causing lapses in attention and inhibitory control. Multiple studies have shown that both children and adults diagnosed with ADHD, DMN activity is not appropriately connected to the attention/control areas compared to controls.[38-40] Treatment with stimulants normalizes DMN activity.[39] Functional MRI can be used to assess general connectivity between a large number of brain regions. A major review showed that children with ADHD have stronger short-range connections (particularly with limbic areas) than controls, but reduced number of long-range connections in the attention and control systems of the brain.[41]

Overall, ADHD is a complex neurodevelopmental disorder involving an array of genetic and environmental risk factors, many of which are shared with other psychiatric disorders. Clinicians can help families to better understand ADHD and minimize its negative impact on outcomes. More background information regarding pharmacogenomics can be found in Chapter e6, "Pharmacogenetics."

CLINICAL PRESENTATION

3 TheAAP guideline for the diagnosis, evaluation, and treatment of ADHD in children and adolescents recommends an evaluation for any child between ages 4 and 18 years who presents with academic or behavioral problems and symptoms of inattention, hyperactivity, or impulsivity.[3] The *DSM-5* diagnosis in children 4 to 12 years old only requires at least six symptoms of inattention or hyperactivity and impulsivity causing impairment in more than one major setting (eg, home, school) for 6 months and an onset of symptoms before age 12. Only five symptoms are required for older adolescents and adults (age 17 and over).[1] Validated rating scales, such as the Connors Rating Scales—revised (CRS-revised) and the Vanderbilt ADHD diagnostic scale, are recommended for objective symptom ratings from parents and teachers in different age groups. (See Chapter e81 for more information.)[3-5] To make a diagnosis of ADHD, the clinician should rule out alternative causes of symptoms (eg, learning disability, situational stressor) and assess for other conditions that may coexist with ADHD including oppositional defiant and conduct disorders (CDs), Tourette disorder, ASD, and sleep and mood disorders.[1,3-5,42]

Preschoolers (3 to 5 Years)

Preschool-age onset of ADHD may be more likely in children with multiple risk factors including maternal smoking, lead exposure, iron deficiency, developmental delay, ASD, intellectual disability, or genetic loading.[43,44] The *DSM-5* diagnostic criteria for ADHD can be applied to preschool-age children, although it may be difficult to document symptoms in multiple settings with different caregivers if the child does not attend preschool.[1,3,12,44] Enrollment in a qualified preschool and a parent training program is often recommended. Both can help parents develop reasonable expectations for their child's development and foster the development of management skills for problem behaviors while diagnostic assessment is underway.

School Age (6 to 11 Years)

Most cases of ADHD are first realized during ages 6 to 9 years, with the child having difficulty academically and/or socially in school and at home. Most children have combined inattentive and hyperactive or impulsive symptoms that cause functional impairment. This period is crucial to the child's success in school, socialization, and the development of his or her sense of self; therefore, accurate diagnosis and treatment are critical. Comorbid oppositional defiant disorder (ODD), CD, and aggression are indicators that the child is at greater risk for issues with the criminal legal system and an SUD in adolescence.[8,10,45] This is the most well-studied age group, with strong data showing benefits of recognition and treatment with behavioral interventions and medications.[4,5]

Adolescents (12 to 18 Years)

Hyperactivity decreases in adolescents, and inattention and impulsivity are the more prominent. There may be fewer numbers of symptoms of ADHD in adolescence, but the symptoms present cause significant functional impairment.[1,8,10] Adolescents with ADHD are increasingly identified as "moody" or having a temper. They are easily overwhelmed by demands and may avoid tasks or approach multiple tasks in a disorganized manner.[8] Decision making is impaired (eg, discontinues ADHD treatment despite functional impairment) and decisions are made based on peer approval.[8] Higher rates of delinquency, substance and alcohol use, and psychiatric comorbidity have been documented in adolescents with ADHD compared with those without ADHD.[3,4,10,11,46] Assessment for substance use and risk of diversion must be considered before starting stimulant medication.[8,46] Speeding and increased motor vehicle accidents occur at higher rates in teens with ADHD compared to those without the disorder.[8,47]

Adults

The presence of multiple comorbid conditions, particularly CD or mood disorder, can increase the likelihood of ADHD chronicity into adulthood. *DSM-5* criteria for ADHD in childhood and adolescence also apply to adults. Inattentive symptoms are the most common and functionally impairing in adults, but hyperactive/restless and impulsive symptoms such as being overly talkative, impatient, and intrusive are experienced by many and are associated with higher rates of bipolar disorder and psychosis.[1,2,10,11,48] Cognitive deficits (eg, executive functioning, working memory, task prioritization, lower IQ) have been documented in adults with ADHD in addition to a greater risk for unstable relationships, unemployment, psychiatric hospitalization, and interaction with the criminal legal system compared with those without ADHD.[2,10,11,48] In 2017, the World Health Organization published a six-item questionnaire to update the Adult ADHD Self-Report Scale (ASRS) with *DSM-5* diagnostic criteria. This validated screening tool can be used as a first step to a more thorough diagnosis with an experienced clinician.[2,49] Gathering collateral information from family and friends is recommended to either support or refute the diagnosis.

Adult-Onset ADHD

Adult-onset ADHD is increasingly recognized although still controversial. A Brazilian study evaluated 5,249 youth in 1993 at age 11 and found 393 (8.9%) met criteria for ADHD. Evaluation of the group in 2015 at age 18 to 19 years revealed 492 (12.2%) youth who had no symptoms in childhood, now meeting criteria for ADHD.[50] Interestingly, the childhood-onset group was predominantly male and the young adult-onset group was predominantly female. Both groups had increased levels of impairment (eg, comorbidities, involved with the criminal justice system, suicide attempts) compared to those without ADHD. United Kingdom investigators studied 2,040 twins longitudinally between 1994 and 2015. In adulthood, 166 met criteria for ADHD and 111 of whom (67%) had no symptoms during childhood.[51] Adult-onset ADHD raises many questions about potential causes (eg, cannabis use, alcohol use, chronic anxiety), diagnostic categorization, and treatment. Is young adult-onset ADHD a different brain disorder with similar symptoms to childhood-onset ADHD; is the course different? More research is needed.

Complex ADHD

A person is said to have "Complex ADHD" when there is moderate-to-severe functional impairment, diagnostic uncertainty, coexisting conditions (eg, neurodevelopmental, mental health, medical, or psychosocial factors adversely affecting health and development), inadequate response to treatment or when functionally impairing symptoms present before age 4, or after age 12. The Society for Developmental and Behavioral Pediatrics developed this designation to encourage expert evaluation and treatment of these individuals beyond usual care.[52]

Clinical Presentation: ADHD

General

- Onset of symptoms must be before 12 years of age

Symptoms

- *Inattention:*
  - Often fails to give close attention to details or makes careless mistakes in schoolwork, at work, or during other activities (eg, overlooks or misses details, or work is inaccurate)
  - Often has difficulty sustaining attention in play activities or tasks (eg, has difficulty remaining focused during lectures, conversations, or lengthy reading)
  - Often has difficulty organizing tasks and activities (eg, poor time management, disorganized work, fails to meet deadlines)
  - Avoids tasks that require sustained mental effort (eg, schoolwork, reviewing lengthy papers, or preparing reports)
  - Often does not seem to listen when spoken to directly (eg, mind seems to wander)
  - Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace
  - Is easily distracted by extraneous stimuli (may include unrelated thoughts)
  - Is often forgetful in daily activities (eg, doing chores, returning calls, paying bills)
  - Loses things necessary for activities (eg, school materials, keys, wallet)
- *Hyperactivity and impulsivity:*
  - Often fidgets with hands or feet or squirms in seat
  - Often leaves seat when remaining seated is expected
  - Often runs about or climbs excessively at inappropriate times (in adolescents or adults may be limited to feeling restless)
  - Often has difficulty playing quietly
  - Often blurts out answers before a question is completed (also finishes the sentences of others; cannot wait for turn in conversation)
  - Often interrupts or intrudes on others; may take over what others are doing
- Six or more symptoms must be present for at least 6 months; significant impairment must be seen in two or more settings (eg, home and school); symptoms must be documented by parent, teacher, and clinician. Only five symptoms are required in older adolescents and adults (17 years of age and older)

Data from Reference 166.

TREATMENT

Stimulants are considered first-line therapy in most cases of ADHD; however, age, comorbid conditions, and patient/family preference impact treatment plan development. Pharmacotherapy should be considered whenever a thorough diagnostic assessment results in an ADHD diagnosis. ADHD-specific educational, cognitive, and behavioral interventions are recognized as necessary components of an overall treatment plan aimed at

symptom relief and optimal functioning. Several studies show combining medications with behavioral interventions produces the greatest symptom relief and the best outcomes.[2-4,17,53]

Desired Outcomes

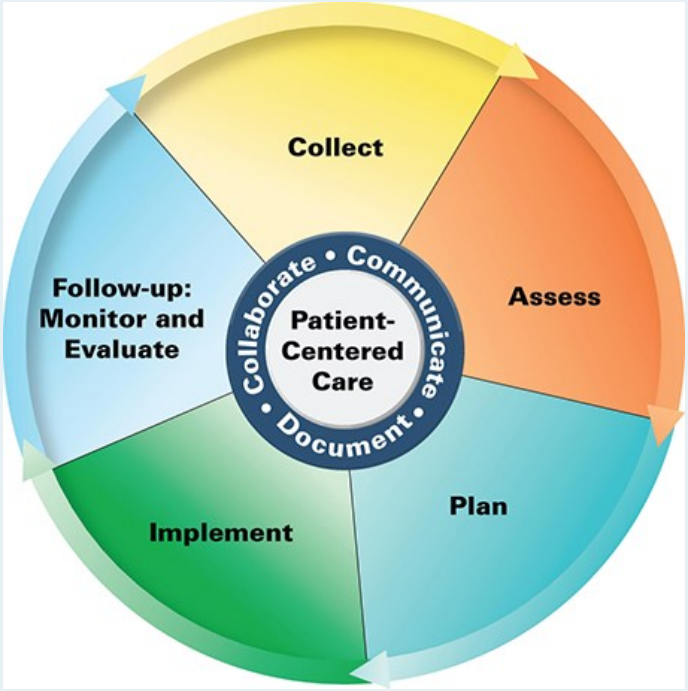
4 Specific goals of treatment or desired outcomes must be identified (eg, able to sit in chair for 20 minutes, completes homework assignments, or no longer blurts out comments in class without being called upon).[3,42] For adults, the desired outcome may be to read an entire newspaper before starting another project, improving safety while driving or successfully completing tasks on time at school or at work.[2,8,48]

Treatment for ADHD may decrease the rate of some serious injuries in youth. Investigators evaluated a large German healthcare database (reflecting 20% of the population) and found that in children with ADHD aged 3 to 17 years, treated with a stimulant or atomoxetine, there was no difference in overall injury rates requiring hospital admission compared to untreated children; however, there was a 34% decrease in severe brain injury in the treated group.[54] Similarly, an international review and meta-analysis of about 13,000 youth found that pharmacologic treatment in pediatric patients with ADHD likely has a protective effect, with a 10% reduction in the incidence of any unintentional injury. Of note, traumatic brain injury was excluded as an endpoint, given the potential to increase a patient's likelihood for being diagnosed with ADHD.[55]

Improvement in academic performance and on-task behavior in the classroom has been associated with stimulant treatment of ADHD.[56] A study of 930 young adults with ADHD found that treatment with pharmacotherapy (eg, stimulants and atomoxetine) was associated with significantly improved scores on higher education entrance exams compared to never-medicated peers.[57] Review of the Icelandic Medicines Registry and the Database of National Scholastic Examinations revealed that delayed initiation of pharmacologic treatment may be associated with academic decline among youth age 9 to 12 years, particularly in math.[58] Additionally, other studies have demonstrated improvement in math productivity, accuracy, and reading speed with methylphenidate treatment, although academic improvements were thought to be small compared to overall symptom improvement.[59]

PATIENT CARE PROCESS

Patient Care Process for Attention Deficit/Hyperactivity Disorder (ADHD)



Collect

- Patient characteristics (eg, age, gender, sex, pregnancy status)
- Social and family history (eg, foster care, single parent home, extended family involvement; marital status for adults)
- Substance use history (eg, cigarettes, cannabis, alcohol, methamphetamine, hallucinogens, cocaine, opioids, kratom, salvia)
- Dietary issues (eg, "picky" eater, gluten-sensitive, food allergies)
- Sleep patterns (eg, latency, duration, restless legs)
- Current medications including OTCs, herbal products, dietary supplements, and prior medications for ADHD
- Cardiovascular health history (eg, history of sudden death in family)
- Goals of treatment (eg, finish homework assignments or work projects, prevent injury, await turn in lines, positive peer/family interactions)
- Information on past and current co-occurring neuropsychiatric conditions (eg, Tourette disorder, CD, bipolar disorder, ASD, epilepsy)
- Objective data
    - Measure symptoms of ADHD with validated rating scales for children or adolescents (eg, Conners, Vanderbilt) and ADHD self-rating questionnaire for adults
    - Gather information on symptoms in multiple settings (eg, school, work, home)
    - Blood pressure (BP), heart rate (HR), respiratory rate (RR), height, weight, body mass index (BMI), growth chart data on percentiles based on general pediatric population
    - Labs including liver function tests (LFTs), electrolytes, renal function, fasting lipid panel, and HgA1c, thyroid tests if co-occurring anxiety or mood symptoms, ECG and/or echocardiogram if history reveals significant cardiovascular disease or sudden unexplained death in family member, and pregnancy status in females

Assess

- Number and predominance of symptoms (eg, are inattentive symptoms the only significant symptom?)
- Severity of symptoms (eg, hyperactivity, impulsivity, and inattention) and associated functional impairment
- Presence and severity of co-occurring conditions (eg, Tourette disorder, CD, bipolar disorder, ASD)
- Presence of active SUD in patient and family members
- Presence of adverse reactions from current medications (Tables 80-3 and 80-4)
- Ability/willingness to participate in nonpharmacologic treatment including psychosocial, cognitive, and behavioral interventions
- Identify barriers to adherence to pharmacotherapeutic interventions and participation in ongoing treatment (eg, cost, frequency of medication administration throughout the day, transportation challenges to follow-up appointments)

Plan*

- Medication therapy regimen including specific medication(s), dose, route, frequency, and duration (Tables 80-2 through 80-4 and Fig. 82-1)
- Monitoring parameters including efficacy (eg, decreased symptoms on rating scales) and safety (eg, heart rate, blood pressure, abnormal involuntary movements); frequency and timing of follow-up (Tables 80-3 and 80-4)
- Patient education (eg, purpose of treatment, dietary and lifestyle modification, medication-specific information, medication administration)

- Referrals to other providers when appropriate (eg, pediatrician, dietician)

Implement*

- Provide patient, parent, caregiver(s), teacher, partner education regarding all elements of treatment plan; education should be delivered in multiple forms (Table 82-1)
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up appointment for monitoring and pharmacotherapy dosage adjustment (Tables 80-1 through 80-3)

Follow-up: Monitor and Evaluate

- Significant improvement in ADHD symptoms (eg, inattention, hyperactivity, impulsivity)
- Presence of adverse effects (eg, insomnia/sedation, appetite change, increased or decreased HR)
- Presence of significant medication interactions (eg, fluoxetine and atomoxetine, or paroxetine and amphetamine salts)
- Patient adherence to treatment plan using multiple sources of information
- Re-evaluate dosage and tolerability every 1 to 3 months

**Collaborate with patient, caregiver(s), and other healthcare professionals.*

Nonpharmacologic Therapy

Educational, Psychosocial, Cognitive, and Behavioral Interventions

5 Education that ADHD is a biologic disorder with brain-derived causes is essential for destigmatizing ADHD and improving treatment acceptance. Parent training and behavioral interventions such as positive rewards for good behavior and structured limit setting are recommended as first-line interventions before medication trials in preschoolers (3- to 5-year-olds) with ADHD. Behavioral interventions for ADHD are described in Table 82-1. It is crucial to get parents, teachers, and clinicians involved to coordinate care and provide consistent behavioral management for the child at home and at school. Although methylphenidate has been found safe and effective for ADHD in 4- and 5-year-olds, behavioral interventions are recommended first by most clinicians and guidelines.[3,60] School-age children (6-11 years) also benefit from these behavioral interventions in addition to strategies, such as breaking up homework assignments into shorter, manageable segments. Although it varies by state, children and adolescents with ADHD may qualify for an individualized educational program (IEP) that allows for more time to take an exam, preferred seating, and modified work assignments.[3,4,45] It is noteworthy that most studies comparing behavioral intervention with stimulant therapy in youth found a much stronger effect on ADHD core symptoms from stimulants.[4,5,7,61] Combined behavioral and stimulant therapy resulted in greater improvements on academic and conduct measures in some studies with greater parent and teacher satisfaction ratings. Lower doses of stimulant were effective when behavioral interventions were administered according to several studies.[4,62]

TABLE 82-1

Cognitive, Behavioral, and Psychosocial Interventions for ADHD

Age	Description of Intervention	Typical Outcomes
Preschool and school age	Parent and family education on ADHD	Improved parental understanding and satisfaction
	Parent/caregiver training on behavioral management	Improved compliance with parental commands
	Classroom management instruction for teachers	Improved teacher satisfaction
Adolescent	Breakup homework assignments into manageable segments. Structured schedule; organizer	Completion of assignments improves; improved self-esteem and sense of self
Adolescent and adult	ADHD-specific cognitive behavioral therapy	Improved productivity and vocational success
	Metacognitive therapy	Improved relationships

ADHD, attention deficit/hyperactivity disorder.

Data from References [3,5,42,53,60,61, and 63].

5 Recommended behavioral interventions for adolescents and adults include keeping an external organizer (eg, smart phone, notebook with "to-do" lists) and breaking up activities into short, manageable tasks. Recognizing triggers for distraction and making a point of thinking before acting are useful interventions and are recommended during cognitive behavioral therapy (CBT) sessions designed to manage adult ADHD.[53,63] Controlled studies have shown that ADHD-specific CBT was more effective than psychoeducation and relaxation in adults with ADHD whose symptoms were only partially responsive to medication.[63] One study in 88 adults compared 12 weekly sessions (1.5 hour long) of manualized CBT administered with a long-acting formulation of methylphenidate or amphetamine salts to CBT alone and found greater benefit in ADHD symptoms, organizational skills, and self-esteem in the combination CBT and medication group at the end of 12 weeks. Of note, the CBT alone group continued to improve according to unblinded clinician assessment and self-report after 6 months of treatment.[53] Yoga, meditation, and some dietary supplements have been recommended for ADHD as well, but they should not take the place of more established effective treatments, such as medications and cognitive interventions.[61,64] External trigeminal nerve stimulation (eTNS) is FDA approved for pediatric patients with ADHD; however, it is not recommended by the AAP guidelines given lack of long-term safety and efficacy data.[3]

Dietary Interventions

Extensive research has evaluated dietary interventions for ADHD, primarily in children with some adolescent data. Omega-3 fatty acids are the most studied dietary intervention for ADHD. While studies have demonstrated variable impact on core ADHD symptoms, omega-3 supplementation is generally well tolerated and has demonstrated and effect size of approximately 0.3.[65] High eicosapentaenoic acid (EPA) to docosahexaenoic acid (DHA) ration may be associated with the largest effect.[65]

When iron and zinc are supplemented in youth with known deficiencies, the therapeutic benefit of stimulant therapy can be enhanced, frequently allowing lower effective doses.[66-68] Vitamin D may also improve symptoms of ADHD, particularly in youth with deficiencies according to a randomized double-blind trial in 96 children of mean age 9 years old.[69]

The role of gingko biloba, Memoemet syrup, and other complementary and alternative products has also been evaluated, with variable efficacy and tolerability.[5] While some evidence is promising, ongoing evaluations are needed before recommending these products, given variability in study design (eg, use of concomitant pharmacotherapy, rating scales to assess symptom improvement, and variability among products used). While it has

been anecdotally suggested that cannabidiol oil is beneficial for ADHD, it has not been rigorously studied for core symptoms and is not recommended.[3]

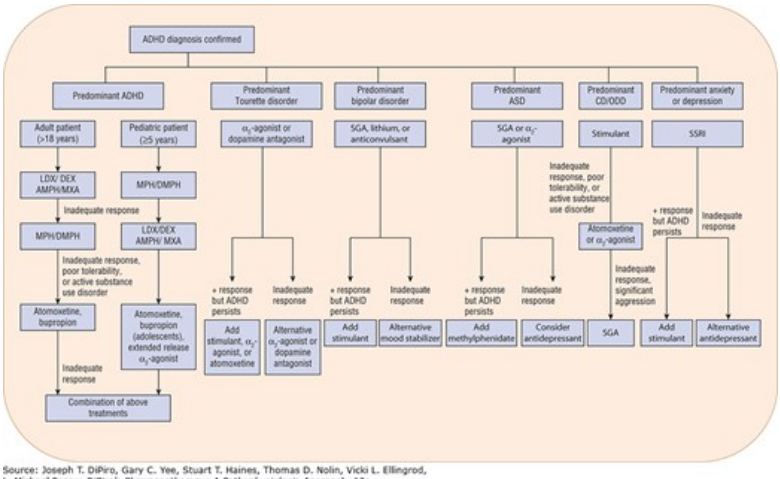
Although scientific evidence is lacking, there is a universal belief among families that the avoidance of sugar and artificial sweeteners improves ADHD symptoms. The attention paid to sugar avoidance and healthy diet is the more likely reason for improved behavior. An overall healthy diet with the proper balance of protein, fresh produce, and fiber is recommended.[12,17,61,66]

Pharmacologic Therapy

Figure 82-1 is an algorithm for medication selection in the treatment of ADHD.

FIGURE 82-1

Algorithm for medication selection in the management of attention deficit/hyperactivity disorder (ADHD). Treat predominant disorder first, reassess, and consider alternative or adjunct medications for optimal symptom control. (AMPH, amphetamine; DEX, dextroamphetamine; DMPH, dexmethylphenidate; LDX, lisdexamfetamine; MPH, methylphenidate; MXA, mixed amphetamine salts; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.) *(Data from References [2, 5, 45, 60, and 70–77].)*



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Several studies demonstrate the superiority of stimulants over other pharmacotherapies and behavioral interventions in alleviating core symptoms of ADHD in schoolage children, adolescents, and adults.[5,17,60] Although the United Kingdom's 2018 National Institute for Health and Care Excellence (NICE) guidelines recommend considering medication as early as 5 years of age, the clinician needs to weigh the risks of starting medication at an early age against the harm of delaying diagnosis and treatment.[3,4,42,44] Clinicians should educate all parents and caregivers regarding realistic expectations of medication therapy, goals of treatment, and the need for adverse effect monitoring in children. Adolescents and adults should be actively engaged in shared decision making regarding medication therapy and monitoring in an attempt to improve treatment persistence. Studies show higher rates of medication non-adherence in adolescents (50%) and adults (30%) compared to children (10–30%).[8] Preventing misuse and diversion of stimulants through frequent communication with patients and family, the use of a controlled substance agreement, and by tracking state-wide prescription medication monitoring databases is recommended.[2]

Stimulants

Stimulants are broadly divided into two main chemical classes: methylphenidate (includes dexmethylphenidate) and amphetamines (includes dextroamphetamine and mixed amphetamine salts). Methylphenidate and amphetamines block presynaptic dopamine and norepinephrine reuptake; amphetamines also increase dopamine release.[7,78] Both medications inhibit monoamine oxidase (MAO), amphetamines more potently than methylphenidate.[78] Because different stimulants work through slightly different mechanisms, the lack of response to one chemical class of stimulant (eg, methylphenidate or dexmethylphenidate) does not preclude response to another class (eg, mixed amphetamine salts, dextroamphetamine, or lisdexamfetamine).[7]

6 Stimulants are the most effective medication treatment options, with a pooled average effect size of 0.7 to 1.0. This is in contrast to nonstimulant medication treatment options such as guanfacine, clonidine, and atomoxetine whose effect sizes range from 0.35 to 0.7 signifying lower efficacy.[4,71,74] A systematic review and meta-analysis of 133 double-blind randomized controlled trials (81 in children and adolescents [*n* = 11,018], 51 in adults [*n* = 5,362], 1 in both) was conducted to assess the efficacy and tolerability of ADHD pharmacotherapy over 12 weeks in different age groups. Overall, the analysis showed stimulants were more effective than nonstimulant medications in all ages; however, stimulants were not as effective in adults compared to children and adolescents.[71]

Among children and adolescents, all approved ADHD medications were superior to placebo (clinician report), with amphetamines superior to methylphenidate, modafinil, atomoxetine, and guanfacine. Methylphenidate was superior to atomoxetine. Per teacher report, only methylphenidate and modafinil were superior to placebo. Guanfacine and amphetamines were less well tolerated than placebo, with amphetamines demonstrating a significant increase in systolic blood pressure and weight loss among children and adolescents, more than methylphenidate.

Because the largest analysis of clinical trial data showed overall better tolerability with methylphenidate in children and adolescents compared to amphetamine compounds, many clinicians recommend methylphenidate first-line in younger age groups. Nonetheless, amphetamine may be used first-line if patient and clinician prefer it.

In contrast to recommendations for pediatric patients, an amphetamine compound is preferred over methylphenidate as a first-line medication for adults based on the analysis of 12-week trials showing greater efficacy and acceptable tolerability of amphetamine compounds in adults versus pediatric patients.[71] In adults, amphetamines, methylphenidate, bupropion, and atomoxetine were superior to both placebo and modafinil. Modafinil did not demonstrate superiority in adults. With the exception of bupropion, all agents in adults were less well tolerated than placebo.[71][

Stimulant dosing should be titrated for maximum individual efficacy and minimum adverse medication reactions[4,5,7,42] (Table 82-2).

TABLE 82-2

Dosing of Stimulant Medications Used in the Treatment of ADHD

Stimulant	Duration of Effect	Initial Dose and Available Strengths	Usual Dosing Range; Maximum Dose
Methylphenidate C-II[a]			
Short-acting IR			
Ritalin, methylin, generics[b]	3-5 hours	5 mg two or three times daily; increase by 5-10 or 20 mg/day at weekly intervals; available as 5, 10, and 20 mg tablets; 5 mg/mL and 10 mg/5 mL solution	5-20 mg two or three times daily; Max: 60 mg/day
Dexmethylphenidate (Focalin) C-II	3-5 hours	2.5 mg every AM or twice daily; available as 2.5, 5, and 10 mg tablets	2.5-10 mg twice daily; Max: 20 mg/day
Intermediate-acting			
Ritalin SR[b]	3-8 hours	20 mg every AM; increase at weekly intervals; available only as 20 mg tablets	20-40 mg every AM or 40 mg every AM and 20 mg in the early afternoon; Max: 60 mg/day
Methylphenidate SR[b]			
Metadate ER[b]			

Methylin ER[b]			
Long-acting			
Ritalin LA 50% IR, 50% ER beads[b]	8-10 hours	20 mg every AM; available as 10, 20, and 30 mg	20-60 mg every AM; Max: 60 mg/day
Metadate CD 30% IR, 70% ER beads[b]	10-12 hours	20 mg every AM; available as 20, 30, and 40 mg	
Concerta (OROS controlled-release delivery)[b] *ER inner compartments coated with IR methylphenidate*	10-12 hours	18 mg every AM; available as 18, 27, 36, and 54 mg; 90% bioavailability of IR	27-72 mg every AM; Max: 72 mg/day
Daytrana methylphenidate transdermal system[b]	12 hours when worn for 9 hours	10 mg (12.5 cm^2) applied to clean, dry area on hip each morning and removed after 9 hours; available as 10, 15, 20, and 30 mg patches	10-30 mg (12.5-37.5 cm^2). Medication active for 3 hours after patch removal
Aptensio XR 40% IR, 60% ER	10-12 hours	10 mg; available as 10, 20, 30, 40, 50, and 60 mg capsules	10-60 mg every AM; Max: 60 mg/day
Cotempla XR-ODT 25% IR, 75% ER[b]	10-12 hours	17.3 mg every AM; available as 8.6, 17.3, 25.9 mg oral disintegrating tablets	17.3-51.8 mg every AM; Max: 51.8 mg/day
Quillivant extended-release suspension 20% IR/80% ER[b] *Must be reconstituted by pharmacist to 25 mg/5 mL concentration. Stable for 4 months after reconstituted*	10-12 hours	10-20 mg in AM; available as 25 mg/5 mL suspension *Only studied in 6- to 12-year-olds*	20-60 mg every AM; Max: 60 mg/day
QuilliChew ER 30% IR, 70% ER	10-12 hours	10-20 mg in AM; available as 20, 30, and 40 mg tablets	
Jornay PM[b] delayed-release, extended-release formulation *(administer at bedtime)*		20 mg in PM; available as 20, 40, 60, 80, and 100 mg capsules	20 mg every evening between 7 and 9 PM; Max: 100 mg/day
Adhansia XR 20% IR, 80% ER	12-16 hours	25 mg every AM; available as 25, 35, 45, 55, 70, and 85 mg capsules	25-85 mg every AM; Max: 70 (child) 85 (adult) mg/day
Focalin (dexmethylphenidate) XR 50% IR, 50% ER beads[b]	10-12 hours	5 mg every AM; available as 5, 10, 15, 25, 30, 35, and 40 mg capsules	5-40 mg every AM; Max: 30 mg/day (children and adolescents); Max 40 mg/day (adults)
Serdexmethylphenidate (SDX)/dexmethylphenidate (Azstarys) 70% SDX, 30% IR dMPH	10-12 hours	39.2/7.8 mg every AM; available as 26.1/5.2, 39.2/7.8, 52.3/10.4 mg capsules (SDX/dMTP)	26.1/5.2–52.3/10.4 mg every AM; Max 52.3/10.4 mg/day

Mixed Amphetamine Salts C-II			
Short-acting IR			
Adderall, mixed amphetamine generics[c] *(dextroamphetamine and levoamphetamine 3:1 ratio)*	4-6 hours	2.5-5 mg every AM to twice daily; available as 5, 10, 7.5, 12.5, 15, 20, 30 mg tablets	5-40 mg every AM or divided 2.5-20 mg twice daily; Max: 40 mg/day
Amphetamine C-II (dextroamphetamine and levoamphetamine ratio 1:1)[c](Evekeo)	4-6 hours	2.5-5 mg every AM to twice daily; available as 5 and 10 mg tablets	5-40 mg every AM or divided 2.5-20 mg twice daily; Max: 40 mg/day
Long-acting			
Long-acting XR (Adzenys XR-ODT) dextroamphetamine and levoamphetamine ratio 3:1[d]3.1 mg Adzenys ODT ~5 mg of Adderall XR	10-12 hours	3.1-9.4 mg every AM; available as 3.1, 6.3, 9.4, 12.5, 15.7, 18.8, extended-release oral disintegrating tablets	3.1-18.8 mg every AM; Max: 18.8 mg/day
Mydayis (triple-bead formulation of mixed amphetamine salts)[e]	12-16 hours	12.5-25 mg every AM; available as 12.5, 25, 37.5, 50, extended-release capsules	12.5-50 mg every AM; Max: 50 mg/day (adults), 25 mg/day (pediatrics)
Adzenys ER-oral suspension[d]	10-12 hours	1.25 mg/mL oral suspension	6.3-18.8 mg every AM; Max: 18.8 mg/day
Dyanavel XR 2.5 mg/mL Dextroamphetamine and levoamphetamine ratio 3.2:1[d]	10-12 hours	2.5 mg/1 mL oral suspension 2.5 mg of suspension ~4 mg of mixed amphetamine salts	5-20 mg every AM; Max: 20 mg/day
Xelstrym dextroamphetamine transdermal system	12 hours when worn for 9 hours	4.5 mg (4.76 cm^2) applied to clean, dry area on hip, upper arm, chest, upper back or flank and remove after 9 hours. Available as 4.5, 9, 13.5, 18 mg patches	13.5-18 mg (14.29-19.05 cm^2); Max:18 mg (19.05cm^2). Medication active for 3 hours after patch removal
Mixed amphetamine salts C-II Extended-release capsule (Adderall XR) dextroamphetamine and levoamphetamine ratio 3:1[d]	10-12 hours	5-10 mg every am; available as 5, 10, 20, 30 mg extended-release capsule	5-30 mg every AM; Max: 30 mg/day
Dextroamphetamine C-II			
Short-acting			
Dextroamphetamine generics[c]	3-5 hours	2.5 mg every AM to two or three times daily; available as 2.5, 5, 7.5, 10, 15, 20, and 30 mg tablets and 5 mg/5 mL solution	5-20 mg twice daily; Max: 40 mg/day
Dexedrine, Zenzedi[c]			
Intermediate-acting			
Dexedrine Spansule[d]	5-8 hours	5 mg every AM; available as 5 and 10 mg	5-30 mg every AM or 5-15 mg twice

			daily; maximum: 40 mg/day
Long-acting			
Lisdexamfetamine (Vyvanse)[d] (prodrug converted to dextroamphetamine)	10-12 hours	30 mg every AM; available as 20, 30, 40, 50, 60 capsules and chewable tablets and 70 mc capsules	Start at low end; titrate weekly to response; give in AM; Slower onset compared with other dextroamphetamine products

ER, extended release; IR, immediate release; OROS, osmotically released oral delivery system; ODT, orally disintegrating tablet; SR, sustained release; XR, extended release.

[a]The Drug Enforcement Administration label C-II, schedule II refers to significant abuse potential.

[b]Methylphenidate and dexmethylphenidate products are FDA approved in ≥6 years old.

[c]Immediate-release amphetamine and dextroamphetamine products are FDA approved in ≥3 years old.

[d]Extended-release amphetamine and dextroamphetamine products are FDA approved in ≥6 years old.

[e]Extended-release amphetamine products (immediate-release bead, small intestine dissolution bead, large intestine dissolution bead) are FDA approved in ≥13 years old.

Data from References 74, 79–81 and stimulant product package inserts or Daily Med.

Stimulants are available in diverse formulations (immediate release, delayed release, extended release, liquids, orally disintegrating tablets [ODTs] and patches) to allow for individualization based on a child's ability to swallow solid formulations and to individualize the duration of symptom control. Once-daily stimulant formulations are the preferred treatment for ADHD in most individuals due to convenience and better medication adherence.[5,74,81] Immediate-release formulations have the advantage of lower cost, less insomnia, and potentially fewer growth effects versus extended-release products; however, they also carry a higher risk of diversion and abuse.[2,45,74]

Administration of stimulant medications with food can delay the absorption and subsequently delay the onset of therapeutic effect by 30 minutes to 1 hour for immediate-release preparations and 1 to 2 hours for extended-release preparations.[74,81] Total bioavailability of stimulant can be decreased by 10% to 30% with coadministration of food, more so for beaded formulations of extended-release stimulant compared with osmotic controlled-release oral delivery system (OROS) methylphenidate or lisdexamfetamine.[17,74,81]

With immediate-release stimulants, most patients require a two or three times daily dosing schedule because of the short half-lives and duration of action of these medications (2-4 hours for methylphenidate and dexmethylphenidate and ~4 to 6 hours for dextroamphetamine or mixed amphetamine salts).[4,7] Medication response is maximal during the absorption phase, is evident in 15 to 30 minutes, and lasts 2 to 6 hours.[4,7]

Drug delivery systems of once-daily products (amphetamine aspartate, amphetamine sulfate, dextroamphetamine sulfate, and dextroamphetamine saccharate [Adderall XR]; methylphenidate [Concerta]; methylphenidate [Daytrana]; dexmethylphenidate [Focalin XR]; methylphenidate [Metadate CD]; and methylphenidate long-acting [Ritalin LA]) provide 8 to 12 hours of symptom control.[74,80] Concerta uses an oral OROS, whereas other oral preparations use combinations of immediate-release and extended-release beads.[74,80] Concerta is a nondeformable tablet, and it should not be given to children with gastrointestinal (GI) narrowing because of the risk of obstruction. Mydayis, a long-acting mixed amphetamine salt, provides up to 16 hours of symptom control in adolescents and adults via pH-dependent, triple bead technology.[79,82] Adhansia XR is an extended release methylphenidate capsule with a duration of action up to 16 hours.[80] A novel evening-dosed delayed-release/extended-release methylphenidate product (Jornay PM) has demonstrated improvement in early morning functional impairment among youth with ADHD. DELXIS technology utilizes a dual-layer (outer delayed-release, inner extended-release layer) microbead delivery system that surrounds an inner methylphenidate loaded core.[81,83,84]

Aztarys is a novel long-acting product composed of 30% immediate release dexmethylphenidate and 70% serdexmethylphenidate, a prodrug of dexmethylphenidate. A long-acting effect is produced through gradual bioactivation of serdexmethylphenidate to dexmethylphenidate in the lower GI tract.[85]

For patients with trouble swallowing pills, several alternative stimulant formulations are available. Methylphenidate transdermal system provides up to 12 hours of symptom control when worn for 9 hours.[74,80] Dyanavel XR, an extended-release amphetamine oral suspension, utilizes ion exchange chemistry (LiquiXR™ technology) to provide continuous release of amphetamine throughout the day.[86] Adzenys ER oral suspension (MXA) is a long-acting mixed amphetamine salt that has demonstrated efficacy in youth 6 to 17 years of age.[87] Cotempla XR-ODT (methylphenidate) and Adzenys XR-ODT MXA should also be considered for youth with trouble swallowing pills. Both products utilize micro-particle technology and have effects for 10 to 12 hours.[87,88] Lisdexamfetamine is a prodrug conjugated to an amino acid that requires cleavage during metabolism to the active dextroamphetamine. It has a longer time to onset of effect (~2 hours) but provides 10 to 12 hours of symptom control. As a prodrug, it has lower risk for misuse compared to other long-acting amphetamines where beads may be crushed or snorted. NICE guidelines recommend it as a preferred long-acting amphetamine formulation due to the extent of evidence for efficacy and safety in children, adolescents, and adults, and a lower misuse risk.[74,80]

Adverse Effects

The most common adverse effects of stimulants and their management strategies are listed in Table 82-3.[45,89] At least 15 cases of priapism (painful prolonged erection), associated with stimulant use, have been reported to the FDA in males with a mean age of 12.5 years. A few cases of priapism have been reported with atomoxetine, and all cases require immediate medical attention.[45,90] The FDA has received at least 51 reports of skin discoloration associated with the methylphenidate transdermal system, also known as chemical leukoderma, that may not be reversible.[74]

TABLE 82-3

Stimulant Adverse Medication Reactions and Their Management

Adverse Reaction	Recommendation/Management Strategy
Common	
Reduced appetite, weight loss	Give high-calorie meal when stimulant effects are low (at breakfast or at bedtime) or consider cyproheptadine at bedtime
Stomach ache	Administer stimulant on a full stomach; lower dose if possible
Insomnia	Give dose earlier in the day; lower the last dose of the day or give it earlier; consider a sedating medication at bedtime (guanfacine, clonidine, melatonin, or cyproheptadine)
Headache	Divide dose, give with food, or give an analgesic (eg, acetaminophen or ibuprofen)
Rebound symptoms	Consider longer-acting stimulant trial, atomoxetine, or antidepressant
Irritability/jitteriness	Assess for comorbid condition (eg, bipolar disorder); reduce dosage; consider mood stabilizer or second-generation antipsychotic
Uncommon to Rare	
Dysphoria	Reduce dosage; reassess diagnosis; consider alternative therapy
Skin discoloration (chemical leukoderma)	Counsel regarding risk before using methylphenidate patch
Zombie-like state	Reduce dosage or change stimulant medication
Tics or abnormal movements	Reduce dosage; consider alternative medication
Priapism (painful erection)	Obtain medical assistance immediately; consider alternative treatment
Hypertension, pulse fluctuations	Reduce dosage; change medication
Hallucinations	Discontinue stimulant; reassess diagnosis; mood stabilizer and/or antipsychotic may be needed
Peripheral vasculopathy, including Raynaud's phenomenon	Obtain medical assistance if severe digital changes observed; consider reducing dosage or alternative medication

Data from References [45, 60, 71, 74, and 89-92.]

Psychiatric, cardiac, and growth effects of stimulants have been extensively studied with key data and recommendations in the sections below.

Psychiatric

Although considered rare, the FDA has added warnings to the labeling of all ADHD medications (ie, stimulants, atomoxetine, α_2-adrenergic agonists) regarding three broad categories of psychiatric adverse effects: psychosis, mood disturbance (ie, irritability, lability, or depression), and severe anxiety

or panic attacks. Treatment-emergent psychosis is estimated to occur in approximately 1.5% of youth with ADHD treated with stimulant medications based on placebo-controlled trials.[45] Hallucinations involving visual or tactile sensations of insects, snakes, or worms were typical in children, with adolescents and adults experiencing hallucinations and delusions.[93] Multimodal Treatment Study of Children with ADHD (MTA), analyzing available data on the emergence of psychosis in 509 youth diagnosed with ADHD at age 7 to 9 years, showed that 5.1% reported psychosis which was not statistically different than 3.9% of the 276 local normal controls who reported psychosis over the same 10-year follow-up period. Therefore, investigators did not correlate stimulant use or an ADHD diagnosis in either group with the emergence of psychosis, but frequent cannabis use was associated with increased risk of psychosis in both groups.[94]

Sadness from stimulants may in part be genetically mediated, as an association was found in 77 youth taking immediate-release methylphenidate and two single nucleotide polymorphisms (SNPS) in the gene encoding for carboxylesterase (CES1), which may impact stimulant metabolism.[95] There is also evidence to suggest that preschool-aged youth are more susceptible to sadness, irritability, and mood lability with stimulant treatment compared with adolescents and adults.[3,45,89]

Literature reviews describe treatment-emergent mania and psychosis with atomoxetine, primarily in those with underlying bipolar disorder or depression. Labeling for atomoxetine includes a warning of increased suicidality largely because of its mechanism of action that is similar to antidepressants. A worldwide analysis of clinical trial and post-marketing data show no increase in suicidality (hazard ratio of 0.96).[96] Both stimulants and atomoxetine/viloxazine have the potential to cause or exacerbate mania, anxiety, panic attacks, or depression. In addition, stimulants and atomoxetine should not be given to manage attention in individuals with a primary psychotic illness such as schizophrenia or schizoaffective disorder due to the high risk of worsening psychosis.[45,96] Clonidine and guanfacine are much less likely than stimulants or atomoxetine to cause psychosis, mania, or anxiety, but treatment-emergent psychosis, irritability, depression, and nightmares have been reported.[97] When psychiatric adverse effects occur, dose reduction or cessation of therapy and supportive treatment is recommended.[45]

Cardiac

Stimulants, atomoxetine, viloxazine, and α_2-adrenergic agonists have well-described cardiac and cardiovascular adverse reactions that are not significant for most youth, but can be intolerable in some, particularly in those with existing cardiac/cardiovascular disease.[45,98] Clinical trial data show that children who take stimulants for ADHD can have an increased heart rate by 3 to 10 beats/min and/or increased systolic or diastolic blood pressure by 2 to 14 mm Hg.[45,98] To explore the extent of cardiac adverse reactions more thoroughly, investigators used ECG and echocardiography to evaluate cardiac function in 58 children (ages 6-18 years old) with ADHD diagnosed, for at least 6 months, who were taking OROS methylphenidate (mean dose 39.40 mg or 0.93 mg/kg/day) and compared them to 58 matched control group children diagnosed with ADHD but not yet started on medication. Overall no significant differences were found in terms of blood pressure or ECG findings including QTc measurements; however, youth taking methylphenidate had lower E'septal values on echocardiography.[99] This difference was considered within normal limits and not indicative of cardiac dysfunction.

Clinical trial and post-marketing surveillance data shows atomoxetine treatment has been associated with increased heart rate at an average of approximately 5 beats/min and increased systolic or diastolic blood pressure of approximately 12 mm Hg. An Eli Lilly cardiovascular safety review showed 8% to 10% of patients taking atomoxetine had more significant increases in pulse at greater than or equal to 20 bpm and increase in systolic and/or diastolic blood pressure of greater than 15 to 20 mm Hg.[96] Clinical trial data demonstrate viloxazine treatment is associated with a greater than or equal to 20 beats/min increase in heart rate and greater than or equal to 15 mm Hg increase in diastolic blood pressure. Heart rate and blood pressure should be monitored prior to the initiation of treatment, following dose increases, and throughout treatment.[100] Clonidine and guanfacine may cause dose-related bradycardia and lowered blood pressure in youth, which may prevent upward titration in addition to modest widening of the QTc interval (5-7 msec) that warrants monitoring, particularly if the child takes another agent known to prolong QTc such as an antidepressant or antipsychotic.[45,97]

A 9.5-year prospective cohort study of children with ADHD found that, although rare, adverse cardiovascular events were twice as likely to occur in stimulant users as in nonusers.[101] There were 111 cardiovascular events in the 8,300 children with ADHD included in this analysis with hypertension, heart disease not otherwise specified, and cardiovascular disease not otherwise specified comprising 62% of adverse cardiac events, while arrhythmias comprised 23%, and cardiac arrest accounted for less than 1%.[45] The same investigators looked at national rates of stimulant use (n =

714,258) and found 1.8 times greater risk of cardiovascular events in those taking stimulants with greater risk seen with higher doses compared with lower doses.[101]

Overall, stimulant products should be used with caution in pediatrics and in adults with known structural cardiac abnormalities. The American Heart Association recommends careful screening of all children and adolescents prior to initiating pharmacologic therapy for ADHD, including a medical and family history and physical examination.[45] Before starting pharmacotherapy for ADHD in youth or adults, the clinician should consider a baseline electrocardiogram (ECG) and consultation with a cardiologist if past medical history or family history suggests cardiovascular disease.[3,98,99]

Growth

The impact of ADHD medications on growth has been investigated extensively over the past 40 years as dose-dependent growth deficits of 1 to 1.4 cm/year have been observed with short-term stimulant treatment, mainly in the first 2 years. Weight deficits are more prominent with a mean 3 kg (6.6 lbs) weight decrease in the first year of treatment and 1.2 kg (2.6 lbs) weight decrease in the second year of treatment according to the MTA data.[102] Long-term studies on stimulants have reported divergent effects on growth, with many studies showing no clinically significant height deficits by adulthood. MTA study investigators assessed the largest cohort of children with ADHD ranging from 7-9 years old to 25 years old ($n = 515$) and compared them to classmates without ADHD ($n = 258$). These authors reported an overall adult height deficit of 4.7 cm among those consistently taking stimulant medication compared to those not taking a stimulant. Growth deficits were less when stimulants were taken inconsistently. Those taking stimulants consistently were 2.36 cm ± 1.13 cm shorter than those in the “inconsistent” group. Proposed mechanisms of stimulant effects on growth include alterations in growth hormone or growth factor, decreased thyroxine secretion, and suppression of appetite leading to reduced caloric intake.[45,102]

If symptoms can be managed with medication during weekends or summers, a medication-free trial may be considered every year.[45] Time off stimulant lessens stimulant growth suppressant effects, but evidence is lacking to firmly determine the impact of medication holidays on growth.[5,102] Consideration must be given to the risks of untreated ADHD symptoms on learning, socialization, and self-image while off stimulant therapy when determining the frequency and duration of the medication-free trial.[7,103] Medication dosage often varies from year to year, largely because of age-related pharmacokinetic changes. As a child develops, hepatic metabolism slows, and volume of distribution increases.[7]

Other

Cases of stimulant-induced peripheral vasculopathy, including Raynaud’s phenomenon, have been reported and are related to the peripheral release of catecholamines, resulting in vasoconstriction. Symptoms are typically intermittent and mild but can include digital ulceration and/or soft tissue breakdown. A retrospective, case–control study demonstrated that among children treated with stimulants, there was a significant association between the development of Raynaud’s phenomenon and past or current use of stimulants.[104] This risk is dose-dependent, with symptoms typically resolving after dose reduction or discontinuation of the medication.[92,105] Additionally, there is a case report of dose-dependent Raynaud’s phenomenon with atomoxetine use.[106] Close monitoring for digital changes is necessary during treatment with stimulants, α_2-adrenergic agonists, and atomoxetine/viloxazine. Rheumatology consultation may be required for some individuals.

Nonstimulants

Compared to the simulants, nonstimulant medications used for the treatment of ADHD are less effective alternatives than simulants in both children and adolescents. However, for most of these agents, the FDA has approved them both as monotherapy and as adjuncts to stimulants in children and adolescents for improving overall response and for managing behavioral symptoms and insomnia associated with ADHD. Some have also received FDA for the treatment of ADHD in adults. Potential advantages of non-simulants relative to stimulants include reduced potential for physical dependence or misuse, less potential for growth effects, and less sleep disturbance.[45] See Table 82-4 for dosing. Antipsychotic use is primarily for symptoms related to comorbid aggression, mood disorders, tics, or irritability associated with ASD and not for the core symptoms of ADHD.

TABLE 82-4

Dosing and Adverse Medication Reaction Monitoring of Nonstimulant Medications Often Used in ADHD

	Dosing Range and Titration Schedule	Adverse Reaction Monitoring
Serotonin norepinephrine reuptake inhibitors		
Atomoxetine (Strattera)	≤70 kg (154 lb): start at 0.3-0.5 mg/kg every AM or twice daily, maximum: 1.4 mg/kg/day; ≥70 kg (154 lb): start at 40 mg every AM or divided twice daily, maximum: 100 mg/day	Nausea, anorexia, ↑ blood pressure, ↑ pulse, insomnia, fatigue, sedation, severe liver injury (rare), suicidality
Viloxazine (Qelbree)	6-11 years: start at 100 mg/day. 12-17 years: start at 200 mg/day. Titrate in 100 mg increments/week, maximum: 400 mg/day	Nausea, vomiting, decreased appetite, sedation, insomnia, irritability, ↑ blood pressure, ↑ pulse, suicidality
Bupropion (Wellbutrin SR, XL)	50-300 mg/day; 3 mg/kg/day by end of week 1; can increase to 6 mg/kg/day or maximum of 300 mg/day as tolerated	Nausea, insomnia, rash, tics; dose-related risk of seizures
Antipsychotics (for comorbid aggression, mood disorders, tics, or irritability associated with ASD)		
Aripiprazole (Abilify)	2-5 mg daily; can titrate weekly as tolerated to response (usual range: 5-20 mg/day)	Nausea, restlessness, insomnia extrapyramidal symptoms, dizziness, sedation
Haloperidol[a] (Haldol)	0.5-1 mg twice daily; can titrate every 3-4 days as tolerated to response (usual range: 0.5-5 mg/day)	Extrapyramidal symptoms, dizziness, ↑ serum prolactin, sedation
Olanzapine[a] (Zyprexa)	2.5-5 mg every day; can titrate every 3-4 days as tolerated to response (usual range: 7.5-15 mg/day)	Sedation, severe weight gain, restlessness, extrapyramidal symptoms
		Diabetes, marked hyperlipidemia (never a first-line treatment)
Quetiapine[a] (Seroquel)	25-50 mg twice daily; can titrate every 3-4 days as tolerated to response (usual range: 200–600 mg/day)	Sedation, dizziness, weight gain, diabetes, hyperlipidemia
Risperidone[a] (Risperdal)	0.25-0.5 mg twice daily; can titrate every 3-4 days as tolerated to response (1-4 mg/day)	Extrapyramidal symptoms, dizziness, ↑ serum prolactin, decreased skeletal bone mass, hepatotoxicity, weight gain
		Diabetes, hyperlipidemia
Ziprasidone[a] (Geodon)	10-20 mg twice daily; can titrate every 3-4 days as tolerated to response (usual range: 40-160 mg/day)	Nausea, restlessness, insomnia extrapyramidal symptoms, sedation, QTc prolongation
Others		
Bupropion (Wellbutrin SR, XL)	50-300 mg/day; 3 mg/kg/day by end of week 1; can increase to 6 mg/kg/day or maximum of 300 mg/day as tolerated	Nausea, insomnia, rash, tics; dose-related risk of seizures
Alpha-2 adrenergic agonists		
Clonidine (Catapres) or	0.05 mg two or four times daily; can increase as tolerated to 0.1-0.4 mg/day. For	Sedation, dizziness, heart block (check ECG),

clonidine extended-release XR (Kapvay)	XR, give 0.1 mg at bedtime; may increase by 0.1 mg weekly; maximum: 0.4 mg/day given twice a day if dose >0.2 mg/day	constipation, headache, upper abdominal pain
Guanfacine (Tenex) or guanfacine extended-release XR (Intuniv)	0.5 once or twice daily; can increase as tolerated to 1-4 mg/day; Max: 4 mg/day in children/adolescents	Same as above with potentially lower risk of sedation. Effective dose higher in heavier children
	For XR, give 1 mg in the AM; titrate weekly to response; Max: 4 mg/day in children; 7 mg/day in adolescents	

[a]Short-term use (1-4 months) only for severe aggression associated with ADHD; may be longer if comorbidity such as bipolar disorder, Tourette disorder, or autism spectrum disorder.

ADHD, attention deficit/hyperactivity disorder; ASD, autism spectrum disorder; ECG, electrocardiogram; SR, sustained release; XL, extended length.

Data from References 42, 45, 97, 100, 105, and 107.

Atomoxetine

Atomoxetine is a selective norepinephrine reuptake inhibitor that should be taken in divided doses in the morning or late afternoon by children for improved tolerability.[108] Adults can take it once daily, usually in the morning.[108,112] Placebo-controlled, short-term trials (6-12 weeks) have shown that atomoxetine is effective in reducing ADHD symptoms in children, teens, and adults, and long-term studies show ongoing benefit and safety for children and adolescent responders out to 4 years.[96,97,109,112] A controlled trial comparing atomoxetine, OROS methylphenidate, and placebo over 6 weeks in 6- to 16-year-old patients showed that both medications were significantly better than placebo at improving ADHD symptoms, but OROS methylphenidate was superior to atomoxetine.[108,112] There was evidence for a preferential response to atomoxetine over stimulants in some individuals.[108]

Atomoxetine has a significantly slower onset of therapeutic effect than stimulants (2-4 weeks vs 1-2 hours with an effective stimulant dose), and full benefit may not be seen for 6 to 12 weeks.[108,109] The practice of combining atomoxetine with a stimulant in partially responsive patients is based on limited data from open trials and case series describing fewer late-day rebound effects and better sleep when atomoxetine is given in the evening; however, the adverse effects are additive.[108,109]

Possible adverse effects of atomoxetine and their management are similar to those of stimulants, including upset stomach and psychiatric and cardiac adverse effects (see Table 82-4 and "Psychiatric" and "Cardiac" sections). Although atomoxetine has less potential for growth suppression compared with stimulants, it has a greater risk of fatigue, sedation, and dizziness compared with stimulants or bupropion. Studies show that adults experience overall similar adverse effects as youth but they are less likely to report decreased appetite and are more likely to report urinary hesitation/retention and sexual adverse reactions (decreased libido and erectile disturbances) compared to youth.[109] Unlike stimulants, atomoxetine labeling includes a bolded warning of potential severe liver injury based on two cases (one adult, one child) of hepatic injury leading to transplant. A comprehensive safety review over 10 years described 133 cases of liver injury "possibly" related to atomoxetine, with liver functioning returning to normal after atomoxetine discontinuation. Although hepatotoxicity is considered rare, patients and families should be counseled to report signs of liver injury including dark urine, jaundice, or right upper quadrant pain.[96,109]

Viloxazine

Viloxazine is a selective norepinephrine reuptake inhibitor, FDA approved for patients 6 to 17 years with ADHD. Compared to atomoxetine, viloxazine is a less potent inhibitor of the norepinephrine transporter. In addition to norepinephrine reuptake inhibition, viloxazine increases 5-HT levels in the prefrontal cortex via modulation of serotonin receptors.[110] Viloxazine extended release capsules are administered once daily in the morning and can be opened and sprinkled onto applesauce.[100]

Improvement in ADHD symptoms was apparent at week 1 in clinical trials, suggesting a possible quicker onset of effect compared to atomoxetine.[111-

[113] Given viloxazine's unique mechanism of action, there is interest in evaluating its role for comorbid depressive and anxiety symptoms.[110] Notably, viloxazine is a strong CYP1A2 inhibitor.[100]

The most common adverse effects associated with viloxazine include somnolence, decreased appetite, nausea/vomiting, insomnia, and irritability.[100] Changes in heart rate and blood pressure should be monitored after initiation and as the dose is titrated (see Table 80-4 and "Cardiac" section). Viloxazine, like atomoxetine, has a boxed warning for emergence of suicidal thoughts and behavior.[100]

α_2-Adrenergic Agonists

Guanfacine and clonidine are central α_2-adrenergic agonists, acting both presynaptically to inhibit norepinephrine release and postsynaptically to increase blood flow in the prefrontal cortex, which enhance working memory and executive functioning. Pharmacologically, both of these medications affect a multitude of neurotransmitter systems, including catecholamine, indolamine, and α_2-adrenergic receptors on parasympathetic neurons, opioids, imidazole, and amino acid systems.[78,97]

7 Guanfacine has a longer elimination half-life and duration of action (18 hours) compared with clonidine (12 hours), and its greater selectivity for the α_{2a}-adrenergic receptor, compared with clonidine, imparts less sedation and dizziness.[97] Clonidine and guanfacine are not as effective as stimulants for monotherapy treatment (effect size 0.22-0.58 vs 0.8-1.2 for stimulants).[97] In addition to being approved as monotherapy, extended-release clonidine and guanfacine are FDA approved as adjuncts to stimulants in children and adolescents. Therefore, both are prescribed frequently as adjuncts to reduce disruptive behavior, control aggression, or improve sleep in youth.[5,97] Neither has been studied sufficiently for ADHD in adults.

Guanfacine XR can be given once daily during monotherapy while clonidine XR should be given twice daily for optimal symptom coverage. Both are considered acceptable second-line agents for children and adolescents unresponsive to or unable to tolerate stomach upset or insomnia with stimulant medications. Extended-release guanfacine and clonidine are more sedating than stimulants or atomoxetine; therefore, sleepiness during the school day requires careful monitoring.[97] Immediate-release α_2-adrenergic agonists are increasingly used to treat symptoms of ADHD in adolescents within the criminal legal system and adults due to no risk of physical dependence and potential benefits in controlling aggression and impulsivity, but this practice requires further study.[114]

The most common adverse medication reactions of clonidine and guanfacine are dose-dependent sedation, hypotension, and constipation.[4,5,97] The sedation seen with treatment usually subsides after 2 to 3 weeks of therapy.[97] Clinical trials show a mean decrease of 3 to 5 mm Hg in blood pressure with mean heart rate decrease of 3 to 5 beats/min. Both heart block and sudden death have been reported rarely with α_2-adrenergic agonists, and further analysis revealed that these events occurred in the context of polypharmacy and/or congenital heart malformation. Regardless, prescreening for existing cardiac problems and increased monitoring when combining medications is warranted.[45,97] Peripheral vasculopathies are well documented with α_2-adrenergic agonists, given their effects on peripheral catecholamine release; however, close monitoring and consideration of a rheumatology referral is warranted should these adverse events occur.[92,105]

Bupropion

Bupropion, a monocyclic antidepressant, is a weak dopamine and norepinephrine reuptake inhibitor with no significant direct effect on serotonin or MAO. Its active metabolites augment noradrenergic and dopaminergic function. While not FDA approved for the treatment of ADHD, investigations with bupropion in children and adolescents demonstrated efficacy greater than placebo in two controlled trials and efficacy comparable with methylphenidate in two separate controlled trials ($n = 18$ and $n = 44$).[114] Bupropion has been found beneficial for adolescents with depression and ADHD and causes less appetite suppression and weight loss compared with stimulants, but it has a greater risk of seizures.[114] An analysis of data evaluating bupropion for ADHD in adults show it is significantly more effective than placebo and modafinil but less effective than methylphenidate or amphetamine salts.[71]

Bupropion's adverse effects include nausea, which can resolve over time or with slower dosage titration, and rash, which can require discontinuation of therapy if severe (see Table 82-4). Due to an elevated risk of seizures, bupropion should not be used in patients with a seizure or eating disorder.

Additionally, it can cause or exacerbate tics and should be dosed early in the day to minimize the risk of insomnia.[114]

Lithium and Valproate

Lithium or valproate can be used to control aggression and explosive behavior in patients with a co-diagnosis of ODD or CD, or those who are not responsive or are only partially responsive to treatment with a stimulant. Given the symptoms heterogeneity and overlap between some mental illnesses, some patients actually have childhood-onset bipolar disorder or combined ADHD–bipolar disorder.[77] Limited data show lithium is ineffective for ADHD alone but it is more likely effective when bipolar disorder coexists with ADHD.[77] Valproate is the most well-studied antiseizure medication (ASM) for aggression associated with ADHD. Dosing starts in low divided doses with titration over 1 to 2 weeks to therapeutic response.[115] See Chapter 75, "Epilepsy," for a more extensive discussion regarding adverse events for ASMs and Chapter 89, "Bipolar Disorder," for lithium.

Antipsychotics

First-generation antipsychotics such as chlorpromazine and haloperidol can improve symptoms of hyperactivity and impulsivity in children with ADHD, but their negative effects on learning, cognitive functioning, and the significant risk of extrapyramidal adverse reactions (eg, dystonia and tardive dyskinesia) limit their usefulness.[107]

Second-generation antipsychotics such as risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole have been used to control severe aggression in refractory cases of ADHD, particularly if CD or bipolar disorder coexists.[9,115] In general, the second-generation antipsychotics pose a lower risk of extrapyramidal adverse reactions compared with conventional agents, but they can cause metabolic adverse reactions such as hyperlipidemia, hyperglycemia, and weight gain in addition to hyperprolactinemia.[107] Ziprasidone has the lowest risk of metabolic adverse reactions among these second-generation antipsychotics. Risperidone is the most well studied for aggression associated with ADHD,[70] but because it has the most potent dopamine antagonism and poses the highest risk of hyperprolactinemia and associated early puberty, gynecomastia, galactorrhea, amenorrhea, and decreased bone density.[70,107,116] Aripiprazole is least likely to elevate prolactin due to its dopamine agonist effects.[107] See Chapter 87, "Schizophrenia," for a more thorough discussion regarding the antipsychotics and their adverse effects.

Comorbidity and Polytherapy in ADHD

8 As previously stated, individuals with ADHD often present with comorbid conditions (Fig. 82-1), which may make polytherapy attractive or necessary. But this can complicate monitoring of therapy, because if multiple medications are started simultaneously, it is impossible to determine the impact of each medication. In general, the predominance and urgency of symptoms guide the medication selection process. For example, if a child presents as severely anxious or depressed with associated attentional problems, then an antidepressant should be initiated first with monitoring to determine if attentional symptoms improve.[4,76] When a child presents with severe ADHD and associated anxiety or depression, a stimulant should be initiated to treat the more severe ADHD. If ADHD symptoms improve significantly, but anxiety or depression persists, then an antidepressant can be added.[4,76] Studies show that stimulants do not routinely make anxiety disorders worse, but they might not improve symptoms either.[7,76]

Bipolar Disorder

9 Childhood bipolar disorder may be difficult to distinguish from ADHD because inattention, hyperactivity, and impulsivity are common with both conditions. When ADHD is diagnosed in an individual with bipolar disorder, the mood must be stabilized first with lithium, an ASM, or a second generation antipsychotic before considering an ADHD-specific treatment.[77,115]

Autism Spectrum Disorders

Autism spectrum disorders are estimated to occur in 20% to 50% of youth with ADHD and 30% to 80% of youth with ASD exhibit symptoms of inattention.[117] Impairments can range from mild to severe with poor language development, poor social skills, sensory over-responsivity, emotional dysregulation, inattention, impulsivity, irritability, oppositional behavior, and aggression.[117] There are few studies to guide treatment of ADHD in individuals with ASD. A Cochrane review of four US randomized controlled trials involving 113 youth with ASD and ADHD treated with methylphenidate for 4 to 6 weeks demonstrated short-term benefit for hyperactivity and possibly inattention in children who could tolerate methylphenidate. Of note,

youth who could not tolerate a test-dose were excluded, and there was no evidence that methylphenidate was helpful for social interaction or stereotypical behaviors.[118]

Available evidence shows that stimulants can be an effective treatment strategy in pediatric patients with ASD, but are less effective and less well tolerated for managing ADHD in youth with more severe forms of ASD or with comorbid intellectual disability.[117-119] Atomoxetine was only slightly better than placebo in managing ADHD symptoms in children with ASD according to a 8-week controlled trial that included 97 children between the ages of 6 and 17 years.[72] Clonidine and guanfacine have small, uncontrolled studies only showing benefit in improving attention and decreasing aggressive/impulsive behavior in children with ASD.[117]

The AAP ASD guidelines recommend starting with a low-dose stimulant and monitoring carefully for worsening stereotypies, obsessional symptoms, sleep difficulties, poor appetite, depressive symptoms, social withdrawal, irritability, or the emergence of seizures.[119] If the stimulant is ineffective or poorly tolerated guidelines recommend atomoxetine, particularly if comorbid social anxiety, or an α_2-adrenergic agonist.[117]

Seizure Disorders

Patients with ADHD are two to three times more likely to experience seizures than age-matched peers, and ADHD is the most common comorbidity in youth with epilepsy.[120] While some reviews have demonstrated seizure aggravation and EEG changes related to stimulant treatment, most studies show methylphenidate is safe and effective for managing ADHD in youth with epilepsy.[120-122] A retrospective review of 18,000 Medicaid-enrolled youth with epilepsy and ADHD treated with a stimulant did not demonstrate an increased risk for seizure-related hospitalizations among current or former stimulant users.[123] Given the risk for stimulants to lower the seizure threshold, all individuals should be stabilized and seizure-free on an ASM prior to initiation of the stimulant.[76,123,124] Notably, valproate use may worsen attentional issues in children with ADHD. Additionally, antiseizure medication polytherapy may be associated with an increase in behavioral problems, although this may be attributed to more severe underlying neurologic symptoms.[120] If new or worsening seizures are suspected, discontinuation of the stimulant should be considered and cautiously reintroduced once stabilized.[60] The impact of atomoxetine, viloxazine, clonidine, and guanfacine on seizure frequency requires further study.[120,124] Bupropion use is contraindicated in patients with a seizure disorder.

Substance Use Disorders

The prevalence of SUD in adults with ADHD is estimated nine times higher than in those without ADHD.[125] Genetics, age (14- to 25-year-olds), psychosocial factors, and comorbidities all influence one's risk for SUDs,[46,126] with ADHD itself being a known risk factor for the development of an SUD. Among individuals with ADHD, persistent symptoms, a diagnosis later in adolescence or adulthood, and co-occurring diagnoses of ODD/CD are known predictors of developing an SUD.[127] A large Danish population-based cohort study (N = 13,116) investigated risk factors for SUD development among individuals with ADHD. Results indicated that age greater than or equal to 13 years at first ADHD diagnosis (OR = 3.28) and comorbid ODD/CD (OR = 2.87) were most strongly associated with SUD development. Male sex and parental factors (eg, SUD, psychiatric condition, low paternal income and education) were also identified risk factors.[127]

A review of 27 longitudinal studies that followed children with and without ADHD into adolescence or adulthood found that compared with control subjects without ADHD, children with ADHD were (1) nearly three times more likely to report nicotine use in adolescence/adulthood, (2) almost two times more likely to meet diagnostic criteria for alcohol use disorder, (3) approximately 1.5 times more likely to meet criteria for cannabis use disorder, (4) twice as likely to develop cocaine use disorder, and (5) more than 2.5 times more likely to develop an SUD overall.[10,126] Observational follow-up of the MTA has provided additional information regarding long-term substance use in children with ADHD. As reported on the Substance Use Questionnaire (SUQ), youth with ADHD compared to their peers were more likely to use cannabis weekly (32.8% vs 21.3%) and cigarettes daily (35.9% vs 17.5%) as adults. Additionally, early substance use, specifically the use of alcohol, cigarettes, and cannabis, was more common in the ADHD group compared to peers.[10] This highlights the need for early substance use screening in adolescence, particularly among those with ADHD.[10]

10 Caregivers frequently express concern that treating their child with a stimulant, particularly early treatment, may increase the risk of substance use. Follow-up studies show that stimulant therapy for ADHD neither increases nor decreases the risk of subsequent SUDs.[10,46] There is evidence that individuals initiating treatment early (before age 8) are less likely to use substances than those who have delayed onset of treatment. Behavioral

therapy may also confer some protection against substance use and issues with the criminal legal system.[10,46,126] Atomoxetine, an α_2-adrenergic agonist, or bupropion is the preferred agent for individuals with ADHD and active SUDs.

Furthermore, other comorbid conditions including depression, anxiety, low self-esteem, CD, ODD, and antisocial personality disorder all increase the risk for developing an SUD in an individual with ADHD.[10,126,127] These comorbidities also increase the risk for issues with the criminal legal system that can prevent treatment and lead to ongoing SUDs. As youth with ADHD transition to adolescence, parents and clinicians should pay attention to whether the teen could be at risk for an SUD or misuse of their prescribed medications.[126,128,129]

Several studies have evaluated protective factors against substance use and issues with the criminal legal system for youth both with and without ADHD. These studies found that a quality parent–youth relationship, involving good communication, regular time together, consistent rules, and sharing of information (eg, how the child or adolescent spends free time and who their friends are) can be effective in deterring alcohol and substance use in youth with or without ADHD.[46,126] Youth support groups at high schools, such as the Gay/Straight Alliance (GSA), are credited with assisting schools with achieving lower rates of substance use and the misuse of the prescribed ADHD medications compared with schools without GSAs.[128]

Eating Disorders

All patients with ADHD should be screened for eating disorders given inattention and impulsivity associated with ADHD increase the risk of aberrant eating behavior and obesity. Inattentive symptoms can lead to mindless eating when not hungry, or impulsive, out of control eating aimed at emotional regulation.[130,131] A meta-analysis of 728,136 participants, 48,161 with ADHD (46,115 children; 2,046 adults), and 679,975 comparison subjects (616,228 children; 63,747 adults) showed that the pooled prevalence of obesity was increased by about 70% in adults with ADHD and 40% in children with ADHD. A genetic association has been found with non-restricting eating disorders such as bulimia nervosa and binge eating disorder, particularly in females.[132] Lisdexamfetamine is an FDA-approved effective treatment for both ADHD and binge eating disorder in adults.[133,134]

Oppositional Defiant and Conduct Disorders

Oppositional defiant disorder and CD occur in 30% to 60% of youth diagnosed with ADHD and are commonly associated with severe aggression and functional impairment.[135] Causes of ODD, CD, and associated severe aggression in youth with ADHD are multifactorial and include psychosocial adversity factors (eg, maternal mental disorder, paternal criminality, violence in the home), learning disability, disruptive mood dysregulation disorder (DMDD), or bipolar disorder.[135-137] Experts consider psychosocial interventions that include parent training and support for the child's family an essential part of the treatment plan for youth with ADHD, co-occurring with ODD or CD.[5,42,60,137-141]

Effective treatment of ADHD and CD/ODD is critical in the reduction of a wide range of psychosocial consequences (eg, substance use, violence, unemployment). Evidence-based guidelines recommend stimulants as first-line treatment for oppositional behavior, conduct problems, and aggression in youth with ADHD and comorbid CD/ODD.[138-140] Optimization of stimulant monotherapy (particularly methylphenidates) has demonstrated rapid, long-lasting improvements in emotion dysregulation, aggression, and ADHD symptoms.[142-144] A 2-year follow-up study of youth (n = 33,835) with ADHD found that patients with higher rates of adherence to stimulants or atomoxetine were less likely to eventually develop CD/ODD compared to those with poorer adherence, suggesting a possible protective effect of medication treatment.[145]

Studies in adolescents and adults with ADHD show that doses of stimulant above the recommended daily maximum are frequently needed for optimal symptom control prompting the American Academy of Child and Adolescent Psychiatry to publish an "off-label maximum dosage of 100 mg/day for methylphenidate and 60 mg/day for dextroamphetamine and mixed amphetamine salts." These dosage ranges appear in the academy's practice parameter on the treatment of ADHD.[42]

A head-to-head, randomized, 24-week open-label trial among youth treated with atomoxetine (n = 80) or OROS-methylphenidate (n = 80) demonstrated improvement in emotional/behavioral/externalizing problems in youth, with greater improvement in aggressive behavior and conduct problems in the OROS-methylphenidate group.[146] Treatment guidelines recommend that atomoxetine be considered in individuals who do not respond to or poorly tolerate stimulants.[138-140] Clonidine and guanfacine can be considered as monotherapy or add-on to stimulant treatment, but evidence to support their use is much lower quality.[138,139]

Unfortunately, optimizing ADHD-specific medications such as stimulant or atomoxetine is not universally effective for aggression and over half of youth with ADHD and ODD/CD need more than one medication for optimal symptom control.[70] The treatment of severe childhood aggression (TOSCA) study included 168 youth with ADHD and either ODD or CD (mean age of 9 years) and showed that adding risperidone 1 to 3 mg daily to parent training, behavioral therapy, and optimized stimulant resulted in moderate improvement in aggression. A 52-week follow-up of study participants demonstrated an overall benefit for youth who remained on medication, with the risperidone augmented-group demonstrating a small added benefit (improved CGI-S scores). This warrants close evaluation considering the long-term use of risperidone was associated with significant increased risk for weight gain and increased serum prolactin.[147] Overall, guidelines recommend that risperidone should be considered as a short-term treatment for severe aggression and/or explosive anger if not effectively managed by traditional ADHD medications.[138,139]

Aggression

Aggressive behavior is a common reason children present to higher levels of psychiatric care and is most prevalent in children with ADHD, often combined with ODD, CD, or DMDD.[148,149] Stimulants are typically considered first line for co-occurring aggression and ADHD, with some pediatric patients requiring adjunct pharmacologic treatment (eg, second-generation antipsychotic, mood stabilizer).[149] A randomized, controlled trial including 6- to 12-year-olds ($N = 175$) with ADHD, a disruptive disorder, significant aggression, and prior stimulant treatment demonstrated significant reduction in aggression (63% experienced remission) with rapid symptom-guided stimulant titration. This suggests that quick optimization of stimulant treatment and concurrent behavioral therapy may minimize the need for additional medications. For those who do not experience a significant reduction in aggression, adjunctive medications like risperidone and valproate may be helpful but are associated with risk (eg, weight gain).[149]

Tourette Disorder

ADHD occurs in 50% to 60% of youth with chronic tics or Tourette disorder, and 20% of children with ADHD go on to develop chronic tics or Tourette disorder.[72,73,91] Experts cautioned that stimulants should not be first-line treatments for ADHD in youth with tic disorders due to the stimulant's ability to increase central dopaminergic and noradrenergic activity, potentially exacerbating tics. However, a meta-analysis of 22 placebo-controlled trials involving 2,385 children with ADHD and Tourette disorder showed that stimulants were not more likely to worsen tics than placebo, and the association between stimulants and new-onset tics was more coincidental than a cause-and-effect relationship.[91] Additionally the timing of tic development in the context of ADHD may have led clinicians to inappropriately attribute new onset tics to stimulant treatment, as epidemiologic studies show that when ADHD and Tourette co-occur, symptoms of ADHD are present 2 to 3 years before tics emerge. Tourette disorder is known for fluctuating symptom severity with tics worsening and remitting in an unpredictable pattern, further diminishing the ability to accurately attribute tic causality.[75,91] When a stimulant trial is necessary to manage functionally impairing ADHD in a person with Tourette disorder, methylphenidate is recommended due to better evidence for effectiveness and tolerability in this population.[150]

A double-blind, placebo-controlled trial compared methylphenidate or clonidine monotherapy with the combination of methylphenidate and clonidine in patients with ADHD and Tourette disorder. Combination therapy demonstrated the greatest benefit in reducing symptoms of ADHD and tics, and clonidine appeared most helpful for impulsivity and hyperactivity, whereas methylphenidate was most helpful for inattention.[75,91] All treatments were well tolerated, but sedation was common (28%) in those receiving clonidine.[75]

Furthermore, guanfacine was administered to 34 children (mean age 10.4 years), with ADHD and tic disorder during an 8-week, placebo-controlled trial at a dose of 1.5 to 3 mg/day. Tic severity decreased by 31% in the guanfacine group compared with 0% in the placebo group.[75] There was a mean improvement of 37% on the teacher-rated ADHD scale compared with 8% improvement with placebo. Therefore, as previously stated, clonidine or guanfacine alone is a less effective alternative to stimulants in the treatment of children with ADHD and this holds true for those with comorbid Tourette disorder.

Atomoxetine appears to be an effective treatment for ADHD and tics in pediatric patients with comorbid Tourette syndrome or chronic motor tic disorder. For this study, 148 children and adolescents were randomized to atomoxetine (0.5-1.5 mg/kg/day) or placebo for up to 18 weeks of treatment. Overall, atomoxetine resulted in improvements in the severity of ADHD (effect size = 0.6) and tics (effect size = 0.3).[109]

Individuals with Tourette disorder and ADHD are more prone to disruptive behaviors including poor frustration tolerance, aggression, and impulsivity,

often requiring behavioral interventions and medications that may include second-generation antipsychotics.[75] Second-generation antipsychotics such as risperidone, aripiprazole, and ziprasidone have evidence from controlled trials to support their use in managing motor and vocal tics associated with Tourette disorder; however, aripiprazole is the only agent FDA approved for managing Tourette disorder.[75] See Chapter 87 for more information about antipsychotics.

Personalized Pharmacotherapy

There are many things to consider when making therapeutic decisions in patients with ADHD such as age, comorbidities, tolerability, potential for medication interactions, and patient preference. In addition, there may be pharmacokinetic and pharmacogenomic factors to consider when personalizing pharmacotherapy. In looking specifically at pharmacogenomics, the functional activity of cytochrome P450 (CYP) 2D6, norepinephrine and dopamine transporters (SLC6A2, SLC6A3), catechol-*o*-methyltransferase (COMT), dopamine receptor (DRD4), carboxylesterases (CES1), and α_2-adrenergic receptor (ADRA2A) has been evaluated as a predictive tool for ADHD medication response and tolerability.[151-155] As the pharmacogenomics of ADHD treatments is a rapidly evolving field, an evidence-based resource available to decipher this work is provided by the Clinical Pharmacogenomics Implementation Consortium (CPIC, www.cpicpgx.org) or the Pharmacogenomics Research Network (PGRN, www.pharmgkb.org).[156] Specifically, the CPIC website contains evidence-based expert guidelines for interpretation of specific gene drug pairs, which may be used when testing is completed. It is important to note that CPIC does not recommend testing, but rather aims to serve as a reference for when testing results are available.

A CPIC guideline is available to guide dosing of atomoxetine based on CYP2D6 genotype in pediatric patients.[157] Exposure to atomoxetine increases 10-fold among CYP2D6 poor metabolizers and has a longer half-life, 20 hours compared to 5 hours, resulting in increased total plasma exposure compared to normal metabolizers.[157] Some studies have shown that CYP2D6 poor metabolizers may experience more insomnia, weight loss, increased heart rate and blood pressure, constipation, and depression associated with atomoxetine treatment compared to normal metabolizers.[158-160] Additionally, poor metabolizers may demonstrate greater therapeutic benefit due to increased exposure to the medication.[155,158] The CPIC guideline provides specific recommendations for starting doses based on CYP2D6 genotype and atomoxetine peak plasma concentrations and the manufacturer recommends dose adjustments based on genotype and concomitant treatment with potent CYP2D6 inhibitors.[157,160,161]

As methylphenidate is de-esterified by CES1 prior to elimination, it is less likely to have metabolic drug interactions compared with mixed amphetamine salts.[162] Sex influences the absorption of methylphenidate, with males having increased bioavailability compared with females.[7] Variability in dosage requirements for amphetamine salts, atomoxetine, and bupropion can be due to inter-individual variability in plasma concentration achieved at a given dose. As all are metabolized via CYP2D6, the bioavailability and half-life of CYP2D6 substrates can be four to eight times greater in those taking a CYP2D6 inhibitor (eg, bupropion, fluoxetine, or paroxetine).[158-160]

While the routine use of pharmacogenomic testing is not recommended prior to initiation of ADHD medication, consideration should be made in particular clinical scenarios: (a) prior to the initiation of atomoxetine in pediatric patients with previous poor response/tolerability to other substrates of CYP2D6 and/or who are particularly sensitive to changes in HR/BP; (b) poor tolerability to atomoxetine/stimulants at starting doses; (c) individuals presenting with several psychiatric comorbidities and a history of psychotropic medication poor response/tolerability; and (d) family history of poor medication tolerability.

EVALUATION OF THERAPEUTIC OUTCOMES

Careful documentation of baseline symptoms and complaints over a 1-month pre-medication period is essential to the evaluation of therapeutic and adverse outcomes. Investigation regarding family history of psychiatric disorders and cardiac disease is essential to determine risk for related adverse medication reactions and to implement appropriate monitoring.[45,60] Baseline symptoms can be measured using videotapes, clinician rating scales (eg, ADHD Rating Scale IV, Vanderbilt ADHD Diagnostic Scale), or both. In addition, height, weight, and eating and sleeping patterns should be recorded at baseline and every 3 months.[5,42,45,60]

After the initiation and titration of any medication treatment, it is necessary that caregivers, teachers, and clinicians assess the overall functioning of the child or adult using standardized rating scales to determine if significant therapeutic benefit justifies continuing medication.[4,42] Therapeutic

effects of the stimulants include decreased motor activity and impulsivity and increased attention span.[4,7,42] This suggests that stimulants are indicated for ADHD symptoms and not for primary learning disorders. The benefits of medication therapy must outweigh the potential for adverse effects to justify continued treatment.[4,42]

There is a lack of standardized assessment tools for adults; however, the adult ADHD screening tool can be useful.[49] Short-term studies (1 year or less) in adults with ADHD show that treatment with stimulants improves subjective quality of life. Long-term studies are needed to better assess the risk versus benefit of stimulant therapy on psychosocial and health outcomes.[163]

Atomoxetine, α_2-adrenergic agonists, and bupropion also require monitoring to detect changes in appetite, weight, and sleep patterns, as well as pulse and blood pressure. A therapeutic trial of atomoxetine or bupropion consists of 6 weeks at maximum tolerated doses unless response occurs at a lower dose.[4,42] Atomoxetine's full therapeutic benefit may continue to build over weeks to months, but if there is no significant benefit in the initial 6 weeks, it is unlikely that atomoxetine will be effective; therefore, it can be tapered off.[109]

When guanfacine or clonidine is given, careful clinical monitoring for fatigue, dizziness, and autonomic changes (eg, blood pressure and pulse) is recommended.[45,97] The American Heart Association has stated that ECG monitoring is not required for α_2-adrenergic agonists treatment in children, although many clinicians continue to assess for ECG changes, particularly if there is a family history of cardiac disease, if the patient is taking other agents that impact cardiac function, or if clinical symptoms warrant.[45] When discontinuing treatment, clonidine and guanfacine should be withdrawn slowly (0.05 mg clonidine/0.5 mg guanfacine reductions every 3-7 days) to prevent rebound hypertension or behavioral dyscontrol.[97,164] A therapeutic trial requires 1 to 2 months to assess therapeutic response, although increased sleep usually occurs immediately.[97,164]

Evaluation of therapeutic outcomes is particularly important when antipsychotics are used in youth as the US Office of Inspector General's peer review of psychiatrists found quality of care concerns in 67% of 475 medical records of youth receiving antipsychotics through Medicaid.[165] Among the biggest problems were lack of appropriate indications and lack of appropriate monitoring to ensure safety. Baseline weight, lipids, and fasting glucose should be monitored every 6 months in addition to the need to monitor for extrapyramidal symptoms and hyperprolactinemia.[9,107,165]

CONCLUSION

ADHD is a heritable, well-studied brain disorder that can present at any age, with or without co-occurring conditions. It is best treated with a combination of psychosocial, educational, cognitive-behavioral, and pharmacologic interventions. Treatments should be selected based on age, co-occurring conditions, and patient/family preference.

ABBREVIATIONS

AAP	American Academy of Pediatrics
ADHD	attention deficit/hyperactivity disorder
ASD	autism spectrum disorder
CBT	cognitive behavioral therapy
CD	conduct disorder
CNS	central nervous system
CNV	copy number variants
CRS-revised	Connors' Rating Scales—revised

CYP	cytochrome P450
DMDD	disruptive mood dysregulation disorder
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*
ECG	electrocardiogram
FDA	Food and Drug Administration
GI	gastrointestinal
IEP	individualized educational program
MAO	monoamine oxidase
MTA	Multimodal Treatment Study of Children with ADHD
NICE	National Institute for Health and Care Excellence
NIH	National Institute of Health
NNT	number needed to treat
ODD	oppositional defiant disorder
ODT	orally disintegrating tablet
OROS	osmotically released oral delivery system
SSRI	selective serotonin reuptake inhibitor
SR	sustained release
TOSCA	Treatment of Severe Childhood Aggression Study
TCA	tricyclic antidepressant

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SELF-ASSESSMENT QUESTIONS

1. A 4-year-old child exhibits severe hyperactivity at preschool and is asked to leave preschool due to aggression, impulsivity, and not following directions. Which of the following statements describes an additional diagnostic criterion needed for a diagnosis of ADHD?

   A. The symptom duration would need to be 6 weeks.

   B. These impairing symptoms are also present at home.

   C. The patient must be at least 6 years old.

   D. Learning disability needs to be ruled out.

2. A teacher's aide asks about the most likely cause of new onset tics (throat clearing) in a 9-year-old with ADHD and Tourette disorder treated with Quillivant 20 mg daily and clonidine 0.1 mg at bedtime (same doses for 3 months)? The best answer is:

   A. Too much sugar in the diet.

   B. Quillivant dose is too high.

   C. Clonidine dose is too low.

   D. Natural course of tic disorder.

3. A deficiency in this substance contribute to ADHD symptoms:

   A. Ferritin

   B. Cyanocobalamin

   C. Folate

   D. Ascorbic acid

4. Which statement should be included when counseling a family on the risks of stimulant therapy for ADHD?

   A. The risk of an adverse cardiac event is two times greater in a child taking stimulant compared to an untreated child.

   B. Stimulant therapy for ADHD increases the risk of accidental injury, including the risk of severe brain injury.

   C. The risk of decreased growth and insomnia is greater with immediate-release stimulants.

   D. Stimulants are more likely to be associated with severe liver injury compared to atomoxetine.

5. Which of the following statements most accurately describes the clinical presentation of adult ADHD?

   A. Hyperactivity and impulsivity are the most prominent symptoms.

   B. Adults frequently report racing thoughts, mood swings, and insomnia.

   C. Disorganization increases in frequency and severity over the adult life span.

   D. Distractibility and difficulty with sustained mental effort are most common.

6. What structural brain change is the most well-established marker for ADHD?

A. Enlarged ventricles and diminished basal ganglia

B. Underdevelopment of the locus coeruleus

C. Overgrown lateral lobe of the amygdala

D. Cortical thinning and delay in cortical thickness

7. Which of the following is an appropriate starting dose of atomoxetine for a 10-year-old (100 lb [45 kg]) child with ADHD?

A. 20 mg twice daily

B. 25 mg in the morning

C. 10 mg twice daily

D. 30 mg at bedtime

8. A 12-year-old female diagnosed with ADHD and conduct disorder is suspended from school for cannibis use. The patient was started on lisdexamfetamine 6 weeks ago, but prescription records show only a 30-day supply was dispensed. Which factor is most likely to have contributed to an increased risk of substance use in this patient?

A. Comorbid conduct disorder

B. Diagnosis of ADHD

C. Female gender

D. Taking lisdexamfetamine

9. Which ADHD medication is most likely associated with excessive daytime sedation requiring counseling regarding possible sleepiness during the school day?

A. Lisdexamfetamine

B. Bupropion

C. Atomoxetine

D. Clonidine

10. Which of the following statements is accurate regarding the treatment of ADHD in a patient with autism spectrum disorder (ASD)?

A. Methylphenidate has the best chance for efficacy in less severe ASD

B. Risperidone is preferred as it can improve irritability and symptoms of ADHD

C. α_2-Adrenegic agonists may improve both ADHD symptoms and irritability

D. Atomoxetine is first-line treatment due to its ability to lessen anxiety over tics

11. A 23-year-old graduate student asks about the most potentially effective treatment for ADHD. The patient took some medication as a child but can't remember the name. Which treatment has the most chance for therapeutic benefit and ease of administration for this patient based on efficacy studies?

A. Mydayis ER

B. Aptensio XR

C. Metadate ER

D. Dyanavel XR

12. In a patient with bipolar disorder and severe inattention and hyperactivity, the following treatment plan is most appropriate:

A. Stabilize mood first with lithium or other mood stabilizer, and then consider whether low-dose stimulant is needed for inattention and hyperactivity.

B. Manage ADHD with bupropion, and then consider adding a mood stabilizer or second generation antipsychotic once ADHD symptoms are controlled.

C. Avoid stimulants as they will worsen mania; give atomoxetine to manage both ADHD and bipolar disorder.

D. Start extended-release guanfacine to manage ADHD and then consider adjunctive lithium or second generation antipsychotic.

13. Potential advantages of α_2-adrenergic agonists over stimulants for ADHD include:

A. More rapid onset of therapeutic effect

B. Less insomnia, anorexia, and growth effects

C. Greater efficacy for inattentive symptoms

D. Effective for children, teens, and adults

14. A 10-year-old with ADHD and conduct disorder with severe aggression is taking 54 mg of osmotically released oral delivery system (OROS) methylphenidate. BP is 116/68, pulse 60, weight is 50 kg (110 lb). What intervention has the most evidence for efficacy in managing aggression in this patient?

A. Increase dose of OROS methylphenidate to 72 mg

B. Add guanfacine 1 mg twice daily

C. Change from OROS methylphenidate to atomoxetine

D. Add risperidone 0.5 mg twice daily

15. Studies have shown that adjunctive behavioral interventions administered to youth with ADHD:

A. Are more effective than stimulant medications.

B. Are not likely to be administered in the classroom.

C. May allow for lower effective doses of stimulant.

D. Are more effective for inattention than hyperactivity.

SELF-ASSESSMENT QUESTION-ANSWERS

1. **B.** The *DSM-5* diagnostic criteria for ADHD states symptoms must be present for 6 months in two different settings such as home or school. A learning disability is a common comorbidity with ADHD but is not required for a diagnosis of ADHD. (See "Clinical Presentation" section.)

2. **D.** At least 50% of Tourette disorder patients have ADHD symptoms. Research investigating causes of tics has shown methylphenidate to be an unlikely cause, with most cases of symptom worsening due to the natural course of Tourette disorder.

3. **A.** Several studies have documented iron deficiency in children with ADHD. Iron supplementation has been associated with improvement in ADHD symptoms.

4. **A.** Although rare, the risk of an adverse cardiac event is two times greater in those taking stimulant medication compared to untreated individuals. This makes sense based on the mechanism of action of stimulants, increasing sympathetic nervous system tone which can increase heart rate and blood pressure.

5. **D.** This is the correct answer because hyperactivity is a prominent symptom during childhood, not adulthood; disorganization is a symptom common in all ages. Mood swings and racing thoughts are not part of the ADHD diagnosis.

6. **D.** Functional and structural brain imaging studies show cortical thinning and a delay in attaining cortical thickness in the brains of persons with ADHD. Cortical thinning is evidence for lack of brain maturation. Lack of brain maturation is associated with the lack of ability to think before acting or poor impulse control.

7. **C.** Atomoxetine dosing recommendations call for a starting dose of 0.5 mg/kg/day, and studies show youth tolerate atomoxetine better when given in divided doses compared to once daily (see Table 82-2).

8. **A.** Conduct disorder is a well-established risk factor for developing a substance use disorder. Having a diagnosis of ADHD is a risk for developing a substance use disorder but the presence of conduct disorder poses a greater risk according to longitudinal studies such as the MTA study.

9. **D.** Lisdexamfetamine and bupropion may both be associated with insomnia. Atomoxetine can cause sleepiness in some individuals but clonidine is much more likely associated with sedation (see Tables 80-3 and 80-4).

10. **A.** Methylphenidate is the treatment with the most evidence for therapeutic benefit in improving ADHD symptoms in individuals with ASD.

11. **A.** Amphetamine-based products are the most effective agents for adults with ADHD according to the available literature. Mydayis and Dyanavel XR are amphetamine products. Aptensio XR and Metadate ER are methylphenidate-based products (see Table 82-2).

12. **A.** A mood stabilizer is first-line in patients with bipolar disorder even if they have comorbid ADHD. If a stimulant or atomoxetine are given without a mood stabilizer, manic and/or psychotic symptoms may be induced. Extended-release guanfacine has not been studied for bipolar disorder co-occurring with ADHD (see Fig. 82-1).

13. **B.** Clonidine and guanfacine are less effective alternatives to stimulants in children and adolescents. The onset of therapeutic effect is 2 to 4 weeks, and they have not been sufficiently studied to recommend for adults with ADHD.

14. **D.** Risperidone is the most well-studied and effective agent for managing aggression in patients with ADHD and conduct disorder. Increasing the OROS methylphenidate dose to 72 mg daily would be exceeding the maximum recommended dose in children below 12 years of age. Guanfacine is less likely to be effective compared to risperidone.

15. **C.** Several studies in school age youth and adolescents with ADHD show medications are generally more effective than behavioral interventions but behavioral interventions can allow for symptom improvement at lower doses.